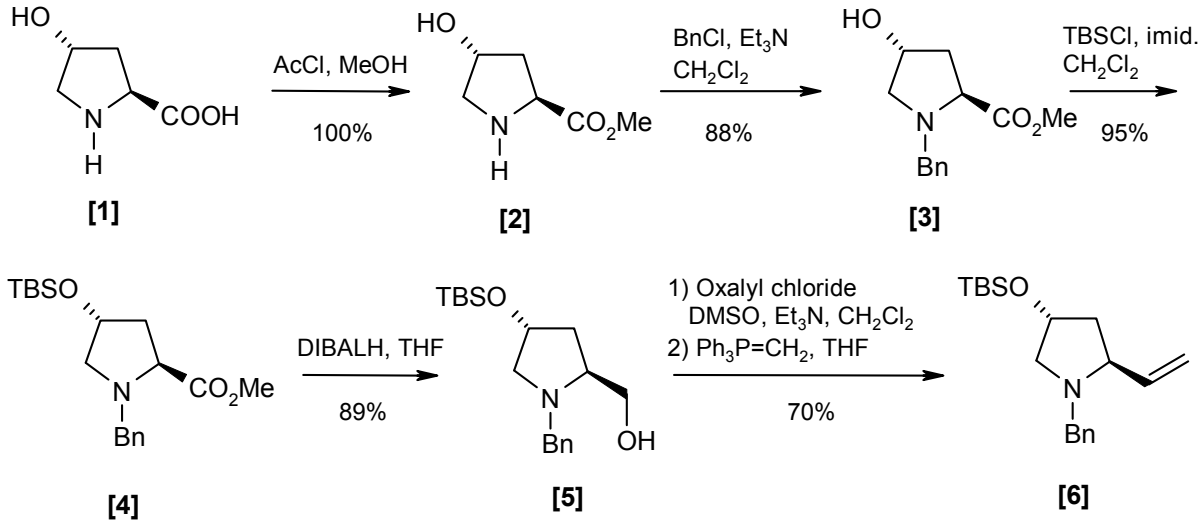
2 Results and Discussion

2.1 Syntheses of Azoninones - Unsaturated Nine-Membered Ring Lactams

2.1.1 Syntheses of Vinyl pyrrolidines

N-Vinyl pyrrolidines are important reactants for the preparation of azoninones by zwitterionic aza-Claisen rearrangement. They can be obtained by derivatisation reactions starting from chiral molecules such as *L*-proline and 2*S*,4*R*-4-hydroxyproline or by metal catalysed cyclisation reactions of N-substituted allenic amines.[66] Since large amounts of vinyl pyrrolidines have to be synthetically available for the systematic examination of the aza-Claisen rearrangement and its application in a total synthesis, especially the ex-chiral pool synthesis of these precursors has been extensively investigated by our group.[67] The following two schemes represent the synthesis of the vinyl pyrrolidines **[6]** and **[11]** that have been used in this work as precursors for the aza-Claisen rearrangement. This synthesis allows the preparation of 50-100g of vinyl pyrrolidines.



Scheme 19 Synthesis of vinyl pyrrolidine **[6]**

Allylamine **[6]** was efficiently generated via a six-step sequence starting from *trans*-4-hydroxy-*L*-(-)-proline **[1]** the overall yield was about 50% (Scheme 19). After esterification,[68] the N-benzyl group

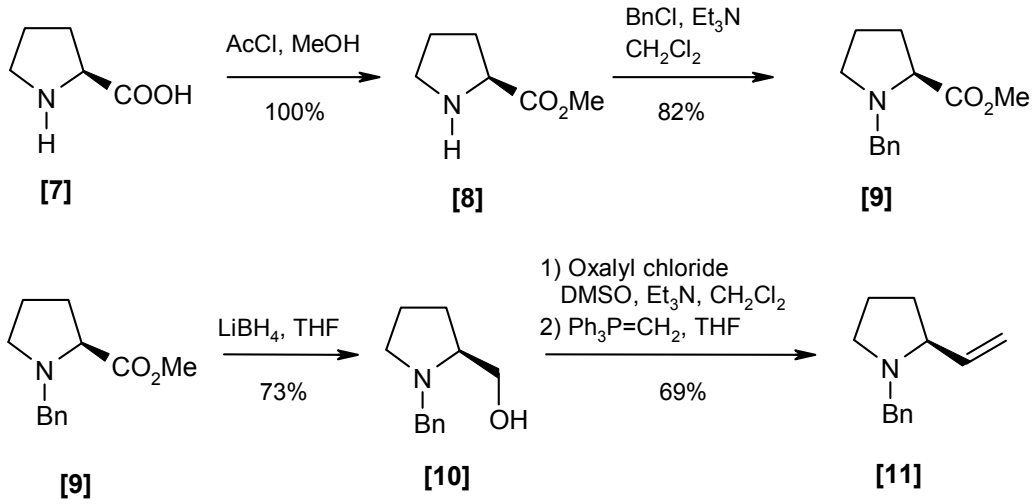
[66] (a) Huby, N. J. S.; Kinsman, R. G.; Lathbury, D.; Vernon, P. G.; Gallagher, T. *J. Chem. Soc. Perkin Trans. I* **1991**, 145. (b) Davies. I. W.; Scopes, D. I.; Gallagher, T. *Synlett* **1993**, 85-87. (c) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, 113, 2652. (d) Katritzky, A. R.; Yao, J.; Yang, B. *J. Org. Chem.* **1999**, 64, 6066-6070.

[67] A. Scherrmann diploma thesis, Berlin 1997; M. Diederich PhD thesis, Freie Universität Berlin (2000); A. Sudau diploma thesis, Freie Universität Berlin (1997).

[68] Tietze, L. F.; Eicher, T. *Reaktionen und Synthesen im Organisch-Chemischen Praktikum*, 2nd ed.; Thieme: Stuttgart, **1991**; p 135.

was introduced by treatment of the secondary amine with benzyl chloride in the presence of triethylamine.[69] Neither epimerisation resulting in the 2,4-*cis* material nor further benzylation of the tertiary amine or the hydroxyl group was found, respectively. The high yield and the short reaction time led to the replacement of the formerly used reductive amination.[64,70] The protection of the alcohol as a TBS ether (TBS = *tert*-butyldimethylsilyl) generated an ester **[4]**.[71] The reduction of the carboxyl function with DIBALH yielded the primary carbinol **[5]**.[72] A subsequent Swern oxidation led to the corresponding aldehyde,[73] which was immediately converted into the vinyl pyrrolidine **[6]** by a Wittig olefination with methylenetriphenylphosphorane, thus avoiding any epimerisation to the 2,4-*cis* product.[74]

The relative configuration of the stereogenic centres at C-2 and C-4 was proven using NOE analysis.[64] Since no isomerisation to the 2,4-*cis* product could be detected, the same reaction sequence was applied for the synthesis of the 2-vinyl pyrrolidine **[11]** (Scheme 20).



Scheme 20 Preparation of vinyl pyrrolidine **[11]**

The reaction sequence **[7]** to **[11]** is similar to the above stated, however instead of the DIBALH reduction a reduction with $LiBH_4$ was used.[75] The overall yield for the reaction sequence was about 41%.

These syntheses enabled the large scale preparation of enantiomerically pure N-Benzyl-vinyl pyrrolidines in only 4 to 5 steps with high overall yields and including only one chromatographic separation (purification of compound **[6]**).

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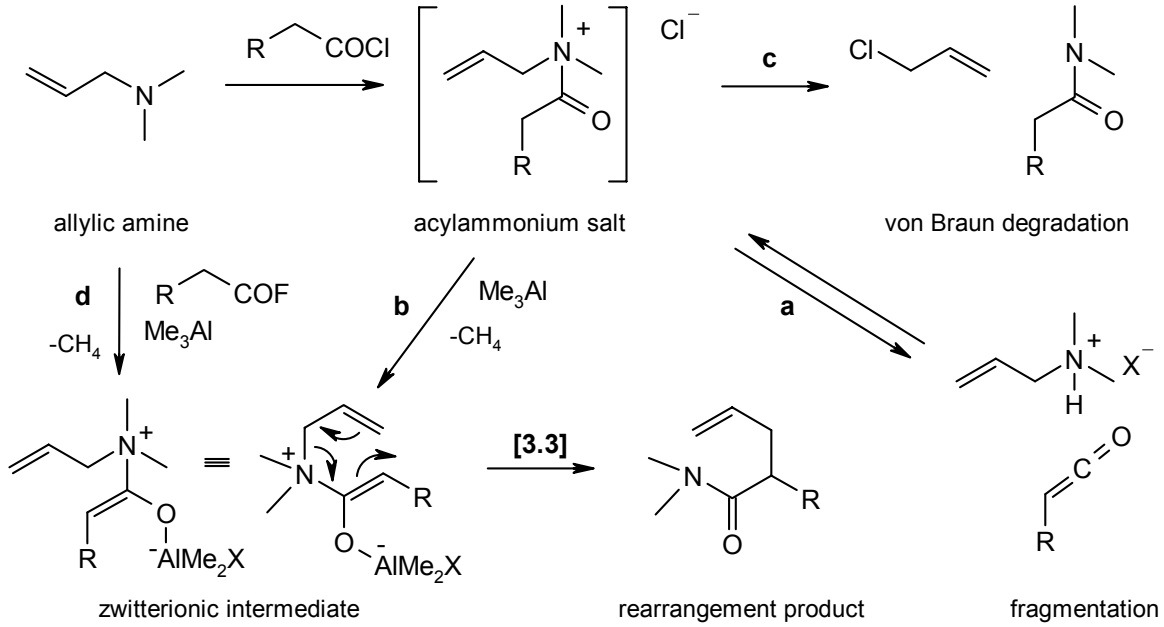
[69] Rosen, T.; Fesik, S. W.; Chu, D.; Pernet, T. W.; Andre, G. *Synthesis* **1988**, 40.
[70] Diederich, M.; Nubbemeyer, U. *Angew. Chem.; Int. Ed. Engl.* **1995**, 34, 1026.
[71] Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, 94, 6190.
[72] Winterfeldt, E. *Synthesis* **1975**, 617.
[73] Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
[74] (a) Corey, E. J.; Greenwald, R.; Chaykovsky, M. *J. Org. Chem.* **1963**, 28, 1128. (b) Marshall, J. A.; Pike, M. T.; Carroll, R. D. *J. Org. Chem.* **1966**, 31, 2933. (c) Marshall, J. A.; Huffmann, W. F.; Ruth, J. A. *J. Am. Chem. Soc.* **1972**, 94, 4691. (d) Magnusson, G. *Tetrahedron Lett.* **1977**, 2713.
[75] Use of $LiBH_4$ in contrast to DIBALH simplified the reaction procedure and the workup due to substantially decreased reaction volumes in large scale reactions.

2.1.2 Aza-Claisen Rearrangement of Vinyl pyrrolidines

The stereochemical and regiochemical control of bond formation offered by the Claisen and Cope rearrangements has made these sigmatropic reactions powerful synthetic tools for the construction of both acyclic and cyclic molecules. Many heteroatom-substituted variations of these two fundamental reactions have been developed, largely in efforts to produce processes with the same useful characteristics but which might occur at lower temperatures (Cope, 210-260 °C; Claisen, 180-255 °C) and offer better stereochemical control in the bond-forming step. With specific regard to nitrogen-substituted variations of these reactions, neutral and ionic variations of aza-Claisen rearrangements have been especially well-investigated in the past few years.[57, 62,76,77] In these studies, the potentially tetracoordinate nature of nitrogen has proven advantageous for the introduction of control elements, which may influence both the stereochemical outcome and the catalysis of the reaction process.

The zwitterionic aza-Claisen rearrangement of various N-allylamines with carboxylic acid chlorides has been developed as a mild and efficient method to form γ,δ-unsaturated amides or lactams. It's schematic mechanism is represented in Scheme 21.



Scheme 21 Postulated reaction mechanism of the zwitterionic aza-Claisen rearrangement

[76] For other zwitterionic variants see: (a) Cid, M. M.; Eggnauer, U.; Weber, H. P.; Pombo-Villar, E. *Tetrahedron Lett.* **1991**, 32, 7233. (b) Cid, M. M.; Pombo-Villar, E. *Helv. Chim. Acta* **1993**, 76, 1591. (c) Ishida, M.; Muramaru, H.; Kato, S. *Synthesis* **1989**, 562. (d) Roberts, S. M.; Smith, C.; Thomas, R. J. *J. Chem. Soc. Perkin Trans.* 1 **1990**, 1493. For anionic amide enolate rearrangements see: (e) Tsunoda, T.; Tatsuki, S.; Kataoka, K.; Ito, S. *Chem. Lett.* **1994**, 543. (f) Tsunoda, T.; Sakai, M.; Sasaki, O.; Sako, Y.; Hondo, Y.; Ito, S. *Tetrahedron Lett.* **1992**, 33, 1651. (g) Ito, S.; Tsunoda, T. *Pure Appl. Chem.* **1994**, 66, 2071. (h) Tsunoda, T.; Nishii, T.; Yoshizuka, M.; Yamasaki, C.; Suzuki, T.; Ito, S. *Tetrahedron Lett.* **2000**, 41, 7667-7671. (i) Lindström, U. M.; Somfai, P. *Chem. Eur. J.* **2001**, 7, 94-98. (k) Lindström, U. M.; Somfai, P. *J. Am. Chem. Soc.* **1997**, 11*9,* 8385-8386. (l) Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem.* **1999**, 111, 23, 3753-3755.

[77] (a) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, 121, 9726-9727. (b) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, 123, 2911-2912. (c) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, 123, 2448-2449.

Originally, the aza-Claisen rearrangement was carried out using carboxylic acid chlorides and Lewis acids (Me_3Al) in the presence of a base (K_2CO_3, Na_2CO_3). The allylic amine formed the acylammonium salt, which presumably was in equilibrium with the fragmentation products - the ammonium salt and a ketene (pathway **a**).[78] After the addition of trimethylaluminium the evolvement of methane was observed and the hypothetical zwitterionic intermediate was formed, which undergoes rearrangement (pathway **b**). The major problems of the process reported was a von-Braun type competing reaction involving a nucleophilic attack of the chloride ion on an intermediate acylammonium salt (pathway **c**).[79] The percentage of the resulting allyl chlorides depended on the substitution pattern of the allyl amines used.[80] When sterically more bulky allylic amines such as **[6]** were used, the amount of von-Braun degradation products was substantially higher. Furthermore, several reactions suffered from partial fragmentation resulting in allylamine hydrochlorides in the presence of the carboxylic acid chlorides. The inactive ammonium salts additionally required the addition of Me_3Al to regenerate the reactive amines.

With the intention of suppressing the competing von-Braun reaction by substitution of the chloride counterion by the less nucleophilic fluoride ion, the reaction of carboxylic acid fluorides with allylic amines was examined.[81] Treatment of allyl amines with carboxylic acid fluorides in CH_2Cl_2 or $CHCl_3$ in the presence of solid Na_2CO_3 at 0°C to 23°C resulted neither rearrangement nor von-Braun degradation suggesting a low reactivity of such activated carboxylic acids with tertiary amines. The addition of Me_3Al (35 to 100 mol%) to the mixture started the reaction. Only the rearrangement products were obtained and no allyl halides were formed pointing out that the competing von-Braun degradations were not detected (pathway **d**). The yield of rearranged unsaturated lactams **[6]** and **[11]** was significantly increased compared to that of the corresponding acid chloride experiments.

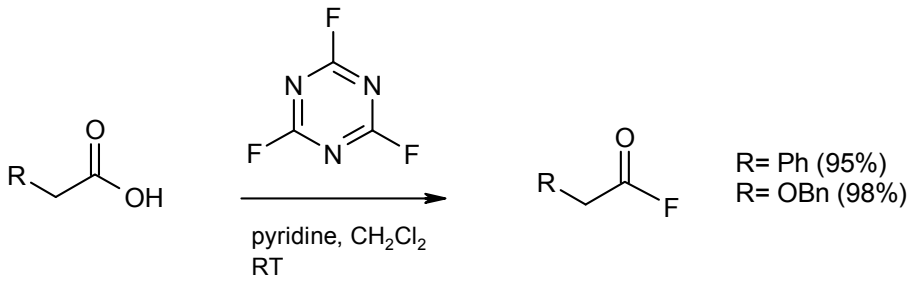
These promising results led to the examination of preparation methods that would provide sufficient amounts of carboxylic acid fluorides.[82]

In the literature several methods for the preparation of carboxylic acid fluorides have been described. First contributions to their preparation were made by Olah *et al*. using acid chlorides and KF or KF/HF at high temperatures.[83] These harsh reactions conditions allowed only the preparation of simple acid fluorides that contained no acid sensitive groups. The demand for mild selective fluorination methods

[78] A free protonated amine and a chloroketene could be observed during the reaction of the allylic amine [6] and chloroacetyl chloride in the NMR tube, A. Sudau diploma thesis
[79] Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1.
[80] Although own studies (M. Diederich, thesis) always showed the high extent of competing von-Braun reaction in the presence of free chloride ions, some authors obviously couldn't observe these degradation on similar systems (cit. 77), however these results could not be reproduced although thoroughly studied.
[81] Laabs, S.; Scherrmann, A.; Sudau, A.; Diederich, M.; Kierig, C.; Nubbemeyer, U. *Synlett* **1999**, 25.
[82] Groß, S.; Laabs, S.; Scherrmann, A.; Sudau, A.; Zhang, N.; Nubbemeyer, U. *J. Prakt. Chem.* **2000**, 342, 1711-1714.
[83] Olah, G. A.; Kuhn, S.; Beke, S. *Chem. Ber.* **1956**, 89, 862.

led to the development of numerous fluorinating agents such as cyanuric fluoride,[84] DAST (diethylamino sulfurtrifluoride),[85] sulfur tetrafluoride,[86] 2-fluoro pyridinium salts,[87] pyridinium tetrafluoroborates,[88] fluoroformamidinium salts[89] and xenon difluoride.[90] Cyanuric fluoride is the widely used reagent for the mild conversion of carboxylic acids into their acid fluorides.[91] Although commercially available, the high price prevents its use for large scale reactions. Based on an early publication of Tullock *et al.*[92] an improved preparation procedure of cyanuric fluoride starting from the cheap cyanuric chloride was developed by A. Scherrmann.[93] This procedure allowed the easy preparation of large quantities of cyanuric fluoride without the handling of toxic HF. Cyanuric chloride and excess sodium fluoride were heated in sulfolane to about 150–200 °C, the cyanuric fluoride was directly distilled off from the reaction mixture.

With the cheap availability of cyanuric fluoride, the formation of carboxylic acid fluorides from carboxylic acids was investigated and some improvements in their preparation have been made.[82] Except the highly activated chloroacetyl fluoride all carboxylic acid fluorides could be easily prepared according to the following Scheme 22.



Scheme 22 Preparation of carboxylic acid fluorides with cyanuric fluoride

Since highly activated acid fluorides gave only insufficient results applying this method, chloroacetyl fluoride was prepared from chloroacetyl chloride and KF/HF in a teflon apparatus according to the method of Olah *et al.*[83]

The zwitterionic aza-Claisen rearrangement of N-Benzyl vinyl pyrrolidines **[6]** and **[11]** with various carboxylic acid fluorides leads to the formation of azoninones **[12]** to **[19]**. The results of the rearrangements are summarised in Table 1.

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[84] (a) Carpino, L. A.; Sadat-Aalaee, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, 112, 9651. (b) Carpino, L. A.; Mansour, E. M. E. *J. Org. Chem.* **1992**, 57, 6371. (c) Carpino, L. A.; Faham, A. E. *J. Am. Chem. Soc.* **1995**, 117, 5401.

[85] (a) Mukkerjee, J. *J. Fluorine Chem.* **1990**, 49, 151. (b) Bourne, G. T.; Meutermans, W. D. F.; Alewood, P. F.; McGeary, R. P. ; Scanlon, M.; Watson, A. A.; Smythe, M. L. *J. Org. Chem.* **1999**, 64, 3095.

[86] (a) Hasek, W. R.; Smith, W. C.; Engelhardt, V. A. *J. Am. Chem. Soc.* **1960**, 82, 543. (b) Jin, A.; Mack, H.-G.; Waterfeld, A. H.; Oberhammer, I. *J. Am. Chem. Soc.* **1991**, 113, 7847.

[87] Picard, C.; Cazaux, L.; Tisnes, P. *Tetrahedron* **1986**, 42, 3503.

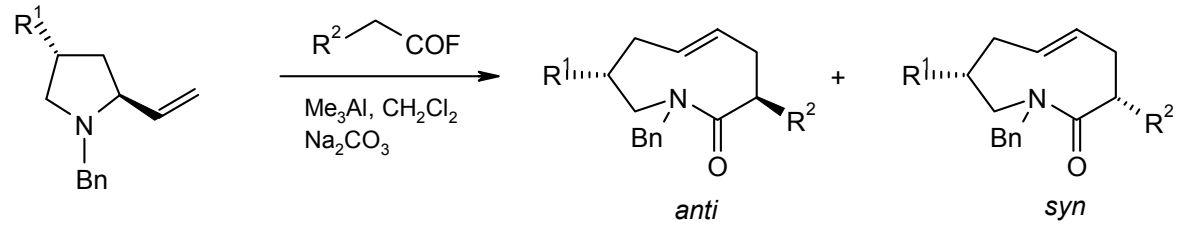
[88] Wagner, R.; Wiedel, B.; Günther, W.; Görls, H.; Anders, E. *Eur. J. Org. Chem.* **1999**, 2383-2390.

[89] Carpino, L. A.; El-Faham, A. *J. Am. Chem. Soc.* **1995**, 117, 5401.

[90] (a) Della, E. W. ; Taylor, D. K. *J. Org. Chem.* **1994**, 59, 2986. (b) Nongkunsarn, P. C.; Ramsden, A. *J. Chem. Soc. Perkin Trans.* 1 **1996**, 121.

[91] Carpino, L. A.; Beyermann, M.; Wenschuh, H.; Bienert, M. *Acc. Chem. Res.* **1996**, 29, 268-274.

[92] Tullock, C. W.; Coffman, D. D. *J. Org. Chem.* **1960**, 25, 2016.



[6],[11] **[12a,b],[13a,b] [14a,b],[16a],[18a]** **[15b],[17a],[19a]**

Table 1 aza-Claisen rearrangement of vinyl pyrrolidines with carboxylic acid fluorides

reactant vinyl pyrrolidine	R^1	R^2	azoninone	yield	*anti*:*syn*
[6]	OTBS	Cl	**[12a,b]**	92%	> 10 : 1*
[6]	OTBS	Ph	**[13a,b]**	83%	> 10 : 1*
[6]	OTBS	OBn	**[14a,b][15b]**	40-65%	~ 10 : 1
[11]	H	Cl	**[16a,17a]**	77%	1.38 : 1
[11]	H	OBn	**[18a,19a]**	35%	2.3 : 1

* only one diastereomer could be isolated

Generally, the yields of the aza-Claisen rearrangements depended on the carboxylic acid fluoride used, phenylacetyl and chloroacetyl fluoride gave better yields while with benzyloxyacetyl fluoride decomposition of the acyl fluoride was observed (cleavage of the ether bond). Especially in large scale reactions this side reaction is responsible for the lower yields. All reactions were found to be completed after 2 to 12 h. In contrast to the investigations involving the acid chlorides, no allyl halides were formed, indicating that the competing von-Braun degradation had efficiently been suppressed. Obviously, the very stable Al-F bond[94] leads to the efficient removal of the weak nucleophilic fluoride ion from the reaction mixture. This assumption is supported by the observation that the rearrangement of silylprotected vinyl pyrrolidines such as **[6]** proceeds without any cleavage of the *tert*-butyldimethylsilyl group.

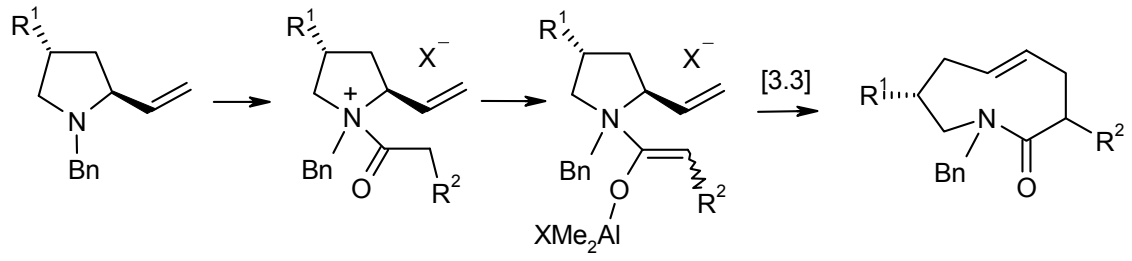
The diastereoselectivity of the rearrangement showed a strong dependence on the reactant vinyl pyrrolidine used. When the bulky TBSO-substituted pyrrolidine **[6]** was used the 1,4-chirality transfer was almost complete. In contrast, the nonsubstituted vinyl pyrrolidine **[11]** obviously showed almost no diastereoselection during the rearrangement. The mechanistic conclusions that can be drawn from these observations are discussed in the next chapter.

[93] Scherrmann A. PhD thesis and lit. [82]
[94] Energy of Al-X bonds: Al-F: 464 kJmol^{-1}, Al-Cl: 233 kJmol^{-1} in: Gmelin, Vol. 35B: *Aluminium*; Pietsch, E. Ed.; VCH, Weinheim, Berlin **1934**, 158 (F), 184 (Cl).

2.1.3 Mechanistic Conclusions

For a better understanding of the experimental results of the rearrangement a model for the stereochemical course of the reaction and the resulting products is introduced firstly. In the following the results of this work are summarised and combined with earlier examinations regarding the transfer of chirality and the simple diastereoselection during the aza-Claisen rearrangement. Finally, a general model is introduced that explains the observed diastereoselectivities during the aza-Claisen rearrangement of N-substituted vinyl pyrrolidines.

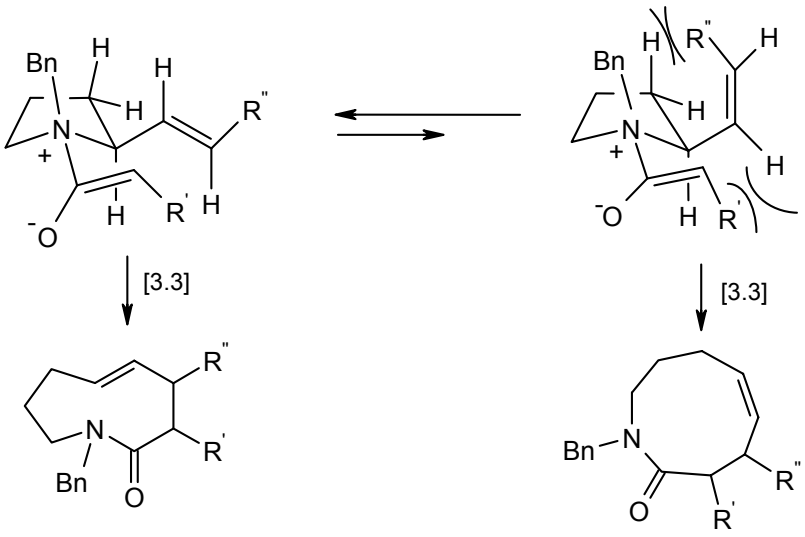
The following factors could be important for the stereochemical course of the aza-Claisen rearrangement of vinyl pyrrolidines and will be discussed :



R-1 **R-2** **R-3** **R-4**

- the arrangement of the vinylic group in the reactant vinyl pyrrolidine **[R-1]**
- the stereoselectivity of the formation of acylammonium salt **[R-2]**
- the geometry of the enolate **[R-3]**
- the conformation of the transition state for the reaction **[R-3]** to **[R-4]**

The great number of potential transition states can be reduced by excluding energetically disfavoured structures due to their steric interactions. Since no *Z*-configured azoninones could be isolated in aza-Claisen rearrangements of vinyl pyrrolidines, the arrangement of the vinylic group represents an energetic minimum due to the minimisation of 1,3-allylic strain in the transition state (Scheme 23).

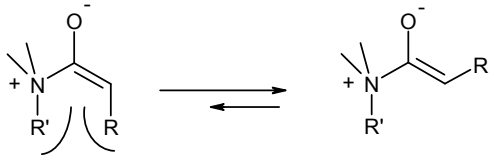


***E*-azoninone** ***Z*-azoninone**

Scheme 23 aza-Claisen rearrangement of vinyl pyrrolidines depending on the orientation of the vinylic group

Conformational analysis of the vinyl pyrrolidine **[6]** using NOE measurements confirmed the preferred arrangement of the double bond as expected from the minimisation of 1,3-allylic strain.[95] An exception to this rule was recently reported by Somfai *et al.*[76i,k] in their studies of the aza-Claisen rearrangement of N-Acylvinylaziridines. The formation of a *trans*-double bond in smaller rings is energetically inhibited due to the high strain on these systems, thus the rearrangement was found to proceed via the disfavoured orientation of the vinylic double bond generating unsaturated azepinones.

The second important restriction of potential transition states arises from the preferred configuration of the enolate ion. According to the observations of Evans, Myers and Sonnet in their amide enolate chemistry[96] and of Tsunoda in the rearrangement of amide enolates,[97] the deprotonation of an acyl ammonium salt should generate the *Z*-enolate structure due to minimised steric (and 1,3-diaxial) repulsions.



The preferred formation of *Z*-amide enolates during aza-Claisen rearrangement was proven by Kim[98] and by Nubbemeyer[99] who showed a high internal and remote asymmetric induction during the course of the reaction (Scheme 24).

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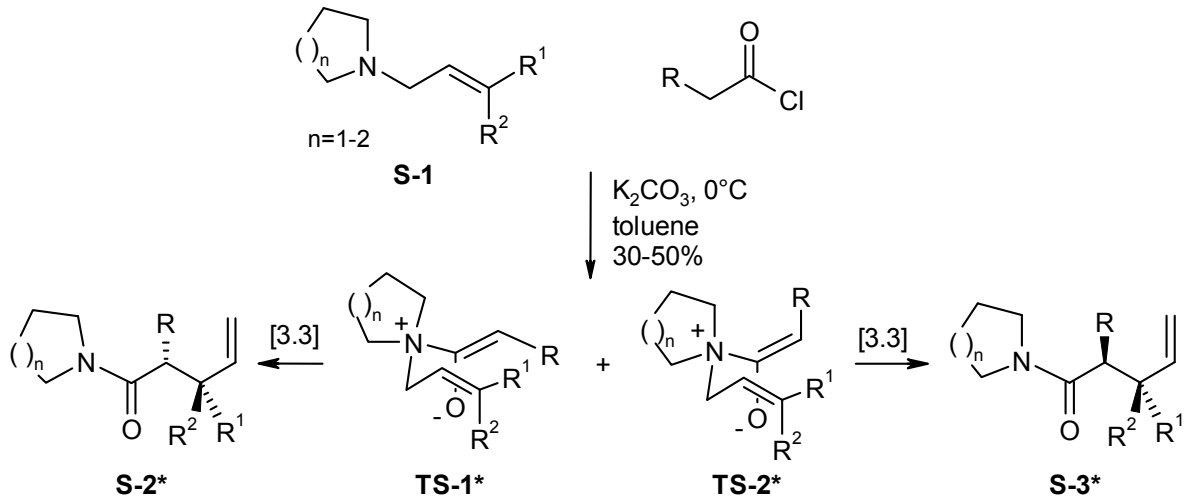
[95] Hoffmann, R. W. *Chem. Rev.* **1989**, 89, 1841-1860.

[96] (a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, 21, 4233. (b) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *Tetrahedron Lett.* **1978**, 3961. (c) Sonnet, P. E.; Heath, J. R. *J. Org. Chem.* **1980**, 45, 3139. (d) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, 119, 6496-6511.

[97] (a) Ito, S.; Tsunoda, T. *Pure Appl. Chem.* **1990**, 62, 1405. (b) Tsunoda, T.; Sakai, M.; Sasaki, O.; Sako, Y.; Hondo, Y.; Ito, S. *Tetrahedron Lett.* **1992**, 33, 1651. (c) Ito, S.; Tsunoda, T. *Pure Appl. Chem.* **1994**, 66, 2071.

[98] Yu, C. M.; Choi, H. S.; Lee, J.; Jung, W. H.; Kim, H. J. *J. Chem. Soc. Perkin Trans.* 1 **1995**, 115.



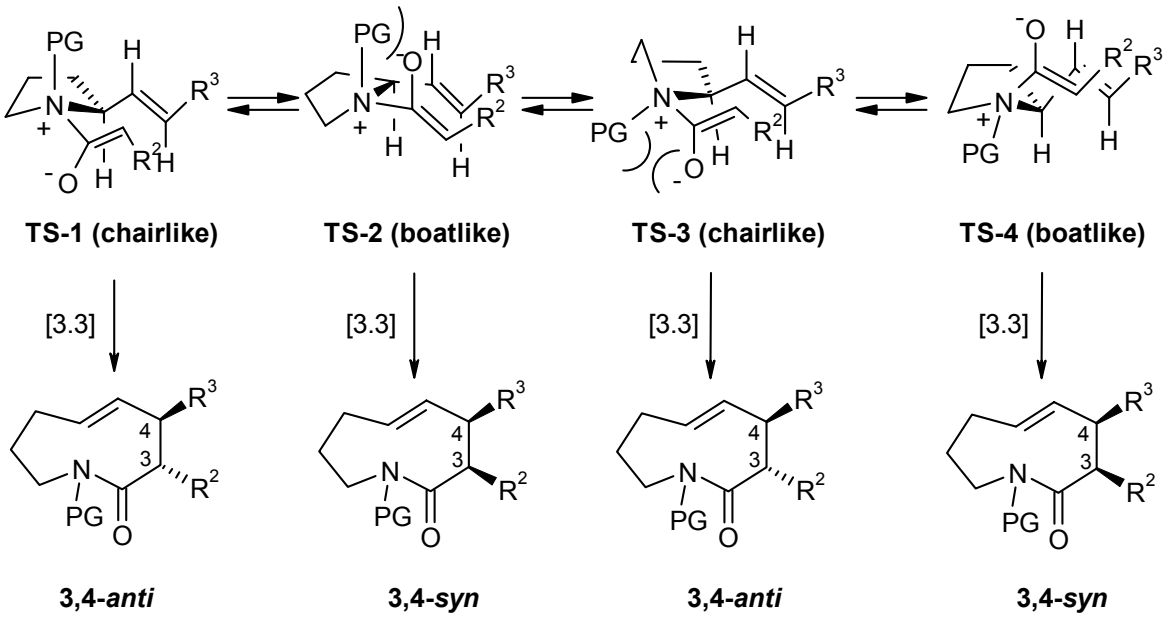
* only one of the two enantiomeric forms are shown

Scheme 24 Asymmetric induction during the aza-Claisen rearrangement

They described the rearrangement of tertiary allylic amines **S-1** with acycl chlorides and investigated the ratio of formation of δ,γ-unsaturated lactams **S-2** and **S-3** (pairs of enantiomers). Assuming that a chairlike transition state in conformationally non restricted systems is energetically preferred, the high diastereoselective formation of lactams **S-2** can only be explained by the high extent of *Z*-selectivity in the formation of the enolate.

Due to these restrictions the number of potential transition states is limited. Since the nitrogen atom in the zwitterion represents an asymmetric centre, two stereoisomeric acylammonium salts can be formed. If one includes both transition state geometries in the mechanistic consideration, four energetically preferred transition states are reasonable. The transition states for the aza-Claisen rearrangement of vinyl pyrrolidines and their resulting products are presented in Scheme 25.

[99] (a) Diederich, M.; Nubbemeyer, U. *Angew. Chem.; Int. Ed. Engl.* **1995**, 34, 1026. (b) Nubbemeyer, U. *J. Org. Chem.* **1995**, 60, 3773.

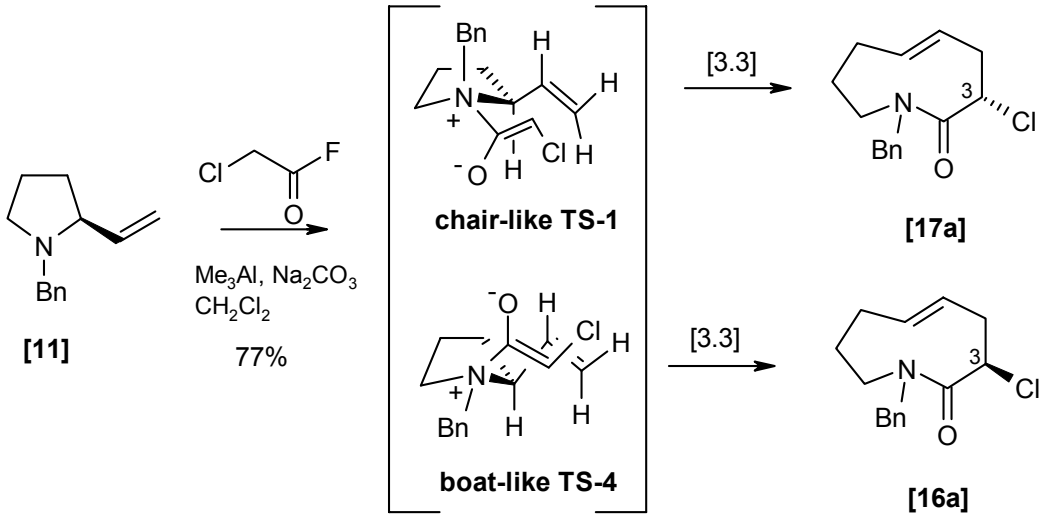


Scheme 25 Transition states during the aza-Claisen rearrangement of vinyl pyrrolidines an their resulting products (R^1=H)

As depicted in this scheme the rearrangement proceeds via two chair-like or via two boat-like transition states. Both boat-like transition states give the same 3,4-*syn* azoninones while the chair-like transition states result in the formation of 3,4-*anti* azoninones. These four diastereomorphic transition states could equilibrate via the ketene-pathway (Scheme 21, pathway a), therefore an asymmetric induction leading to the generation of a distinct chiral acylammonium intermediate appeared to be of no importance for the course of the rearrangement.

When combining the results of the aza-Claisen rearrangement of vinyl pyrrolidines the postulation of a sole defined transition state is difficult. In contrast, it is clear that the rearrangement proceeds either via a boat- or a chair-like transition state. The reactant vinyl pyrrolidine has a strong influence on the energetically preferred transition state and in many cases the exclusion of transition states by minimisation of repulsive interactions led to a high stereoselective course of the reaction. The following examples introduce our preliminary mechanistic model and explain the stereoselectivity of the aza-Claisen rearrangements described in this work. Moreover, the reaction mechanism is directly connected to the 3-dimensional structure of the azoninones and their planar chiral properties.

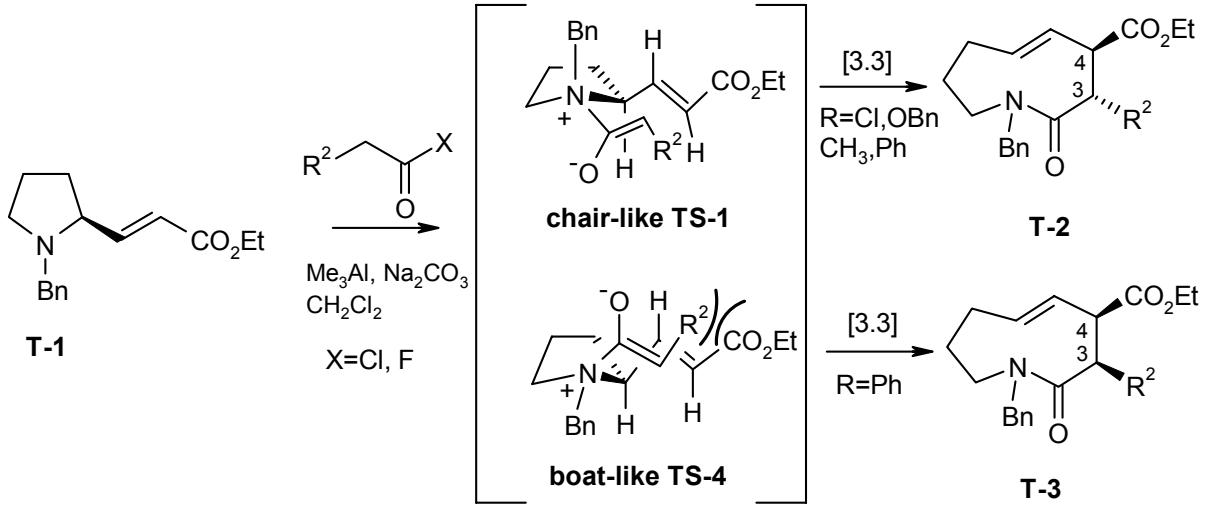
Starting from the unsubstituted vinyl pyrrolidine **[11]** the aza-Claisen rearrangement with chloroacetyl fluoride provides two diastereomers **[16a]** and **[17a]** in a nearly equimolar ratio (Scheme 26).



Scheme 26 aza-Claisen rearrangement of vinyl pyrrolidine **[11]**

The formation of azoninone **[17a]** can only be explained by the presence of a chair-like transition state whereas the formation of **[16a]** requires a boat-like transition state, thus both transition states are involved in the rearrangement.[100] The nature of the substituent at the carboxylic acid fluoride (R= OBn, Ph[101]) can be changed without a substantial increase in the diastereoselection.[102] Therefore, the boat-like transition state is not generally energetically disfavoured and must be taken into mechanistic considerations.

When the vinylic group of the reactant vinyl pyrrolidine was substituted,[70,81] a change in the diastereoselectivity was observed (Scheme 27).

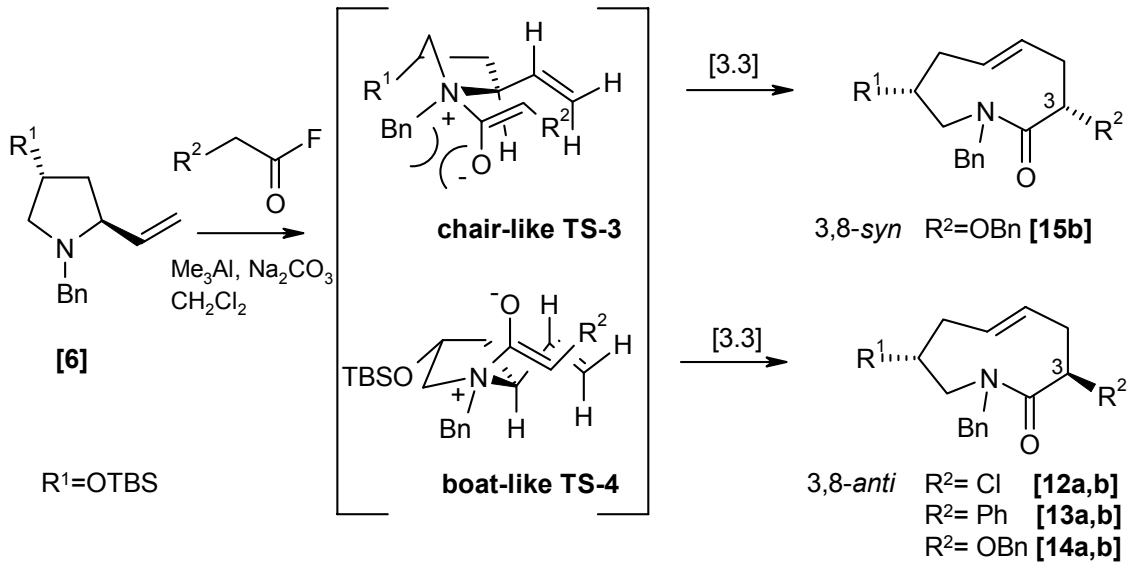


Scheme 27 Stereoselection during the aza-Claisen rearrangement of carboxyethyl-vinyl pyrrolidines

[100] The two transition states with the assumed lowest-energy conformations are drawn from the four potential transition states (chair-like TS1 and boat-like TS4) are drawn.
[101] Manuela Krause, research project.

In the rearrangement of vinyl pyrrolidine **T-1** with various carboxylic acid halides the preferred formation of 3,4-*anti* substituted azoninones **T-2** was observed. This high degree of asymmetric induction and chirality transfer arises from the preference for a chair-like transition state, such as **TS-1**. This can be attributed to repulsive interactions of the substituents R and the ester group leading to an increased energy in boat-like transition states, such as **TS-4**. The only exception to the observed stereoselectivity was found when phenylacetic acid halides (R= Ph) were used. Since the ratio of **T-3**/**T-2** was substantially increased (1:1 when X=Cl to 2:1 when X=F) it appears reasonable that in these cases the energy of a boat-like transition state was lowered, presumably by π-π-interactions between the phenyl ring and the ester group.

None of these examples allow conclusive predictions as to which of the possible chair- and boat-like transition states are energetically preferred. Although the consideration of steric interactions imply that the **boat-like TS-2** and the **chair-like TS-3** (Scheme 25) are disfavoured by 1,2 repulsive interactions, these examples do not provide clear experimental evidences. The assumption of increased energies of the **boat-like TS-2** and the **chair-like TS-3** was supported by an additional investigation of the diastereoselectivity of the aza-Claisen rearrangement during this work.
Here, the rearrangement of TBSO-substituted vinyl pyrrolidines **[6]** with various carboxylic acid fluorides was examined (Scheme 28, for data see Table 1, page 27).[103]



Scheme 28 aza-Claisen rearrangement of TBSO-substituted vinyl pyrrolidines

Compared to the rearrangements of unsubstituted vinyl pyrrolidines **[11]**, a high degree of diastereoselection was observed, although the rearrangement system appeared to bear no further

[102] The azoninones include two stereogenic centres, a stereogenic C-3 atom and the stereogenic plane of the double bond. This phenomenon is described later in detail.

constraints. This high level of stereoselection caused an efficient chirality transfer during the rearrangement. The formation of 3,8-*anti* azoninones via a boat-like transition state raised the question concerning the role of the bulky TBSO group on the conformation of the transition states and the reactant vinyl pyrrolidines. Since it appeared unlikely that the introduction of the TBSO group strongly increases the energy of both chair-like transition states without affecting the boat-like transition states, its influence on the acylation of the reactant vinyl pyrrolidine has to be considered.
Indeed NOE investigations supplied strong evidence that 4-TBSO substituted N-alkyl vinyl pyrrolidines preferentially adopt conformations (NOE enhancements of 3-4% between the axial protons 2 and 5) similar to that, shown in Fig. 4. [104]

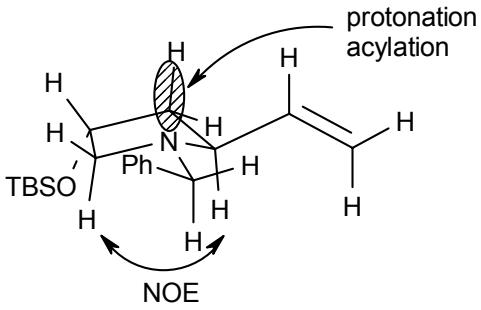


Fig. 4 Conformation of vinyl pyrrolidines

This can be explained by the 1,2 repulsive interaction between the N-benzylic group and the vinylic group. In the presence of an additional bulky TBSO group, one side of the pyrrolidine ring is effectively sterically shielded. An electrophile should thus preferentially attack from the less shielded *re*-face. An experiment with the smallest available electrophile - the proton, consequently led to the stereoselective formation of the corresponding *R*-ammonium salt.[105] These findings support the assumption that in the presence of sterically demanding groups a stereoselective acylation of the nitrogen atom occurs excluding **TS-1** and **TS-2**. This has consequences on the assumed mechanism for the aza-Claisen rearrangement. Since only small amounts of 3,8-*syn* azoninones (Scheme 28) were isolated, the participation of a chair-like transition state **TS-3** in the rearrangement is low.
Summarising these experimental results, some general conclusions of the stereochemical course of aza-Claisen rearrangements of vinyl pyrrolidines can be made:

[103] These results were in full accordance with earlier investigations using carboxylic acid chlorides, see lit. 64
[104] Due to a potential inversion of the nitrogen (for N-methyl pyrrolidine ~8 kcal taken from ref [104a]), the NOE analysis showed only an approximated conformation. For a discussion of the barriers for the nitrogen inversion in polycyclic amines see: (a) Belostotskii, A. M.; Gottlieb, H. E.; Hassner, A. *J. Am. Chem. Soc.* **1996**, 118, 7783-7789. (b) Anderson, J. E.; Ijeh, A. I.; Storch, C. *J. Org. Chem.* **1998**, 63, 3310-3317. (c) Belostotskii, A. M.; Gottlieb, H. E.; Aped, P.; Hassner, A. *Chem. Eur. J.* **1999**, 5, 449-455.
[105] A. Sudau, diploma thesis (The protonation was carried out using the N-methyl-4-*tert*-butyldimethylsilyloxy-2-vinyl pyrrolidine and trifluoroacetic acid, configuration was proven by NOE measurement)

- during the rearrangement the orientation of the vinylic group is determined by a minimisation of the 1,3-allylic strain (high degree of 1,3-chirality transfer) and leads to the generation of (*E*)-alkenes
- rearrangement of systems with low steric strains can proceed via a boat- and a chair-like transition state without significant differences in transition state energies (assumed **TS-1** and **TS-4**). This leads to a mixture of 3*R* and 3*S* configured products.
- Substitution at the vinylic appendage allows an energetic preference of a single defined transition state **TS-3** and the high stereoselective course of the reaction (1,3-chirality transfer).
- Substitution within the pyrrolidine ring (4*R* configuration) prefers a boat-like transition state **TS-4** and causes a high degree of 1,4-chirality transfer. Thus, by varying the vinyl group- or pyrrolidine-substituents, the 3*R* or the 3*S*-configuration of the corresponding azoninones can be selectively generated.

2.2 The Planar Chirality of Azoninones

During the examination of the 1,4-chirality transfer in aza-Claisen rearrangements of vinyl pyrrolidines[106] an unexpected observation was made when storing the azoninone **[12a]** at room temperature. The ^{1}H-NMR spectrum of **[12a]** showed a slow conversion into a second compound characterised by a considerable change in the 3-dimensional structure, as indicated by simultaneous variations of coupling constants and shifts in the NMR spectrum (Fig. 5).

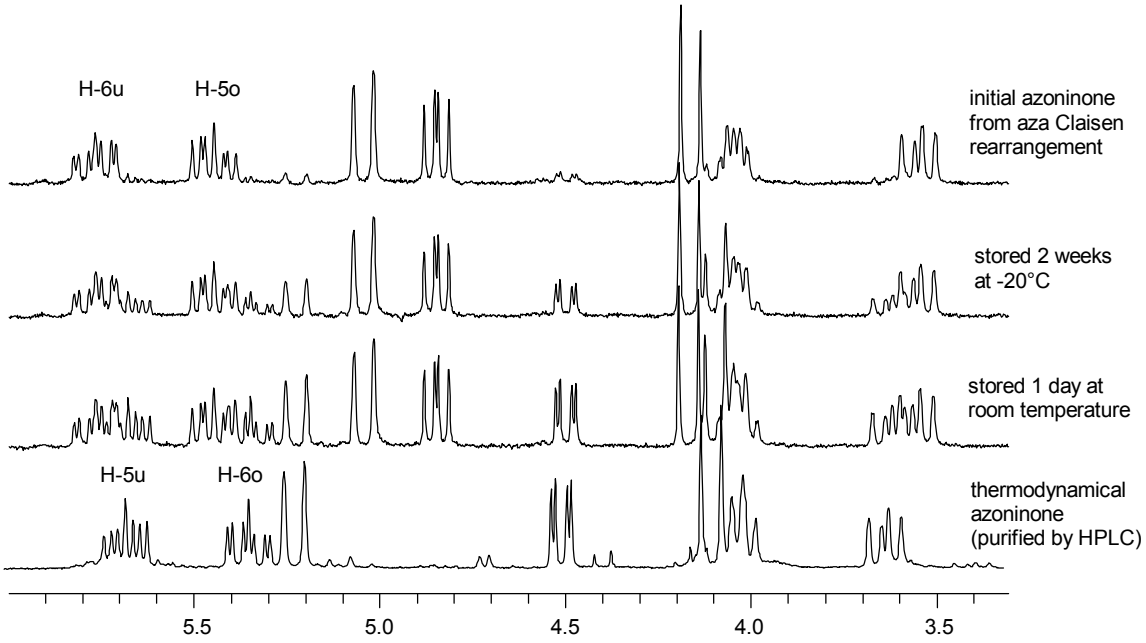


Fig. 5 Change in ^{1}H-NMR spectrum of azoninone **[12a]** during the storage at different temperatures

The relaxational process showed a strong temperature dependence and could be substantially inhibited at temperatures below -20°C. The initial assumption of a slow epimerisation of the acidified proton at C-3 could not be confirmed. In contrast, a conformational change of the molecule caused by a rotation of the double bond with respect to the ring was found and proven by NOE experiments (Fig. 6).

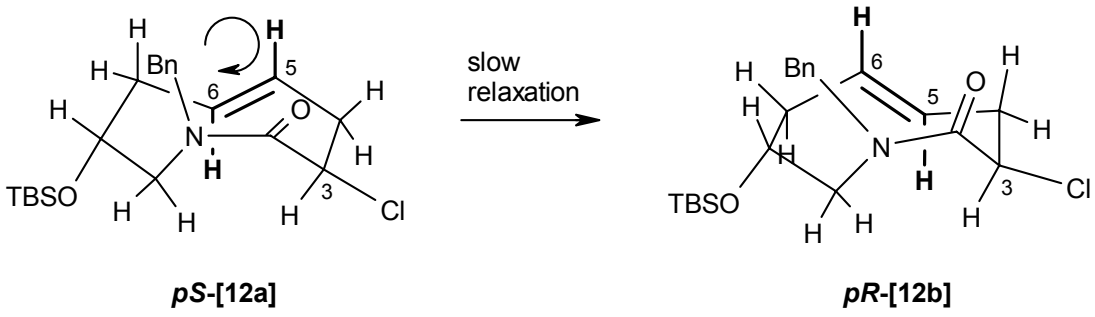
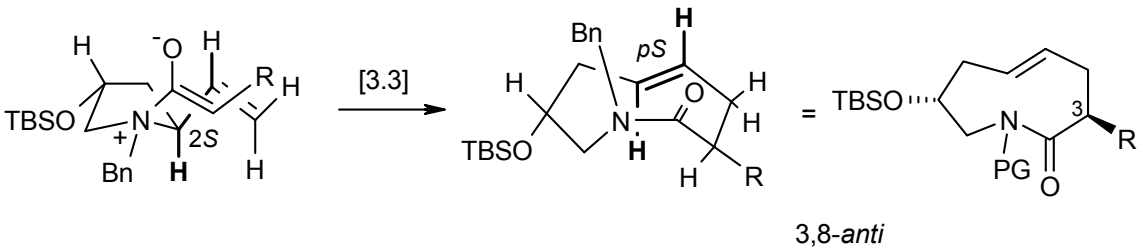


Fig. 6 Unexpected conformational change of azoninones

[106] Alexander Sudau, diploma thesis (Berlin 1997).

This conformational isomerisation led to a considerable change in the optical rotations (-79.8° for ***pS*-[12a]** to -122.0° for ***pR*-[12b]**) indicating the formation of a diastereomer during the course of this process. Since the formation of a diastereomer requires a change of a stereochemical element in the molecule and the epimerisation at C-3 could be excluded by NOE investigations, the character of the double bond plane as a stable chiral element became evident. The perpendicular arrangement of the double bond with respect to the ring led to the occurrence of planar chirality in unsaturated azoninones such as **[12]**. A rotation of this double bond changes the planar chirality and forms in the presence of another stereogenic centre a diastereomer that can be analysed by spectroscopic methods.[107]

This intriguing observation showed an important aspect of the aza-Claisen rearrangement of vinyl pyrrolidines that has to be taken into account. Induced by the minimisation of allylic strain, the defined geometry of vinyl pyrrolidines led to an efficient transfer of chirality from the stereogenic centre (central chirality) in the reactant vinyl pyrrolidine into planar chiral information of the product (Scheme 29).



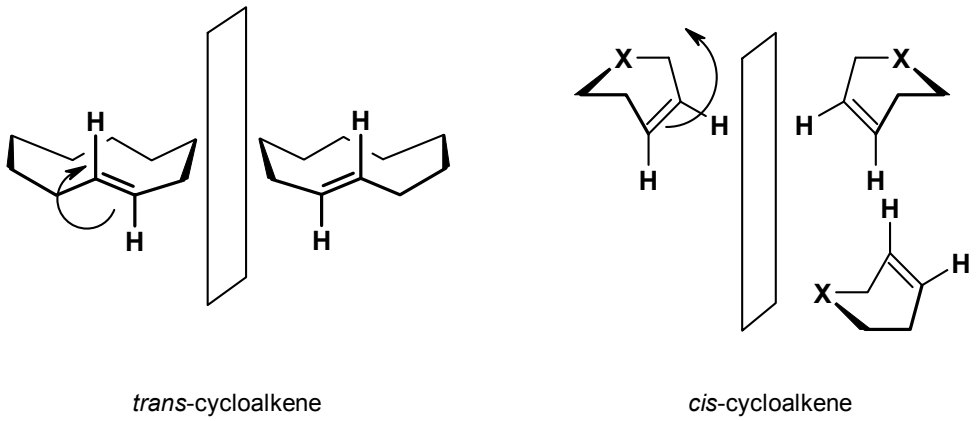
Scheme 29 Chirality transfer : central chirality (2*S*) into planar chirality (*pS*) during aza-Claisen rearrangement

Additionally, this observation raised questions regarding the generality of this phenomenon and its synthetic applicability. Therefore, the examination of the planar chiral stability of various unsaturated azoninones and the influencing factors during this isomerisation has been a major part of this work.
In the following section, a short introduction to planar chirality in medium-sized rings is presented and earlier reports of the occurrence of planar chiral isomerisation by double bond rotation are discussed.

[107] For the explanation of the stereochemical descriptors see the following chapter 2.2.1

2.2.1 Planar Chirality in Medium-Sized Rings

The term planar chirality can be described as a form of chirality originating from a stereogenic plane, e.g. a planar arrangement of at least four centres (atoms) with a fifth centre placed outside of this original plane.[108] The smallest type of a planar arrangement of atoms is an olefin subunit. In the case that a nonplanar arrangement of the ring system and the olefin is enforced by the inclusion of an (*E*) double bond into a ring, the prerequisites for a planar-chiral compound are fulfilled.
If the ring is unsymmetrically substituted even a (*Z*) double bond can form a planar chiral compound (Fig. 7)[109]



trans-cycloalkene *cis*-cycloalkene

Fig. 7 Cyclic planar chiral enantiomers and their interconversion by ring flipping of the double bond

As shown in Fig. 7, the planar chiral isomers can be transformed into each other by a rotation of the double bond with respect to the ring.
The nomenclature of planar chiral compounds was developed by Schlögl.[110] For the descriptor assignment of planar chirality the following objects have to be present in a system: first, a plane, formed by at least three atoms **A**, **B** and **Y** (see Fig. 8) and an atom **Z**, standing out of this plane, must be present. Second, a fourth atom **X** located within the plane, formed by the atoms **A**,**B** and **Y**. The objects **A**, **B**, **X**, **Y** and **Z** are assigned to atoms or atom groups according to the following rules :

- the outstanding substituent **Z** is connected with **Y**
- **A** has a higher priority than **B**

[108] Eliel, E. L.; Wilen, S. H.; *Organische Stereochemie* (Eds. : H. Hopf, J. Mulzer), Wiley-VCH, Weinheim, **1998**.
[109] For an example of a Z-configured planar chiral azoninone see : Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, 44, 330-336.
[110] Schlögl, K. *Topics Stereochem.* **1967**, 1, 39.

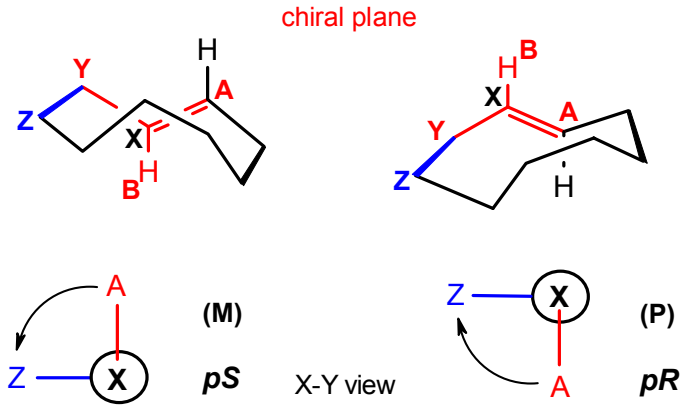


Fig. 8 Nomenclature of planar chiral unsaturated cyclic compounds

The assignment of a topographic descriptor is assigned according to the direction of rotation from **A** to **Z,** *pR* refers to a clockwise rotation while *pS* refers to an anti clockwise rotation. Using this nomenclature the azoninones initially formed can be described as *pS*-azoninones, their resulting ring-flip isomers as *pR*-azoninones. Alternatively, planar chirality can be defined by the torsion angle of a sequence of three nonplanar vectors with a topographic descriptor *P* (plus) or *M* (minus), depending on its sign.[111]

Common planar-chiral compounds are cyclophanes, ansa-compounds, η^n-arene metal and η^n-olefin metal complexes.[112] In addition to these synthetic compounds some naturally occurring planar chiral compounds have been found in the last decades, for examples the Germacranes,[113] Caryophyllenes[114] and Xenicanes[115] (Fig. 9).

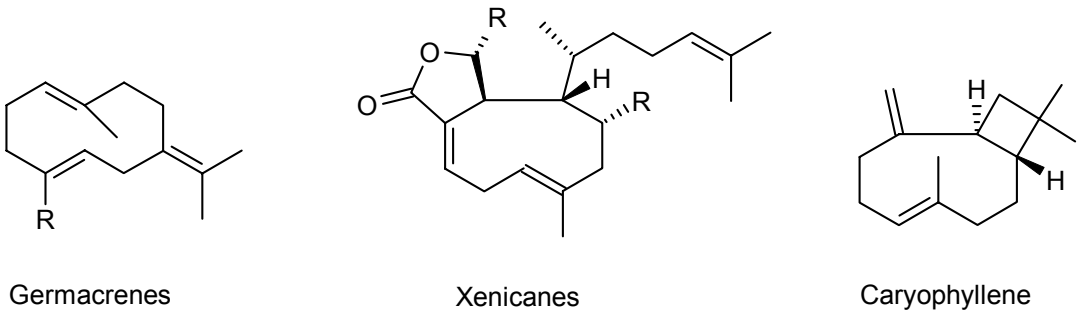


Fig. 9 Planar chiral natural products

The occurrence and the thermal stability of planar chirality in unsaturated cyclic compounds is mainly affected by the ring-size and the double bond geometry. In small rings, steric interactions of the double

[111] (a) Prelog, V.; Helmchen, G. *Angew. Chem.* **1982**, 94, 614. (b) Prelog, V.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 507.
[112] Nubbemeyer, U. *Eur. J. Org. Chem.* **2001**, 1801-1816 and references cited therein.
[113] Minnaard, A. J.; Wijnberg, J.; de Groot, A. *J. Org. Chem.* **1997**, 62, 7346-7350.
[114] Clericuzio, M.; Alagona, G.; Ghio, C.; Toma, L. *J. Org. Chem.* **2000**, 65, 6910-6916.
[115] (a) Guella, G.; Chiasera, G.; N'Diaye, I.; Pietra, F. *Helv. Chim. Acta* **1994**, 77, 1203-1221. (b) Renneberg, D.; Pfander, H.; Leumann, C. J. *J. Org. Chem.* **2000**, 65, 9069-9079.

bond and transannular positioned groups increase the energy of the transition state passed during the conformational flip. Therefore, *trans*-cyclooctenes exhibit high activation energies for the racemisation process and both enantiomeric forms can be isolated at ambient temperature.[116] If a second double bond is introduced into the *trans*-cycloocten, a *retro*-Cope rearrangement occurs due to an increased steric strain and the sterically less strained *cis*,*cis*-cyclooctadiene is formed with complete loss of chirality.[117] (*E*)-cycloheptene also exhibits chiral properties but due to its very short half-life it can only be detected via trapping experiments.[118]

When the ring-size is increased, the steric strain is substantially reduced by each additional ring atom. Thus *trans*-cyclononene has a much lower racemisation barrier than *trans*-cyclooctene and an optically active *trans*-cyclodecene cannot be isolated[119] (see Table 2). Although unsymmetrically substituted cyclic compounds including a (*Z*) double bond could also build planar chiral isomers, the barriers for their racemisation are much lower since the conformational change requires no increased strain (see Fig. 7 page 38). Therefore, planar chirality in cyclic compounds containing (*Z*)-configured double bonds only appears when additional chiral substituents within the ring lead to an energetically preferred conformation.[120]

Table 2 Activation barriers of different planar chiral carbocycles

compound	Ea (kcal/mol)	$t_{1/2}$ (T)	reference
(*E*)-cyclooctene	35.6	10^5 y (30°C)	116d
(*E*)-cyclononene	20	6s (30°)	119
(*E*)-cyclodecene	10.7	-	121
(*E*,*Z*)-cyclononadiene [a)]	26.4	208 min (30°)	122
caryophyllene	16.1	-	115a

a) substituted ring

Furthermore, the introduction of an additional double bond into the ring increases the rotation barrier due to the increase of the steric strain energy of the transition state or the decrease in ring-size as result of the shorter C=C double bond.

One example of the formation of diastereomers on substituted (*E*,*Z*)-cyclononadienes has been introduced by Hoppe[122] who described the cyclisation of an (*E*,*Z*)-nonadiene generating slow inter-converting planar chiral diastereomers.

---

[116] (a) Isaksson, R.; Roschester, J.; Sandström, J.; Wistrand, L. J. Am. Chem. Soc **1985**, 107, 4074. (b) Cope, A. C.; Ganellin, C. R.; Johnson, H. W.; Jr.; Van Auken, T. V.; Winkler, J. S. *J. Am. Chem. Soc.* **1963**, 85, 3276. (c) Cope, A. C.; Mehta, A. S. *J. Am. Chem. Soc.* **1964**, 86, 5626. (d) Cope, A. C.; Pawson, B. A. *J. Am. Chem. Soc.* **1965**, 87, 3649. (e) Tsuneishi, H.; Hakushi, T.; Tai, A.; Inoue, Y. *J. Chem. Soc.* Perkin Trans. 2 **1995**, 2057.
[117] Martin, H. D.; Kunze, M.; Beckhaus, H. D. *Tetrahedron Lett.* **1979**, 33, 3069-3072.
[118] Hoffmann, R.; Inoue, Y. *J. Am. Chem. Soc.* **1999**, 121, 10702-10710.
[119] Cope, A. C.; Pawson, B. A.; Whang, J. J.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1965**, 87, 3644.
[120] For an example see: White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, 65, 9129-9142.
[121] Pawar, D. M.; Davis K. L.; Smith, S. V.; Brown, B. L.; Noe, E. A. *J. Org. Chem.* **1999**, 64, 4580-4585.
[122] Deiters, A.; Mück-Lichtenfeld, C.; Fröhlich, R.; Hoppe, D. *Org. Lett.* **2000**, 2, 16, 2415-2418.

The prerequisites for a synthetic applicability of planar chiral compounds are the control of the thermal interconversion of both planar chiral diastereomers and a method to isolate both chiral forms. The given examples demonstrate that only the nonadiene systems comply with these requirements. However, a functionalisation of the flipping double bond (via epoxidation, dihydroxylation etc.) appears difficult since the high reactivity of both included olefins prevents selective transformations.[123]

To overcome these problems the replacement of the second C=C bond by a heteroatom-C bond appears to be useful, since this bond shows similar steric interactions and a decreased reactivity as compared to an olefin. Ester- and amide groups especially may be applicable due to their additional allylic strain or partial double bond character.

In the past, some planar-chiral heterocycles have been synthesised. However, only few reports describe an utilisation of their special chiral properties in chemical transformations. A recent example of interconverting planar-chiral diastereomers was reported by Belluŝ and Malherbe[124] who described the preparation of ten-membered unsaturated lactones via a ketene-Claisen rearrangement (Fig. 10).

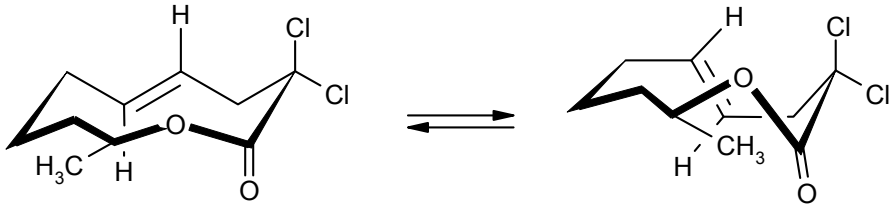
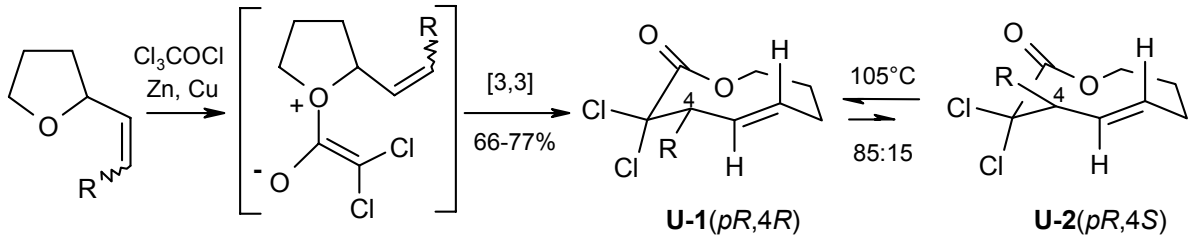


Fig. 10 Planar chiral enantiomers of ten-membered unsaturated lactones

Belluŝ and Malherbe assumed that these compounds exist as a mixture of rapidly interconverting planar chiral diastereomers. The argumentation was based on deviations of the well known vicinal vinylic-allylic coupling constants. A representative structure allowed the assignment of the signals of the separated diastereomers and to determine the activation energy (13±2 kcal/mol) via temperature dependent measurement of signal coalescence. An analogous rearrangement of 2-vinyl-tetra-hydrofurans led to nine-membered cyclic lactones (Scheme 30).[125]

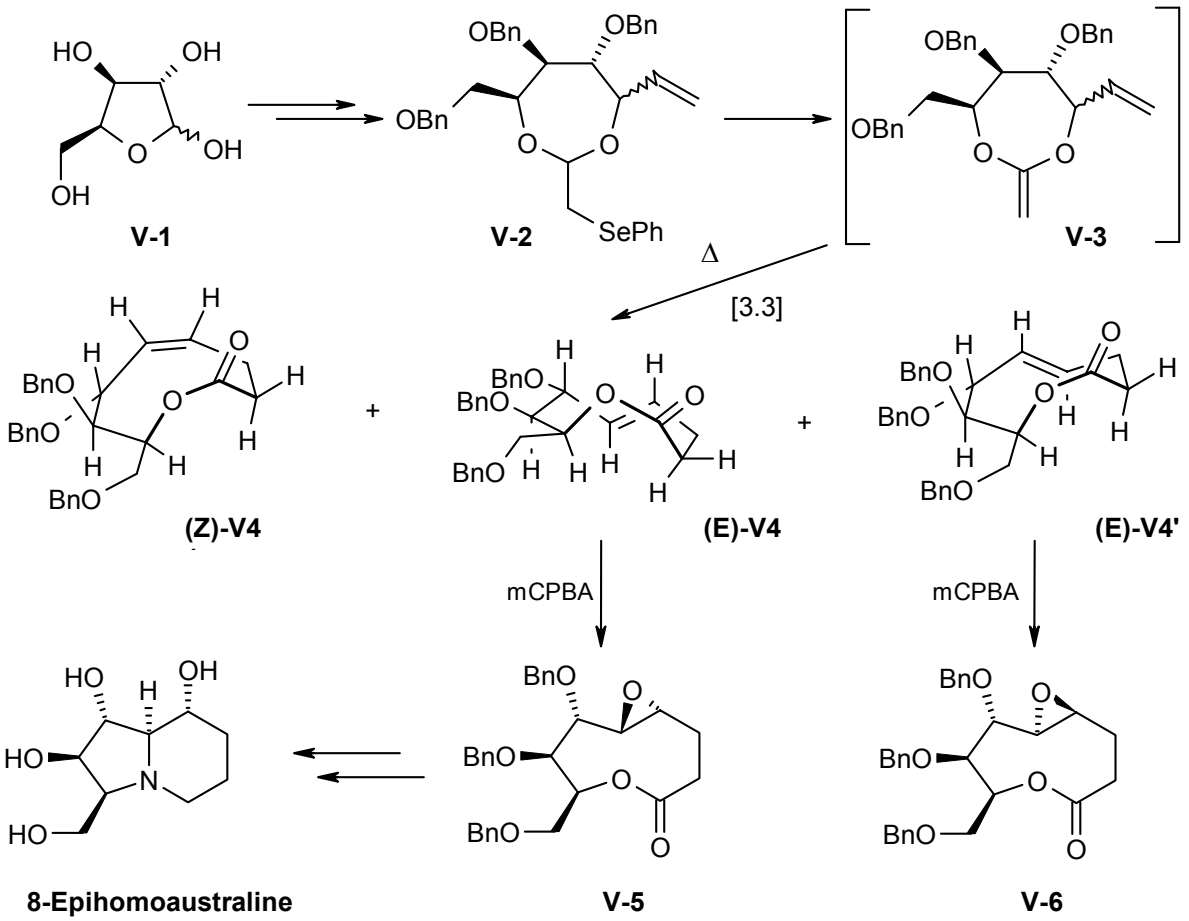


Scheme 30 Formation of nine-membered cyclic lactones by a ketene Claisen-rearrangement

[123] The different reactivities of a silyl enol ether and an olefin towards dihydroxylation were used in the synthesis of (+)Taxusin. see : Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, 120, 5203-5212.
[124] Malherbe, R.; Rist, G.; Bellus, D. *J. Org. Chem.* **1983**, 48, 860.
[125] Kling, M. R.; McNaughton-Smith, G. A.; Taylor, R. J. K. *J. Chem. Soc. Chem. Commun.* **1993**, 1593-1595.

In this rearrangement a mixture of (*E*)- and (*Z*)-olefins was used and the *E*/*Z* ratio of the reactant vinyltetrahydrofurans was reflected in the product mixture. When this mixture was heated to 105°C, independent on the starting ratio of both isomers, an equilibration of both isomers was observed resulting in a 85:15 mixture. This was explained by an epimerisation of the alkyl group at C-4. However, the isomerisation observed can also be consistently explained by a ring flip of the double bond plane. This motion changes the planar chirality of the double bond. Starting from **U-1** (*pR*, 4*R*) the *enantiomer* of **U-2** (*pS*, 4*R*) is formed, which is spectroscopically identical to **U-2** (*pR*, 4*S*). Thus, the re-equilibration and the formation of a distinct ratio in the heated **U-1**/**U-2** mixture reflects the energetic difference between both planar-chiral diastereomers.

The increased barrier for the double bond rotation in unsaturated nine-membered lactones was also confirmed by contributions of Pearson *et al.*[126] in synthesising ring-expanded analogues of the pyrrolizidine alkaloids alexine and australine as novel glycosidase inhibitors (Scheme 31).



Scheme 31 Planar chiral lactones in the synthesis of novel glycosidase inhibitors

Starting from *L*-(-)-xylose **V-1**, the acetal **V-2** was built up in several steps. The selenoacetal was then converted into the corresponding ketene acetal **V-3** by an oxidation-elimination sequence. A Claisen

[126] Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, 61, 7217-7221.

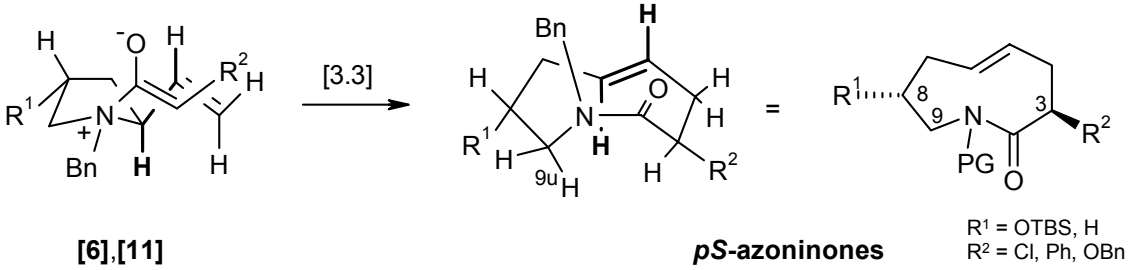
rearrangement then permitted the formation of the desired nine-membered ring **V-4**. A mixture of ***(E)*-V4** and ***(Z)*-V4** olefins was obtained. The *(E)*-configured unsaturated lactone **(*E*)-V4** was found to occur as a mixture of two planar diastereomers *pS* and *pR*, which could be separated by column chromatography. The *pS*-lactone **(*E*)-V4** underwent a slow conversion into the *pR* conformation **(*E*)-V4'** on heating to about 110°C. It proved possible to use the planar diastereomeric properties of the (*E*)-olefins to produce new stereogenic centres. The epoxidation of the double bonds led stereospecifically to the diastereomeric epoxy lactones **V-5** and **V-6**. The oxidising reagent always attacked the unshielded face of the double bond, permitting the complete conversion of the planar-chiral information into new stereogenic centres. After introduction of the nitrogen atom these epoxy lactones could be employed as key intermediates in the total syntheses of the glycosidase inhibitor analogs homoalexine and 8-*epi*-homoaustraline.

This work by Pearson *et al*. represents the only example of a synthetic application of planar chirality in medium-sized rings. Starting from our initial observation of the occurrence of planar-chirality in nine-membered ringlactams the question was raised whether these compounds generally show such a phenomenon and whether it can be applied in chemical transformations.

2.2.2 Kinetic Studies of the *pS*-*pR* Isomerisation in Azoninones

The challenge for the successful application of planar chiral compounds in chemical transformations lies in their stereocontrolled generation without any planar chiral epimerisation. The aza-Claisen rearrangement of vinyl pyrrolidines is the key step towards this objective, since the rearrangement proceeds via a transition state that efficiently converts the central chirality of a vinyl pyrrolidine into the planar chirality of the product.

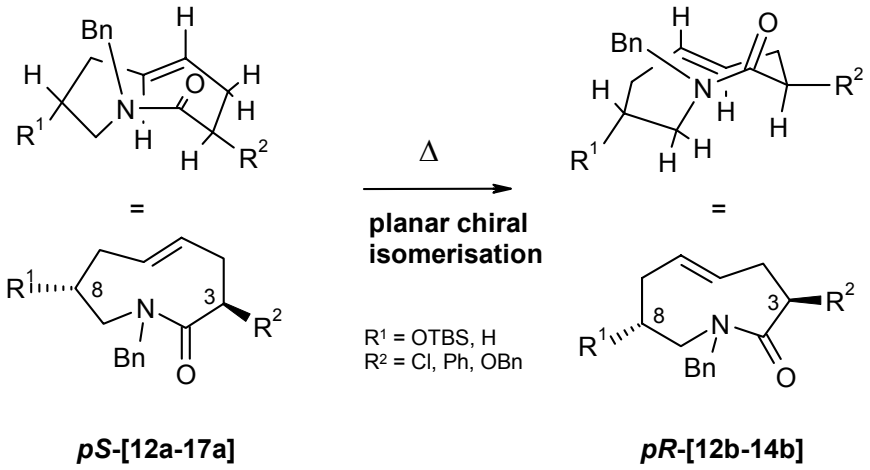
Earlier aza-Claisen rearrangements delivered mixtures of the azoninones and von-Braun degradation products as discussed in chapter 2.1.2. These mixtures had to be separated by HPLC, which often led to epimerisations because of the workup time required and the temperatures applied. In the presence of acid fluorides no degradation products could be observed and the purification of the products by means of HPLC was unnecessary. When the reaction was carried out at 4°C and workup below 30°C all prepared azoninones retained in their initial *pS*-configuration (Scheme 32).



[6],[11] ***pS*-azoninones**

Scheme 32 Preparation of *pS*-azoninones **[12a-14a]** via aza-Claisen rearrangement

Directly after the reaction 3,8-*trans*-azoninones **[12a]-[14a]** with *pS*-arrangement of the double bond were isolated, as indicated by the proximity of the protons H-3, H-6 and H-9u (NOE). The lactam unit showed a *cis* arrangement of C-3 and C-9 (about 20% NOE enhancement regarding H-3 and H-9u) with respect to its partial double bond character and a *syn* arrangement of the carbonyl O-atom and H-5. Subsequent heating of the *pS*-azoninones led to the rotation of the double bond with respect to the ring providing the *pR*-azoninones (Scheme 33).



Scheme 33 Transformation of *pS*-azoninones into the *pR*-azoninones

Usually, these conversions were performed at temperatures between 50° and 60°C yielding mixtures of *pS* and *pR*-isomers. The results of thermal isomerisations are presented in Table 3.

Table 3 Ratio of *pS*/*pR*-isomers after thermal equilibration

compound	R^1	R^2	heating conditions	ratio *pS*/*pR*
***pS*-[12a]**	OTBS	Cl	3h 65°C	1:5.5[a)]
***pS*-[13a]**	OTBS	Ph	3h 60°C	1:6[a)]
***pS*-[14a]**	OTBS	OBn	3h 60°C	1:13[b)]
***pS*-[16a]**	H	3*R*-Cl	4h 75°C	34:66[b)]
***pS*-[17a]**	H	3*S*-Cl	3h 73°C	63:37[b) c)]

a) determined from product ratio of following cycloaddition reactions b) determined by ^{1}H-NMR
c) deviation from the theoretical value of are caused by the integration error, NMR integration is complicated by the occurrence of amide isomers

The 8-*tert*-butyldimethylsilyloxy-azoninones **[12a]-[14a]** showed a nearly complete epimerisation to the thermodynamically stable *pR* azoninones **[12b]-[14b]**. In contrast, the azoninone **[16a]** (R^1=H) showed a much lower *pS*/*pR*-ratio after the thermal equilibration, potentially caused by smaller energy differences between the *pS*- and the *pR*-isomer. The 3-chloro isomer **[17a]** yielded a 1:0.6 ratio of ***pS*-[17a]** and ***pR*-[17a]** after thermal epimerisation indicating that in this case the kinetic *pS*-isomer possesses a lower energy than the corresponding *pR*-isomer. The NOE analyses of **[12b]-[14b]** proved that the 3,8-*trans* configurations of the stereogenic centres and the *E*-double bonds were maintained.

In contrast to the preceding *pS* lactams **[12a]-[14a]**, the proximity of the protons H-3, H-5 and H-9u was found by NOE, indicating an almost complete flipping of the olefin from the *pS* to the *pR* arrangement in **[12b]-[14b]**. Again, the lactam unit showed a *cis* arrangement of C-3 and C-9 (about 20% NOE enhancement between H-3 and H-9u) with respect to its partial double bond, in contrast to **[12a]-[14a]** in which an *anti* arrangement of the carbonyl O-atom and H-5 was found. Finally, the conformational change and the absolute configuration of both azoninones could be unambiguously confirmed by X-ray analysis of the 3*R*-chloro lactams **[12a]** and **[12b]** (Fig. 11 and Fig. 12).[127]

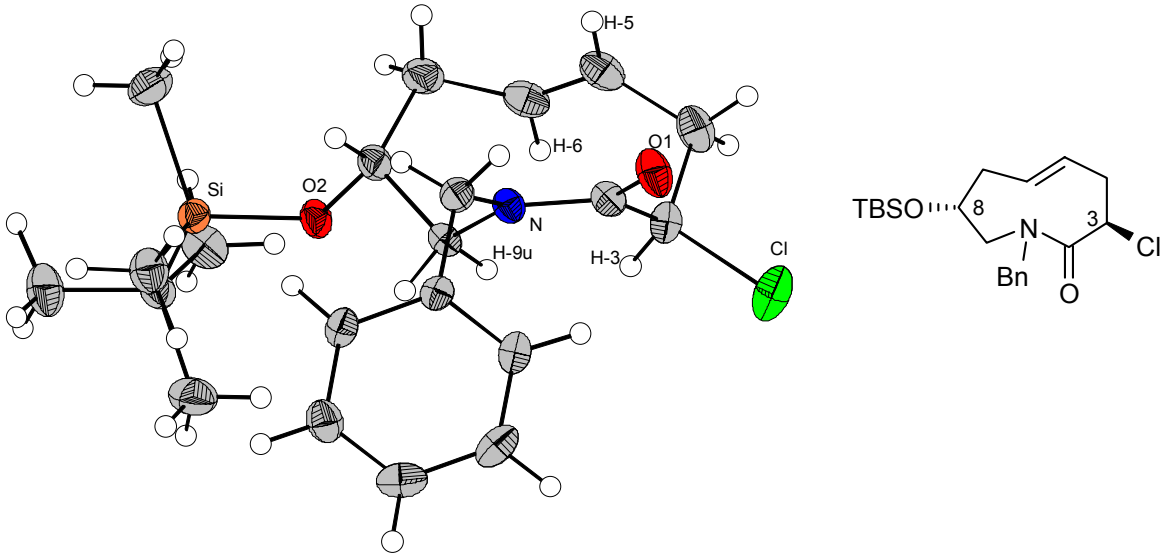


Fig. 11 Crystal structure of *pS*-azoninone **[12a]** [128]

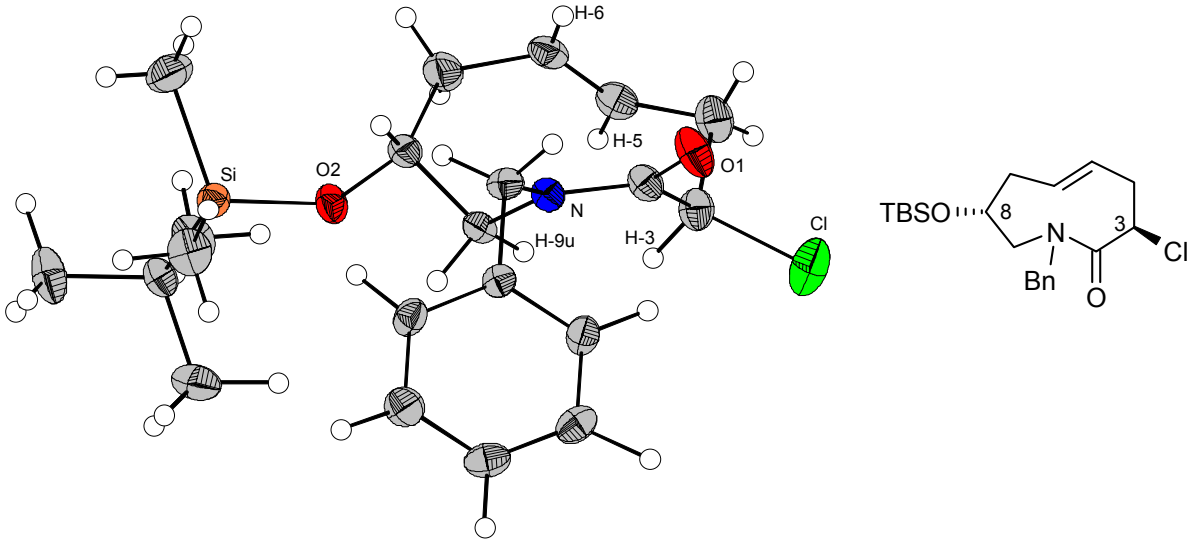


Fig. 12 Crystal structure of *pR*-azoninone **[12b]**[128]

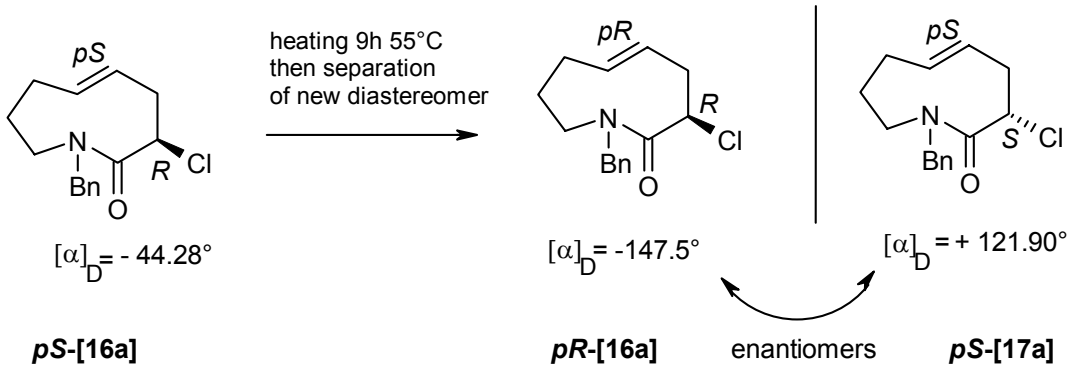
[127] The absolute configuration was determined using the anomalous X-ray dispersion of the Cl and Si atoms located directly at the stereogenic centre C-3 and C-8, respectively. For a detailed discussion of anomalous X-ray dispersion see : W. Massa, Kristallstrukturbestimmung, 2. Aufl.; Teubner, Stuttgart, **1996**, p. 168-176.

[128] For crystal data see Appendix.

The crystal structures of both azoninones confirmed the *trans* configuration for the C5-C6 double bond and a *cis* configuration for the amide bond. The amide bond showed only a small deviation from planarity with a C9-N-C2-C3 torsion angle of 3.9° and -2.2°. The C5-C6 double bond showed a considerable deviation from planarity: the C4-C5-C6-C7 torsion angle is 147.4° (2) for ***pS*-[12a]** and -150.0° (2) for ***pR*-[12b]** rather than the 180° expected for a planar bond. This characteristic indicates that the nine-membered rings are considerably strained.

The X-ray structures confirmed the short intramolecular distances between H-9u, H-3 and the olefinic protons as assigned from the strong NOE enhancements observed.

In contrast to TBSO substituted azoninones, the absolute assignment of the *pS*- or *pR*-configuration to the unsaturated azoninones **[16a]** and **[17a]** by NOE was not possible due to the absence of a reference stereogenic centre.[129] However, the X-ray structures of the epoxy azonanones **[35a]** and **[36a]** (3-chloro-5,6-epoxy-azonanone) confirmed the correct absolute configuration of ***pS*-[16a]** and ***pS*-[17a]**. Heating experiments performed with the azoninones **[16a]** and **[17a]** confirmed the possibility of a *pS*/*pR*-isomerisation by rotation of the double bond. The thermal equilibration of ***pS*-[16a]** at 55°C led to a new compound, its spectroscopic data was identical to that of ***pS*-[17a]** but the major change in its optical rotation indicated the presence of the enantiomeric form. This observation can be unambiguously explained by the formation of ***pR*-[16a]** by a rotation of the double bond with respect to the ring (Scheme 34).



Scheme 34 Proof for the ring flip in TBSO free azoninones[130]

After the clarification of this dynamic behaviour of unsaturated azoninones, first kinetic measurements were performed to determine the rate of conformational relaxation and its activation energy.

The following Table 4 presents the half-life for the conversion of the azoninones **[12a]**, **[13a]**, **[16a]** and **[17a]** from the initial *pS*-conformation into the corresponding *pR*-conformation.

[129] The possible enantiomeric combinations of *pS*,3*R*/*pR*,3*S* and *pS*,3*S*/*pR*,3*R* give identical spectra and NOE enhancements and can therefore not be differentiated at this stage.

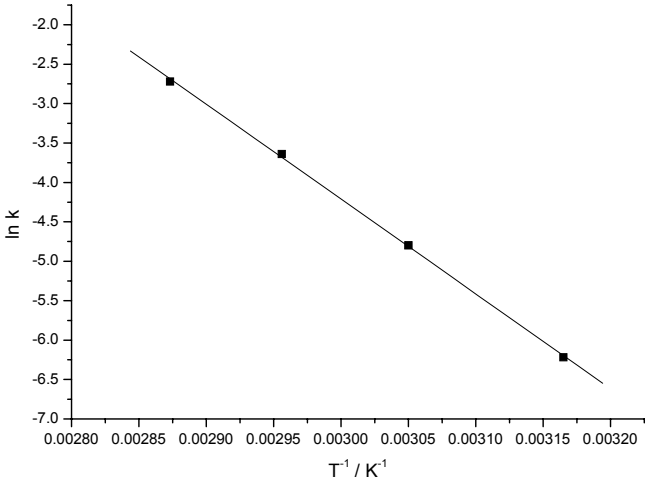
[130] Deviation from the expected optical rotation value of ***pS*-[17a]** arises from minor impurities of ***pR*-[17a]** formed by a reequilibration of the double bond during the HPLC process.

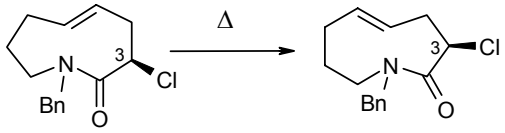
Table 4 Half-life times for the conversion of *pS*-azoninones into *pR*-azoninones

Compound	T_1 [K]	$t_{1/2}$ (T_1)	T_2 [K]	$t_{1/2}$ (T_2)	T_3 [K]	$t_{1/2}$ (T_3)	T_4[K]	$t_{1/2}$ (T_4)
***pS*-[12a]**	313	430 min	333	50.9 min	-	-	-	-
***pS*-[13a]**	313	191 min	333	16.9 min	-	-	-	-
***pS*-[16a]**	316	347 min	328	84 min	338	26.4min	348	10.5 min
***pS*-[17a]**	320*	>250 min*	335	60.6 min	338	39 min	346	14.6 min

*excluded, since epimerisation had not reached $t_{1/2}$ concentration

The activation energy for the epimerisation of ***pS*-[16a]** into the *pR*-isomer was determined using the data in an Arrhenius plot and conducting a linear regression (Fig. 13).





***pS*-[16a]** ***pR*-[16b]**

entry	$(T/K)^{-1}$	$t_{1/2}$ (min)	lnk
1	0.003165	347	-6.2158
2	0.00305	84	-4.7973
3	0.002956	26.4	-3.6399
4	0.002873	10.5	-2.7179

Fig. 13 Arrhenius plot of the epimerisation of ***pS*-[16a]** → ***pS*-[16b]**

An activation energy of 23.9 kcal/mol was determined for the isomerisation of ***pS*-[16a]**. This value is comparable to measurements of other 4-substituted azoninones.[131]

The following conclusions can be drawn from the half-life measurements of **[12a]-[17a]** that are in agreement with earlier E_A determinations performed in our group, (i) the 3-chloro substituted azoninones show a higher stability than 3-phenyl substituted azoninones, (ii) the introduction of the TBS group decreases the activation energy and (iii) the configuration of the substituting atoms has an influence on the conversion rate, as determined from the comparison of **[16a]** and **[17a]**.

However, the influences of the substitution pattern on the activation barrier are not yet fully understood. Presumably, the height of the activation barrier is influenced by a mixture of steric and electronic effects. The stabilisation or destabilisation of the reactant conformers can therefore not be exclusively explained by the analysis of E_A measurements.

Although the structures determined of the azoninones prepared in solution and in solid state appear to be very similar, some ^{1}H-NMR observations indicated the presence of another isomery that had to be

[131] See: M. Schröder, diploma thesis (Berlin 1999). The activation energies varied between 17 and 27 kcal/mol depending on the substitution pattern of the azoninone.

taken into account. The ^{1}H-NMR spectrum of pure ***pS*-[16a]** indicated the presence of two isomeric forms in a 3:1 ratio. A possible explanation for this behaviour is the existence of (*E*)- and (*Z*)-amide isomers (Fig. 14). Usually, cyclic amides prefer solution structures with a *trans*-arrangement of both amide chains.[132] In contrast, the presence of a second bulky substituent attached to the nitrogen leads to an increased ratio of the (*Z*)-isomer.[133]

In addition to the formation of amide isomers a further isomery could be responsible for the presence of the diastereomers observed. Due to its partial double-bond character and its perpendicular arrangement, the amide bond also exhibits planar chiral properties. As discussed in 2.2.1 the flip of a *cis* double-bond (represented by a *cis*-amide isomer) in an unsymmetrically substituted ring generates two planar chiral forms.[134] Consequently, a conformational change of the amide group within a cyclic system could lead to the occurrence of another pair of diastereomers. The number of potential diastereomeric arrangements of the same azoninone is increased to $2^3 = 8$.

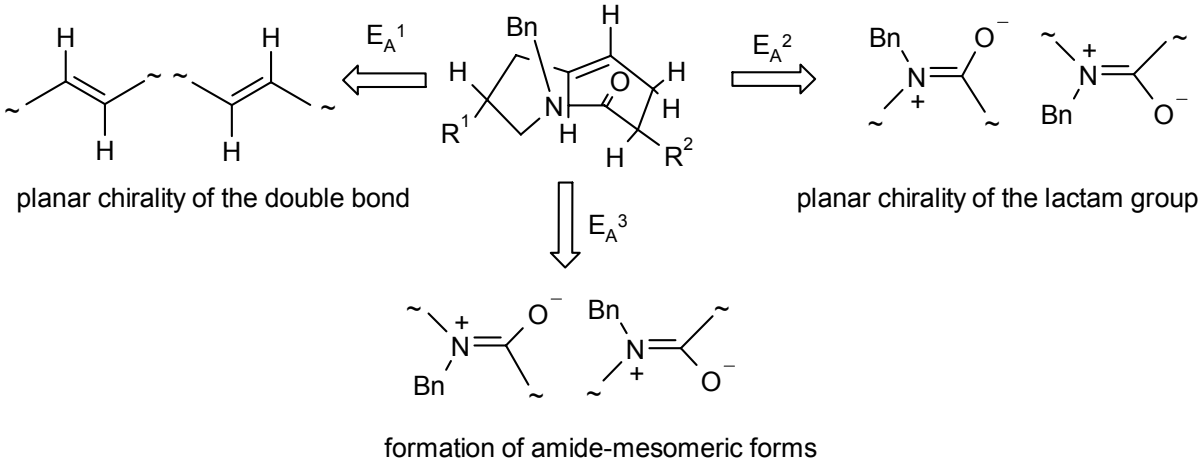


Fig. 14 Formation of diastereomers by conformational isomery in unsaturated azoninones

With the intention to distinguish between these potential azoninone isomers and to explain the driving force for their conformational relaxation, an analysis of their spatial structures in solution is necessary. Furthermore, this analysis is a prerequisite to understand the regio- and stereoselectivity during chemical transformations of azoninones. The 1D-NOE spectroscopy is an important tool for the investigation of azoninone structures in solution and enables the enlightenment of 3D structures of molecules and their dynamic interconversions.

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[132] An unsaturated azoninone with *E*-amide conformation was reported by : Olson, G. L.; Voss, M. E.; Hill, D. E.; Kahn, M. *J. Am. Chem. Soc.* **1990**, 112, 323-333 (same reference as ref.[56a]).

[133] Cyclic peptides including proline have a small difference in free energy between the *cis* and *trans* conformers, allowing both conformations to be significantly populated.

[134] Presumably, this flip requires a lower activation energy than isomerisation of the amide group, the experimentally determined activation free energy for the rotation barrier of methyl N-benzyl-N-methyl-carbamate (298K, CH_2Cl_2) was 17.95 kcal/mol as reported by Rablen, P. R. *J. Org. Chem.* **2000**, 65, 7930-7937.

2.2.3 Conformational Analysis of Azoninones via NOE Spectroscopy

The restricted free rotation of atom groups within a cyclic system often enables their structural elucidation using NOE techniques and allows exact conformational analysis particularly in combination with the coupling constants observed. This method could be successfully applied in the conformational investigation of azoninones, since their ^{1}H-NMR spectra are often characterised by a large number of nonequivalent protons with defined shifts and coupling constants. The spectroscopic examination of azoninones provided some characteristics that are directly caused by their conformation and can therefore act as indicators for a distinct conformation.

The most observed conformations of 3*R*-azoninones[135] that have been prepared in this work are shown in Fig. 15 (NOE enhancements are marked as arrows, for details see Experimental Part).

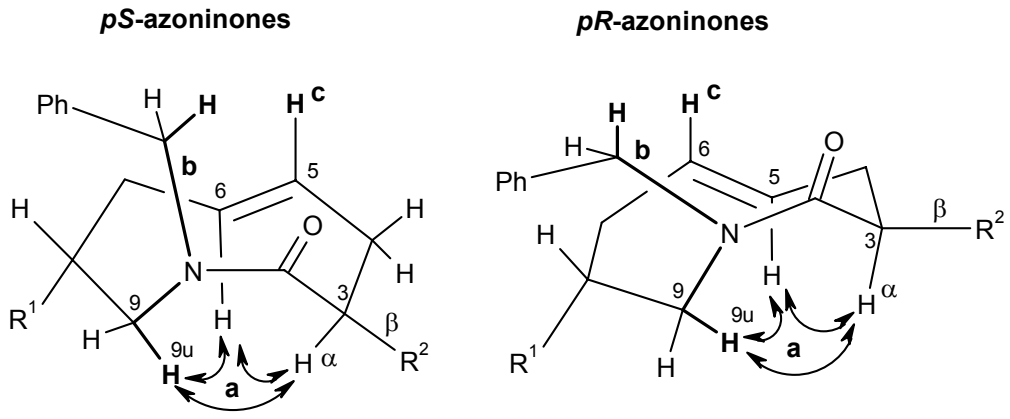

Fig. 15 Main conformations of 3β-azoninones and structural characteristics (R^1=OTBS, R^2=Ph, Cl, OBn)

Based on the NOE analysis of all protons[136] these conformations can be described by the occurrence of the following spectroscopic characteristics:

- the presence of strong NOE enhancements between H-3, H-9u and H-6 in *pS*-conformation or H-3, H-9u and H-5 in *pR*-conformation. The enhancements of 15-28% can only be explained by a short intramolecular distance between these protons.

- the presence of a ^{4}J coupling (~ 1Hz) between one proton of the N-Bn group and the proton H-9u indicating a "W" arrangement of both protons.

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[135] The conformations of 3*S*-phenylazoninones **[13a]** and **[13b]** are included in these examples. Although in these azoninones the stereochemical nomenclature has changed due to Kahn-Ingold-Prelog rules, the spatial arrangement of the C-3 phenyl substituent is identical to azoninones, bearing OBn and Cl substituents (3β).

[136] In this analysis the C-8 TBSO substituent served as reference stereogenic centre that maintained its configuration during the preparation of vinyl pyrrolidines and their aza-Claisen rearrangements.

- the deshielding effect of the carbonyl group leads to a low-field shift of protons located in the nodal plane of the π-system. Therefore, the resonance of the N-Bn proton that exhibit the ^{4}J-coupling is shifted downfield in comparison to its geminal neighbour (Δδ 0.5-0.8 ppm). Furthermore, the shielding effect of the carbonyl group induces a high-field shift of the olefinic proton that has the smallest distance to the C=O group and is located parallel to this π-plane. Thus, in the *pS*-conformation the H-5 proton is shifted to the high field, in the *pR*-conformation H-6 appears at higher fields.[137]

As already discussed in 2.1.2 the aza-Claisen rearrangement of unsubstituted vinyl pyrrolidine **[11]** with various carboxylic acid fluorides resulted in mixtures of C-3 diastereomers that could be separated by means of HPLC. The conformations adopted by these compounds depended on the configuration of the C-3 substituent. The 3β-configured azoninones consisted of a mixture of two conformations, one of which is similar to those of the TBSO substituted derivatives (Fig. 15). In 3α-substituted azoninones, a conformation with a flipped amide group was found, presumably energetically stabilised by the preference of large substituents for equatorial positions (Fig. 16).

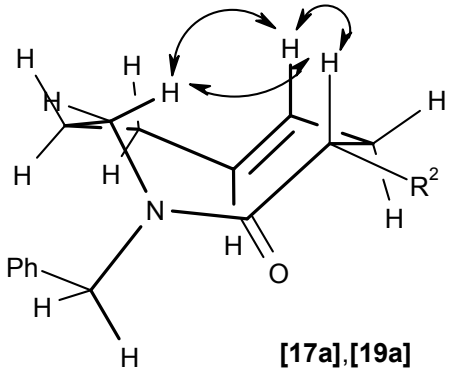


Fig. 16 Main conformation of 3α-azoninones (*pS*-form)

In analogy to the conformation discussed earlier, the characteristic NOE enhancements (H-3o / H-5 / H-9) and the ^{4}J-coupling (H-9 / H-NBn) allowed their spectroscopic identification.

An important hint for the existence of a conformational relaxation of the amide group was given by the NOE investigation of ***pS*-[16a]** (Fig. 17). In addition to the expected NOE enhancements a chemical transfer was observed during the course of the measurement resulting in signal saturation of corresponding protons. As a result of the chemical transfer a second series of positive NOE effects appeared in the spectra. This finding was very helpful since some NOE effects that had been observed analysing various azoninones could not be explained hitherto.

[137] For more insight into shielding effects of various groups see : Günther, *H-NMR-Spektroskopie*. 3rd ed., Georg Thieme Verlag, Stuttgart **1992**.

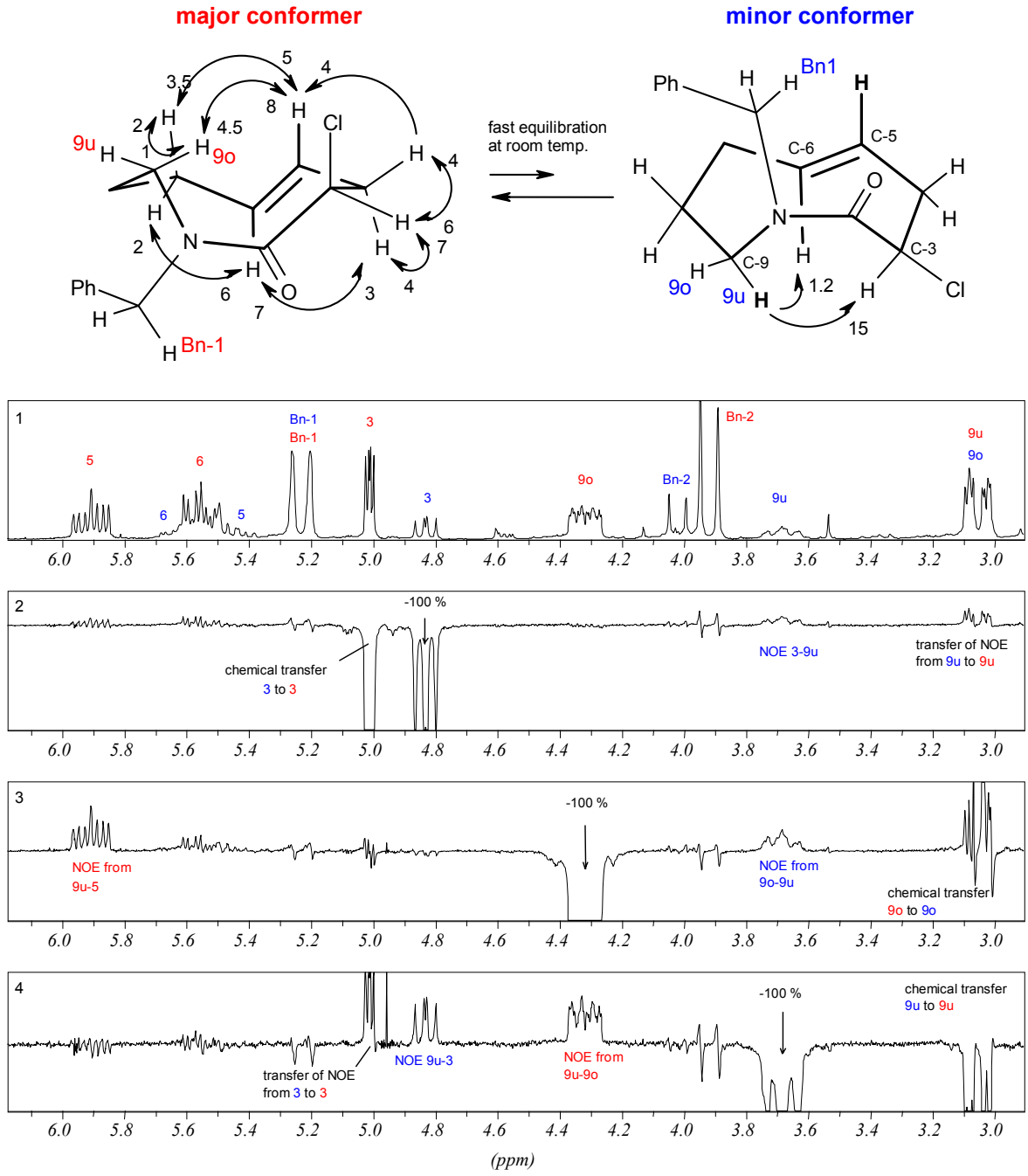


Fig. 17 Detection of amide isomers by NOE measurements of **[16a]**[138]

Spectrum 1 represents the ^{1}H-NMR spectrum of **[16a]**, the spectra 2-4 are part of the 1D-NOE measurement. In the ^{1}H-NMR spectrum two species are evident that differ especially in chemical shifts of the olefinic protons (H-5 and H-6) and the protons at C-9. In the ^{1}H,^{1}H-COSY spectrum two ^{4}J couplings could be detected between the pairs Bn1/9o in the major isomer and Bn1/9u in the minor isomer (typical for a "W" arrangement of both protons). A flip of the double bond could be excluded as a result of the NOE enhancements (H-3 is always located in proximity to H-6).

[138] NOE enhancements are marked by arrows (numbers refer to percentage enhancement).

The flip of the whole amide unit,[139] excluding additional C-3 diastereomeric forms, was proven by the following observations:

- Saturation of a signal during NOE was followed by the appearance of a negative signal for the respective proton of the second species. This indicated a transfer of saturation during the measurement caused by a fast conformational change which can only be observed in case of interconverting diastereomers.

- The transfer of saturation allowed the assignment of proton pairs (H9o^{major}/H-9o^{minor} and H-9u^{major}/H-9u^{minor}). During this conformational process the shifts and the characteristic ^{4}J couplings changed. As depicted in Fig. 17 proton H-9o^{major} is shifted highfield (H-9o^{minor}) and looses its ^{4}J coupling. Furthermore, proton H-9u^{major} is shifted downfield (H-9u^{minor}) and shows a ^{4}J coupling. Based on the "W" arrangements of the observed ^{4}J couplings in other azoninones these facts can only be explained by a flip of the N-Bn group.

- The comparison of the changes in the chemical shifts of olefinic protons and the protons at H-5 supplied strong evidences that during the conformational movement the carbonyl group and the N-Bn group change their places simultaneously. In this manner, the H-5^{major} proton is placed in close spatial proximity to the carbonyl group and is therefore shifted to the highfield (H-5^{minor}). The low-field shifted proton H-9o^{major} is located in the nodal plane of the carbonyl group and is moved out of this plane during the conformational change. The result is a strong highfield shift of H-9o^{minor}.

This example demonstrates the applicability of NOE and saturation transfer experiments for the conformational analysis of azoninones. However, if only small amounts of a second amide mesomer are observable in the spectrum, a full assignment of the conformation as described in the preceding example is not possible. Moreover, the structural influence on the different *pS*/*pR* ratios after thermal equilibration was not fully explained. Therefore, the empirically provided structure models of azoninones were expanded by theoretical calculations using force-field methods.

[139] The observed high rotation barriers for amides support this assumption, for further discussion on this topic see (a) Cox, C.; Leckta, T. *Acc. Chem. Res.* **2000**, 33, 849-858. (b) ref. [134]

2.2.4 Comparison of Experimental and Theoretical Structural Models of Azoninones

The main conformations observed in the azoninones **[12]-[19]** as determined by NOE investigations are summarised in Table 5. The conformations are assigned to 8 classes of diastereomeric forms arising from potential orientations of the double bond and the amide unit (combinations of the subunits as drawn in Fig. 14, page 48). Within these classes minor conformational changes can occur (change of torsional angles of ring-atoms and atoms included in ring substituents) that can not be resolved by 1D NOE measurements.

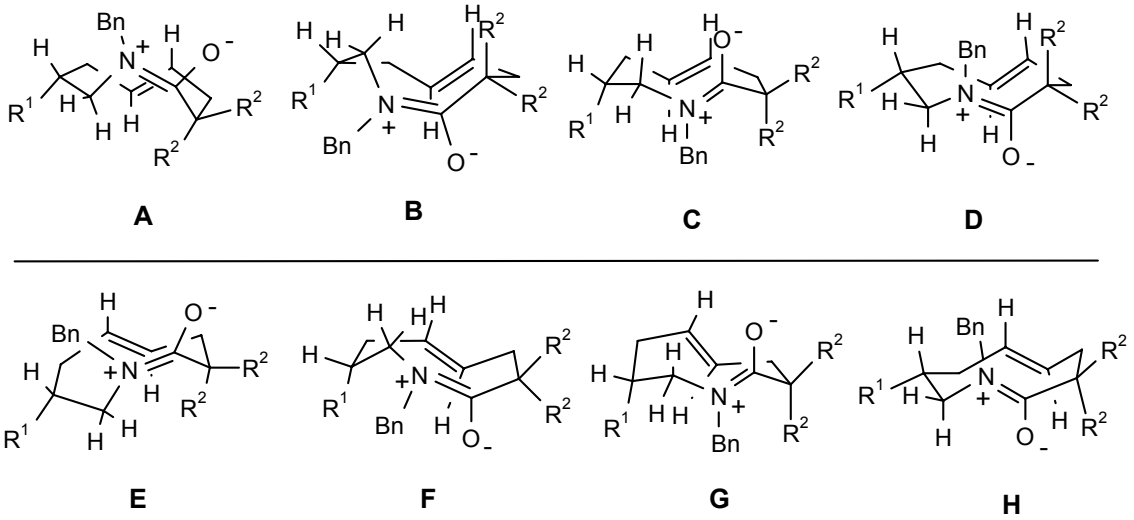


Table 5 Spectroscopically observable distribution of conformeric azoninones

compound number	R^1	R^2	chirality at C-3	planar chirality	ratio of conformers	presumed **major** (minor) conformations
[12a]	OTBS	Cl	*R* (β)	*pS*	99:1[a]	**A** (B) [b]
[12b]	OTBS	Cl	*R* (β)	*pR*	> 100:1	**E**
[13a]	OTBS	Ph	*S* (β)	*pS*	90:10	**A** (B) [b]
[13b]	OTBS	Ph	*S* (β)	*pR*	> 100:1	**E**
[14a]	OTBS	OBn	*R* (β)	*pS*	72:21:7	**A** (B, C)[b] see footnote[140]
[14b]	OTBS	OBn	*R* (β)	*pR*	> 100:1	**E**
[15b]	OTBS	OBn	*S* (α)	*pR*	> 100:1	**E**
[16a]	H	Cl	*R* (β)	*pS*	76:24	**B** (A)
[17a]	H	Cl	*S* (α)	*pS*	> 100:1	**B**
[18a]	H	OBn	*R* (β)	*pS*	> 100:1	**B**
[19a]	H	OBn	*S* (α)	*pS*	> 100:1	**B**

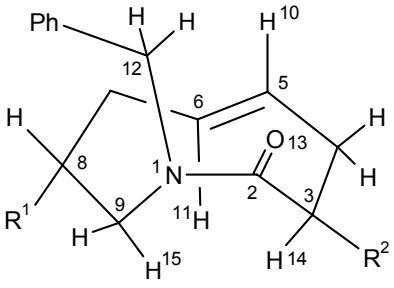
a = determined from saturation transfer, b = signal change analogue to *pS*-[16a] during conformational isomerisation

[140] Both minor conformations showed an analogous changing of signal shifts, presumably in both cases the N-Bn group had flipped, in contrast to **[16a]** where all three isomers had the same shift order for H-5 and H-6

Considering these data, some first conclusions can be drawn. The TBSO group has an influence on the preferred conformation as evident from the comparison of ***pS*-[12a]** and ***pS*-[16a]**. An interaction of the TBSO group with the N-Bn group, as found in the chair-like conformation **B**, is avoided in the boat-like conformation **A** which stabilises this conformation. Moreover, the relative configuration of the substituent at the C-3-position, built-up during the aza-Claisen rearrangement, appears to be an important factor as determined by the comparison of ***pS*-[16a]** and ***pS*-[17a]**. The chloro-substituent oriented pseudoaxially in ***pS*-[16a]** (3β) leads to a destabilisation of the chair-like conformation **B** by 1,3 and 1,4 interactions. Thus, a mixture of conformations **B** and **A** occurred. In compound ***pS*-[17a]** (3α) these interactions are avoided by the equatorial position of the chloro-substituent leading to **B** as major conformation.

To understand the influences of structure and configuration of the stereogenic centres on the conformation of azoninones a conformational analysis of some azoninones was performed. The examination of the conformational space of azoninones **[16]-[19]** was carried out by the Monte Carlo approach[141] included in the Conformational Search module of the HyperChem program package[142] and based on the force-field method MM+.[143]

As starting conformations 8 assumed local minima conformations **A-H** (2 planar-chiral * 4 amide isomeric forms see Table 5), were used. Each of these conformations was minimised using the Conformational Search module. To find further local minima, 2-3 dihedral angles were simultanously changed. The dihedral angles chosen depended on the azoninone substituents. It proved to be more efficient to change the dihedral angles of the N-, C-3 and C-8-substituents to find local minima rather than change dihedral angles of atoms included in the cycle (e.g. 9-1-2-13). The obtained groups of conformations ($A_{1..N,}$ $B_{1..N}$ etc.) were reduced by combining all conformers included in a 0.5 kcal range. The conformer with the lowest energy was chosen as local minimum of the conformeric class. This approximation was used to decrease the number of conformers to be considered in the discussion. For further and more accurate investigations of azoninone conformations all populated conformations of the 8 conformeric subclasses should be taken into consideration.



[141] Kolossvary, I.; Guida, W. C. J. Comput. Chem. **1993**, 14,691.
[142] HyperChem, v. 6.0, from HyperCube, Waterloo, Ontario, Canada.
[143] MM+ is a trademark of HyperCube Inc. and is derived from the public domain code developed by Dr. Norman Allinger, referred to as MM2 (1977). The parameters distributed with HyperChem include the public domain values, generally referred to as the MM2 (1991) parameter set that Dr. Allinger contributed to HyperCube, Inc. (a) Allinger, N. L.; *J. Am. Chem. Soc.* **1977**, 99, 8127-8134. (b) Allinger N. L. MM3(92); QCPE: Bloomington IN, 1992.

The results of the conformational analysis of azoninones are summarised in Table 6.

Table 6 Conformational analysis of azoninones

compound number	R^1	R^2	chirality at C-3 (α,β)	class of conformer	energy [kcal/mol]	N-C-5	N-C-6	N-C-5 (X-Ray)	N-C-6 (X-Ray)	Boltzmann distrib. 298K (258K)
***pS*-[12a]**	OTBS	Cl	*R* (β)	**A-1**	**21.28**	3.18	3.48	-	-	72.2 (75.5)
***pS*-[12a]**	OTBS	Cl	*R* (β)	A-2	21.87	3.09	3.16	3.09	3.21	26.7(23.9)
***pS*-[12a]**	OTBS	Cl	*R* (β)	B	23.80	3.30	3.03	-	-	1.0 (0.6)
***pS*-[12a]**	OTBS	Cl	*R* (β)	C	25.13	3.11	2.80	-	-	0.1 (0)
***pS*-[12a]**	OTBS	Cl	*R* (β)	D	29.75	2.86	2.83	-	-	0 (0)
***pR*-[12b]**	OTBS	Cl	*R* (β)	**E**	**19.17**	3.32	2.97	3.31	2.98	100 (100)
***pR*-[12b]**	OTBS	Cl	*R* (β)	F	26.79	3.04	3.27	-	-	0 (0)
***pR*-[12b]**	OTBS	Cl	*R* (β)	G	24.41	3.00	2.90	-	-	0 (0)
***pR*-[12b]**	OTBS	Cl	*R* (β)	H	27.28	3.09	2.79	-	-	0 (0)
***pS*-[13a]**	OTBS	Ph	*S* (β)	**A**	**18.93**	3.16	3.48	-	-	98.2 (99.1)
***pS*-[13a]**	OTBS	Ph	*S* (β)	B	21.35	3.30	2.98	-	-	1.65 (0.8)
***pS*-[13a]**	OTBS	Ph	*S* (β)	C	22.67	3.13	2.81	-	-	0.18 (0.1)
***pS*-[13a]**	OTBS	Ph	*S* (β)	D	25.74	2.91	2.87	-	-	0 (0)
***pR*-[13b]**	OTBS	Ph	*S* (β)	**E**	**17.21**	3.30	2.95	-	-	99.9 (100)
***pR*-[13b]**	OTBS	Ph	*S* (β)	F	24.05	3.02	3.26	-	-	0 (0)
***pR*-[13b]**	OTBS	Ph	*S* (β)	G	21.27	2.95	2.92	-	-	0.1 (0)
***pR*-[13b]**	OTBS	Ph	*S* (β)	H	22.29	3.07	2.78	-	-	0 (0)
***pS*-[16a]**	H	Cl	*R* (β)	**A**	**20.68**	3.09	3.16	-	-	91.4 (94.0)
***pS*-[16a]**	H	Cl	*R* (β)	B	22.10	3.31	3.01	-	-	8.3 (5.9)
***pS*-[16a]**	H	Cl	*R* (β)	C	23.99	3.09	2.80	-	-	0.3 (0.1)
***pS*-[16a]**	H	Cl	*R* (β)	D	28.45	2.85	2.85	-	-	0 (0)
***pR*-[16b]**	H	Cl	*R* (β)	**E**	**19.05**	3.32	2.97	-	-	99.9 (100)
***pR*-[16b]**	H	Cl	*R* (β)	F	26.22	3.10	3.50	-	-	0 (0)
***pR*-[16b]**	H	Cl	*R* (β)	G	23.15	2.96	2.93	-	-	0.1 (0)
***pR*-[16b]**	H	Cl	*R* (β)	H	26.21	3.07	2.78	-	-	0 (0)
***pS*-[17a]**	H	Cl	*S* (α)	A	26.22	3.10	3.50	-	-	0 (0)
***pS*-[17a]**	H	Cl	*S* (α)	**B**	**19.05**	3.32	2.97	3.31*	3.00*	99.9 (100)
***pS*-[17a]**	H	Cl	*S* (α)	C	26.20	3.07	2.78	-	-	0 (0)
***pS*-[17a]**	H	Cl	*S* (α)	D	23.15	2.96	2.93	-	-	0.1 (0)
***pR*-[17b]**	H	Cl	*S* (α)	E	22.10	3.31	3.01	-	-	8.3 (5.9)
***pR*-[17b]**	H	Cl	*S* (α)	**F**	**20.68**	3.09	3.16	-	-	91.4 (94.0)
***pR*-[17b]**	H	Cl	*S* (α)	G	28.45	2.85	2.85	-	-	0 (0)
***pR*-[17b]**	H	Cl	*S* (α)	H	23.99	3.09	2.80	-	-	0.3 (0.1)

*values taken from an X-Ray structure where the 3-Chloro substituent was replaced by a Phenyl group

The calculated energies and structural parameters of the low energy azoninone conformers are in accordance with the experimental data obtained by NOE-measurements and X-Ray structure analysis. Furthermore, the conformational relaxation of the initially formed *pS*-azoninones (***pS*-[12a]** and ***pS*-**

[13a]) into thermodynamically stable *pR*-azoninones (***pR*-[12b]** and ***pR*-[13b]**) can be rationally explained as a result of the different strain energies of the planar chiral compounds. The stability of the initial *pS*-conformation in azoninones with inverted configuration at C-3 (3α in ***pS*-[17a]**) arises from the stability of conformation **B**, in which the C-3 substituent adopts an equatorial position. The low strain energy of this highly populated conformation (a difference of ~4 kcal to the next local minimum was calculated) explains the observed thermal stability of azoninones with 3β-configuration at C-3 as well as the absence of amide-isomers.[144]

The observed presence of amide-isomers in the ^{1}H-NMR spectra of ***pS*-[12a]**, ***pS*-[13a]** and ***pS*-[16a]** is confirmed by the results of the calculations. Although calculated and spectroscopically observed populations of amide isomers differ in the values, their occurrence or absence in the azoninones are predicted correctly. The deviations may be explained by the approximation applied in that only the conformer with the lowest energy of each subclass was considered. Thus, further populated conformations of azoninones are excluded from the analysis. An example for the potential existence of additional local minima is azoninone ***pS*-[12a]**. The X-Ray analysis of this azoninone (Fig. 11, page 45) reveals a structure that is identical to the conformation **A-2** in the A-subclass for this compound. However, this structure does not represent the global energetic minimum in solution since a conformation **A-1** with a lower energy was found as result of the force-field calculations. Both conformations differ in the dihedral angle the N-Bn group and the N-C-9 bond.

Comparing these findings with the mechanistic model of the aza-Claisen rearrangements, some conclusions can be drawn. Our findings indicate that the stability of the resulting azoninones is directly connected with the conformation of the transition state during the aza-Claisen rearrangement. If the aza-Claisen rearrangement proceeds via a transition state including no additional strain (as the chair-like **TS-1** see Scheme 27, page 32) the resulting azoninone adopts a conformation that represents the thermodynamic minimum (conformation **B** for ***pS*-[17a]**). In contrast, if the process via a thermodynamically favoured chair-like transition state is inhibited, e.g. by pyrrolidine substituents, a less favoured non-stable azoninone conformation is built (conformation **A** for ***pS*-[12a]** and ***pS*-[14a]**). Thus, a similarity in the boat-like conformation **A** and a boat-like geometry of the transition state (**TS-4**) appears reasonable.

[144] Azoninones with 3*S*-configuration showed a remarkable stability towards planar-chiral isomerisation, for further details see : M. Diederich, PhD thesis, Freie Universität Berlin, 2000.

2.2.5 Conclusions

Azoninones display interesting conformational properties. The rotation of the double bond with respect to the ring is an extraordinary conformational motion, since it changes the chiral information of planar chiral azoninones. Initially the *pS*-conformation can be prepared stereoselectively by a transformation of central chirality into planar chirality during the aza-Claisen rearrangement. Then, the planar chirality of azoninones can be changed in a controlled manner. By storing at -20°C the initially formed *pS*-azoninones are stable for months. Any heating for several hours at 50-60°C causes a flipping of the double bond. This conformational relaxation can be explained by a lower energy of the *pR*-conformation, comparable to the energetic difference between a boat-like and a chair-like conformation.

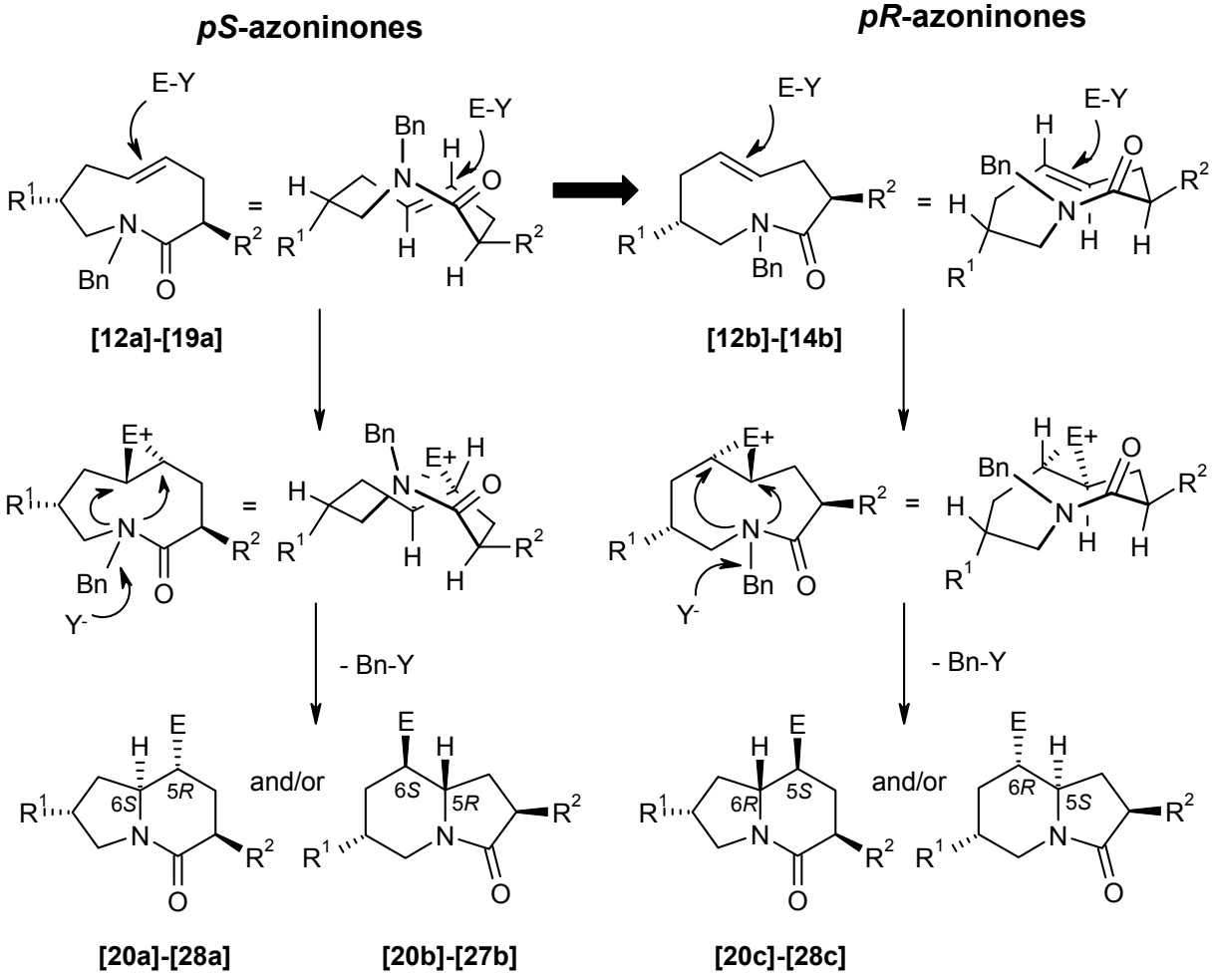
Additionally, some azoninones show the presence of amide isomers, which quickly interconvert at ambient temperatures. NOE measurements and X-Ray analysis indicated a flip of the amide unit without a change of its (*E*)-configuration during this process. The amide isomers differ in their transannular distances between the nitrogen atom and the carbon atoms of the double bond.

With respect to the total synthesis of indolizidine alkaloids, e.g. pumiliotoxins, the prerequisite for a synthetic applicability of azoninones is the selective conversion of the adjustable planar chiral information into a new central chirality. A chemical transformation that fulfills this condition should require a lower activation energy for the reaction than that required for the planar chiral isomerisation. Therefore, a suitable reaction should proceed quickly at room temperature or below. As discussed in chapter 1.2.2 transannular cyclisations of unsaturated azoninones are key transformations for the synthesis of various classes of indolizidine alkaloids. The directed synthesis of the indolizidine core starting from planar chiral isomers of the same azoninone could be a useful new method for the preparation of natural products that are derivatives of the *D*-proline or the *L*-proline series.

2.3 Transannular Reactions of Optically Active Azoninones

The planar chirality of azoninones is only of synthetic importance if it can be selectively transformed into new stereogenic centres. A suitable transformation that fulfills this requirement is the transannular ring contraction[145] of azoninones leading to indolizidinones. Recent investigations have shown that azoninones undergo regio- and diastereoselective ring contractions to indolizidinones (see chapter 1.2.2) but the factors that direct the stereo- and regioselectivity of this process were not fully understood.

The stereospecifity of transannular ring contraction reactions can be a consequence of the spatial arrangement of the double bond included in azoninones. Since one side of the double bond is considerably shielded by the nitrogen atom, an electrophile exclusively attacks at the unshielded face (Scheme 35).



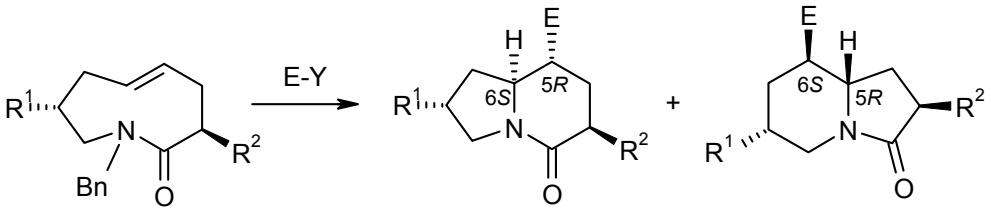
Scheme 35 Stereochemical course of transannular ring contractions of azoninones - possible products

[145] For a review on electrophilic cyclisations of unsaturated amides see (a) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, 54, 13681-13736.

The nascent cation is intramoleculary trapped by the lactam nitrogen. Then, the so formed intermediate N-Benzyl acylammonium ion undergoes a von-Braun degradation. The counterion of the electrophile removes the benzyl group resulting in indolizidinones and benzyl halides. In view of the actual knowledge, the different stereochemical patterns of indolizidinones observed in ring contractions described earlier by Hegedus[62] and Nubbemeyer[63,64] can be explained by the assumption that different planar-chiral azoninones were used as reactants. However, it remains unclear if the stereochemical outcome of the reaction was determined by an energetically favoured conformation of azoninones or if the reaction could be selectively performed with both planar chiral azoninones. In the latter case both planar chiral conformations should give reactions to different indolizidinones. With the intention to investigate regio- and stereoselectivity of transannular ring contractions of azoninones in detail, both planar chiral conformations of some azoninones were prepared and treated with various electrophiles in analytical and preparative scale experiments.

2.3.1 Cyclisation Reactions of Kinetically Formed *pS* Lactams

In the first series of experiments the *pS*-lactams **[12a]-[19a]**, possessing the conformations A (respectively B) were treated with PhSeBr, I_2 and Br_2. The reactions were found to be completed within minutes, generating indolizidinones **[20]-[31] a/b** in moderate to high yields[146] (detailed information is outlined in Table 7). In contrast to earlier investigations where N-methylazoninones were applied in the reactions, no intermediate acylammonium salts could be detected.[147]



[146] Change of workup conditions during this study substantially increased the yields, the formation of H-Hal during the purification and the cleavage of the TBSO group could then be suppressed by the aqueous $Na_2S_2O_3$-workup prior to the chromatographic purification.

[147] M. Diederich, PhD thesis, Freie Universität Berlin (2000) and ref. [63]

Table 7 Result of transannular ring contractions of *pS*-azoninones

entry	azoninone	R^1	R^2	reagent E-Y	method*	scale**	yield	product	ratio indolizidinones a - b - c
a	***pS*-[13a]**	OTBS	Ph	PhSeBr	A	p	95%	**[20a]**	12 - 0 - 1
c	***pS*-[13a]**	OTBS	Ph	I_2	A	p	99%	**[21a]**	9 - 0 - 1
d	***pS*-[13a]**	OTBS	Ph	Br_2	A	p	55%	**[22a]**	3.7 - 1 - 0.8
b	***pS*-[13a]**	OTBS	Ph	PhSeBr	B	p	44%	**[20b]**	0 - 1 - 0
e	***pS*-[13a]**	OTBS	Ph	I_2	B	p	63%	**[21b]**	1.3 - 4 - 1
f	***pS*-[13a]**	OTBS	Ph	Br_2	B	p	40%	**[22b]**	0 - 1 - 0
g	***pS*-[14a]**	OTBS	OBn	PhSeBr	B	p	46%	**[23a]**	1 - 4.8 - 0
h	***pS*-[14a]**	OTBS	OBn	I_2	B	a	36%	**[24b]**	2 - 1 - 0
i	***pS*-[14a]**	OTBS	OBn	Br_2	B	a	8%	**[25b]**	0 - 1 - 0
k	***pS*-[14a]**	OTBS	OBn	PhSeBr	A	p	84%	**[23a]**	7 - 0 - 1
l	***pS*-[14a]**	OTBS	OBn	I_2	A	p	80%	**[24a]**	7 - 0 - 1
m	***pS*-[12a]**	OTBS	Cl	PhSeBr	B	a	20%	**[26b]**	1 - 12 - 0
n	***pS*-[12a]**	OTBS	Cl	Br_2	B	a	25%	**[27b]**	0 - 1 - 0
o	***pS*-[12a]**	OTBS	Cl	PhSeBr	A	p	81%	**[26a]**	1 - 0 - 0
p	***pS*-[12a]**	OTBS	Cl	Br_2	A	a	15%	**[27a]**	1 - 0 - 0
q	***pS*-[12a]**	OTBS	Cl	I_2	A	p	82%	**[28a]**	1 - 0 - 0
r	***pS*-[16,17]**	H	Cl	I_2	A	p	63%	**[29][30]**	1 - 0 - 0
s	***pS*-[19a]**	H	OBn	I_2	A	p	50%	**[31]**	1 - 0 - 0

* method A: addition of electrophile B: addition of azoninone, ** scale : a - analytical p - preparative

The relative configuration of the newly formed stereogenic centres and the position of the ring junction were proven by NOE analyses and, if necessary, by HETCOR (heteronuclear correlation) spectroscopy. The regioisomeric indolizidinones **[a]** and **[b]** gave nearly identical NOE enhancements but they could be identified by their characteristic IR-absorption of the C=O group (γ-lactam 1690-1720 cm^{-1} ; δ-lactam 1640-1660 cm^{-1}).

As expected from the spatial arrangement of the double bond, the experiments confirmed the assumed high level of stereoselectivity during the transformation of planar chiral information into central chirality. The *pS*-azoninones yielded indolizidinones with 6*S*,5*R*-configuration. However, in some cases inverted indolizidinones with 6*R*,5*S*-configuration were obtained as minor products (entry *a*, *c*, *e*, *k*, *l*). The formation may be explained by the presence of minor amounts of *pR*-azoninones in *pS*-azoninones as a result of a slow conformational relaxation of kinetically formed *pS*-azoninones.

The regioselectivity of transannular ring contractions was found to be strongly dependent on the reaction conditions used. The slow addition of the dissolved reagent to azoninones at room temperature gave six-membered indolizidinones **[a]** as major products; the ratio of **[a]**/**[b]** was between 4:1 and 15:1 (method a). Due to the high reaction rate, completion of the reaction was found, as soon as the colour of the unreacted reagent remained. Changing the reaction conditions altered the regiochemical course of the reaction. Adding the azoninones to a solution of electrophiles at -20°C,

five-membered lactams **[b]** were preferentially generated; the ratio of the regioisomers **[a]**,**[b]** was between 3:1 and 15:1.[148]

To verify the comprehensive stereoselective conversion of planar chirality into central chirality, transannular reactions of *pR*-azoninones with electrophiles were also investigated.

2.3.2 Cyclisation Reactions of Thermodynamically Formed *pR* Lactams

In the second series of transannular ring contractions thermodynamically stable *pR*-azoninones were generated by heating of the initial *pS*-azoninones. Depending on the azoninone, varying amounts of *pS*-azoninones remained in the sample (ratio *pR*/*pS* 6:1 → 10:1) causing the formation of indolizidinones type **[a]** or **[b]** (depending on the reaction condition) as side products. In analogy to the prior described series, the reactions were found to be completed within minutes. In contrast to the *pS*-azoninones, the thermodynamically stable *pR*-azoninones always yielded the six-membered regioisomer **[c]** independent on changes in the reaction conditions (see Table 8).

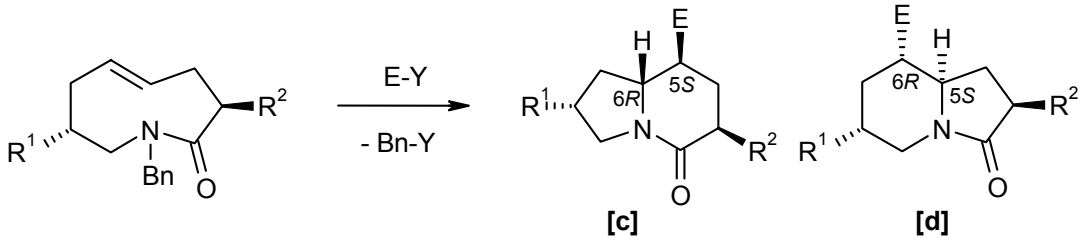


Table 8 Result of transannular ring contractions of *pR* -azoninones

entry	azoninone	R^1	R^2	reagent E-Y	method*	scale**	yield	product	ratio indolizidinones a - b - c
a	***pR*-[13b]**	OTBS	Ph	PhSeBr	A or B	p	68%	**[20c]**	0 - 1 - 9
c	***pR*-[13b]**	OTBS	Ph	I_2	A or B	p	50%	**[21c]**	0 - 1 - 11
d	***pR*-[13b]**	OTBS	Ph	Br_2	A	p	72%	**[22c]**	1 - 0 - 17
g	***pR*-[14b]**	OTBS	OBn	PhSeBr	B	a	20%	**[23c]**	0 - 1 - 7
h	***pR*-[14b]**	OTBS	OBn	I_2	A or B	p	40%	**[24c]**	0 - 0 - 1
m	***pR*-[12b]**	OTBS	Cl	PhSeBr	A or B	p	64%	**[26c]**	0 - 0 - 1
n	***pR*-[12b]**	OTBS	Cl	I_2	A or B	p	64%	**[28c]**	0 - 0 - 1

* method A: addition of electrophile B: addition of azoninone, ** scale : a - analytical p - preparative

The formation of a regioisomeric lactam **[d]** has never been observed. The interpretation of these results in combination with theoretical structure models of azoninones is discussed in the next chapter.

[148] The selective transannular ring contraction of *pS*-**[14a]** by I_2 (entry *h*) failed, only varying mixtures of **[24a]** and **[24b]** have been found to Predominantly result in lactam **[24a]**.

2.3.3 Mechanistic Conclusions

Considering the stereochemical part of transannular ring contraction reactions, azoninones underwent the known *anti*-addition of electrophile and nucleophile to the olefin. Regarding *pS*-azoninones, the electrophile attacks at the unshielded *Re*-face of the double bond stereospecifically forming an intermediate cyclic cation. The cation is opened by the attack of amide nitrogen forming *5R,6S* configured indolizidinones. In *pR*-azoninones the electrophile attacks the unshielded *Si*-face due to the changed planar chirality. As stereochemical consequence inverted indolizidinones with *5S,6R* configuration are formed. Although the thermal stability of azoninones have to be carefully considered during the preparation and workup, the planar chiral information can be selectively transformed into central chiral information. The activation energy for the epimerisation of the planar chiral information was significantly higher than that of the transannular reaction (*anti* Curtin-Hammett).

The explanation for the regiochemical outcome of the cyclisation reactions is not undoubtedly proven yet, but a preliminary interpretation to explain the experimental results should be given here. As discussed in chapters 2.2.3 and 2.2.4 (see Table 5) the azoninones adopt defined conformations. The regiochemical course of the transannular reaction can be described by the assumption that the shortest intramolecular distance between the nitrogen atom and both carbon atoms of the olefinic double bond determines the direction of intramolecular attack and hereby the regiochemical outcome of transannular cyclisations.

As indicated by NOE and NMR measurements and confirmed by the conformational analysis, the *pR*-lactams **[12b]**-**[14b]** adopt in solution a thermodynamically stable and highly populated conformation **E** (as discussed in 2.2.3). Transannular distances (Table 6, page 55) between the nitrogen atom and both olefinic carbon atoms in these *pR*-lactams were determined by X-ray analysis and by conformational analysis and showed that N-1 was positioned somewhat closer to C-6 than to C-5.[149] Thus the ring contraction always proceeded regioselectively, the new bond was formed between N-1 and C-6 as found in the indolizidinones **[20c]**-**[28c]**.

In the case of *pS*-azoninones **[12a]**-**[19a]** the coexistence of several isomeric forms concerning the arrangement of the amide unit was shown by NMR methods and also confirmed by conformational analysis. The investigation of intramolecular distances between N-1 and the olefinic carbon atoms showed a close proximity of N-1 and C-5 (Table 6, page 55) in the major conformation **A**. In contrast, the supposed minor conformation **B** was found to have a smaller intramolecular distance between N1 and C-6. Performing the ring contraction at lower temperatures (- 20°C, method B) and with an excess of electrophile, transannular ring contraction was significantly faster than the interconversion of amide isomers (*anti* Curtin-Hammett). The predominant conformation **A** in the *pS*-azoninones leads to the preferential formation of five-membered indolizidinones. Performing the reaction at room temperature

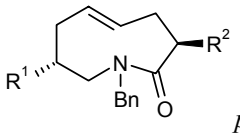
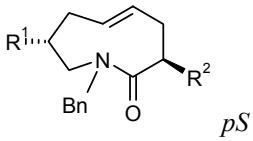
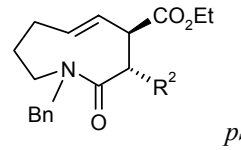
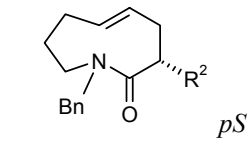
[149] Considering the intramolecular distances for ***pR*-[12b]**, the agreement of the values obtained by X-ray structure analysis and by calculation is evident.

by a slow addition of the electrophile, the regioisomeric indolizidinones **[20a]-[28a]** were obtained. Presumably, the somewhat increased temperatures allowed the fast equilibration of amide-isomeric forms, leading to a preferred reaction of the more reactive (shorter N-C6 bond) conformer (presumably **B**), although sparsely populated (Curtin-Hammett).

This assumption is supported by earlier investigations of transannular ring contractions of 3*S*-azoninones.[147] Analogous to azoninones **[17a]** and **[19a]**, the conformation **B** adopted in these compounds was found to be highly populated causing the preferred formation of six-membered indolizidinones.

A short summary of the cyclisation products, prepared in this work and during earlier investigations in our group in relation to the hypothetical azoninone conformations are outlined in Table 9.

Table 9 Summary of the formation of ring contraction products with respect to transannular distances

	conformation	distance N-C5 calc. (X-Ray) [Å]	distance N-C6 calc. (X-Ray) [Å]	formed indolizidinone
 *pR*	**E**	3.32 (3.31)	2.97 (2.98)	exclusively six-membered lactams[a)]
 *pS*	**A** **B**	3.09 (3.09) 3.30	3.16 (3.21) 3.03	six-membered or five-membered lactams, depending on reaction conditions [a)]
 *pS*	**B**	3.30	2.93	exclusively six-membered lactams[147]
 *pS*	**B**	3.32 (3.31)	2.97(3.00)	exclusively six-membered lactams [a)]

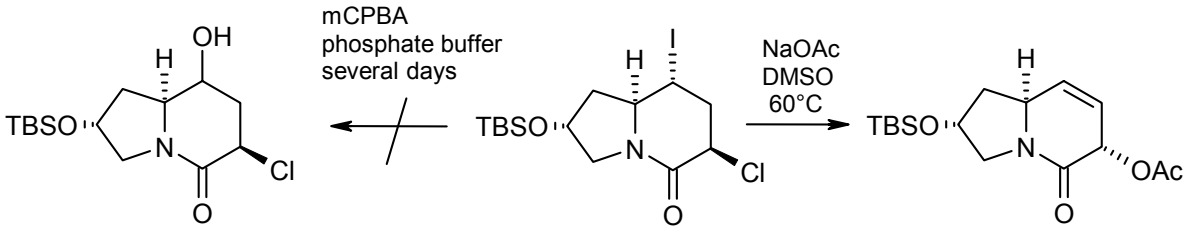
a) this work

Considering the transannular cyclisation products with the intention to synthesise pumiliotoxins, a substitution of the substituent E (Br, I) by an oxygen could lead to the required core hydroxy indolizidinone (see retrosynthetic analysis, Scheme 18, page 20). In the next chapter synthetic studies towards this goal are summarised.

2.3.4 Synthesis of Hydroxy Indolizidines from Transannular Cyclisation Products by Nucleophilic Substitution

Envisaging the synthesis of hydroxy indolizidinones, the exchange of secondary iodo-substituent by oxygen nucleophiles was investigated. In the literature some examples for oxidative or substitutive methods have been described. Oxidative replacements include peroxytrifluoroacetic acid[150] or meta-chloroperbenzoic acid[151] and a weak nucleophile (such as water). Substitution reactions of secondary alkyl iodides were obtained either by S_N2 type reactions[152] or by S_N1 type reactions in the presence of various silver salts ($AgBF_4$,[153] $AgNO_3$,[154] Ag_2CO_3[155]).

To test the applicability of these reactions, some experiments were performed with the iodoazoninone **[28a]**. Attempts using oxidative replacement gave no observable reaction, whereas medium nucleophiles resulted in elimination and chlorine-exchange reactions (Scheme 36).

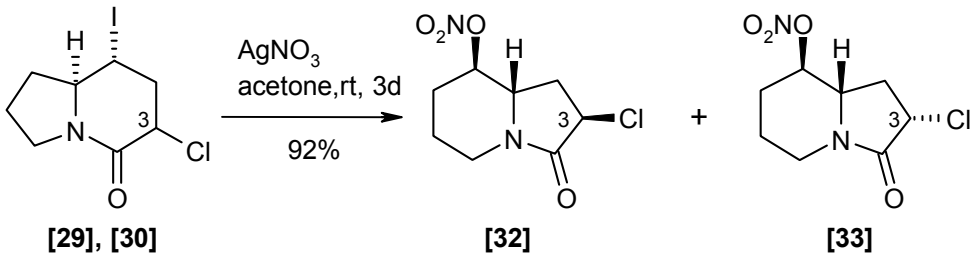


[28a]

Scheme 36 Attempts for I,O-substitution

The next reaction examined was a substitution of the alkyl iodide by silver salts. Due to the high affinity of Ag^+ and I^- a weak nucleophile is sufficient for this purpose. Using silver nitrate in acetone a smooth reaction was obtained to generate **[32]** and **[33]** in a high yield. According to mass spectra and NMR analyses the iodide was replaced by the nitrate ion. Indicated by analysis of IR-bands and later confirmed by an X-ray structure, suprisingly a change of the ring junction occurred. A five-membered lactam was stereoselectively formed. Since a diastereomeric mixture of 3-chloro-5-iodo-indolizidinones **[29]** and **[30]** was used, both diastereomers of the nitro-indolizidinones were obtained (Scheme 37).

[150] Askani, R.; Andermann,T.; Mueller, K. M. *Chem. Ber.* **1992** 125, 8, 1927-1938.
[151] Cambie, R. C.; Chambers, D.; Lindsay, B. G.; Rutledge, P. S.; Woodgate, P. D.; *J. Chem. Soc. Perkin Trans.* 1 **1980**, 822-827.
[152] Taguchi; E. *J. Am. Chem. Soc.* **1958**, 80, 4075-4078.
[153] Williams, D. R.; Osterhout, M. H.; McGill, J. M. *TetrahedronLett.* **1989**, 30, 11, 1331-1334.
[154] Cambie, R. C.; Hume, B. A.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1983**, 36, 12, 2569-2574.
[155] Kang, S. H.; Kim, G. T. *Tetrahedron Lett.* **1995**, 36, 28, 5049-5052.



[29], [30] **[32]** **[33]**

Scheme 37 Iodide-nitrate exchange reaction

The absolute configuration of the nitroindolizidinone **[32]** and the change of ring junction was proven by X-ray structure analysis (Fig. 18).[156]

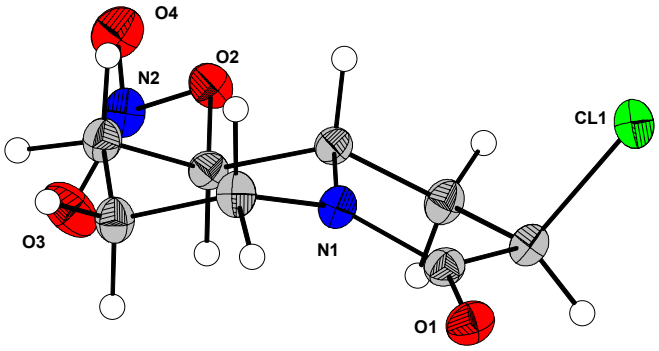


Fig. 18 Crystal structure of nitroindolizidinone **[32]**

A preliminary mechanistic explanation for the rearrangement of the indolizidine core is outlined in Scheme 38. According to a S_N1 type reaction, the electrophile Ag^+ ion attacks at the iodine substituent, leading to a cleavage of the C5-I bond followed by an attack of the nucleophilic nitrogen from the backside. Thus, an acylaziridinium ion is formed. After the reaction, the aziridinium ion is opened by the weak nitrate nucleophile, obviously in a regioselective manner, since no six-membered lactam could be isolated. The participation of an aziridinium ion during this reaction is reasonable, since this intermediate has been described in core rearrangements of indolizidines.[157] Alternatively, the origin of the regioselectivity could arise from a substitution mechanism including solvent separated ion pairs. However, no selectivity for the formation of a six-membered or a five-membered lactam has been obtained so far.[158] A potential influence of the acceptor group at the nitrogen should therefore be further studied in detail to determine the scope of this reaction.

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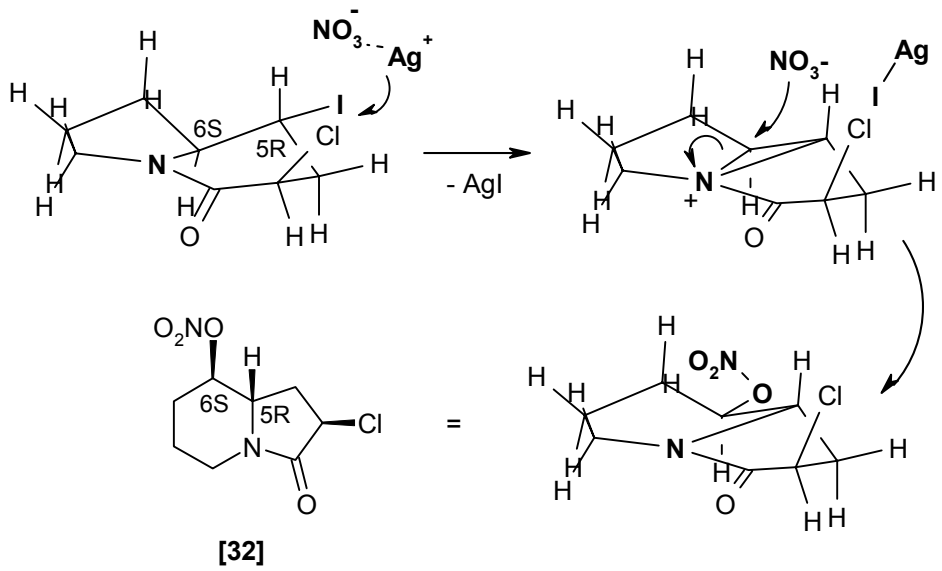
[156] Cambridge Crystallographic Data Centre (CCDC) ref. code no. 172938

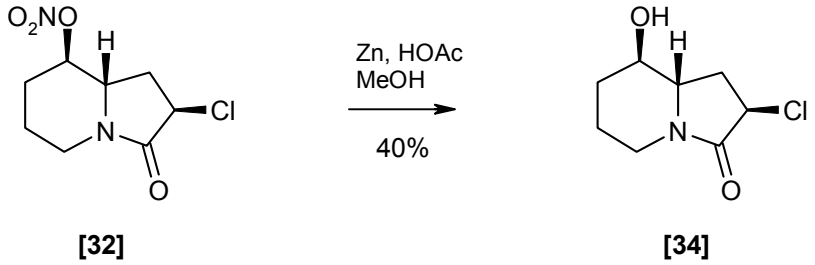
[157] (a) Iimura, Y.; Hotta, Y.; Fukabori, C.; Tadano, K.; Suami, T. *J. Carbohydr. Chem.* **1986**, 5, 147. (b) Furneaux, R. H.; Gainsford, G.; Mason, J. M.; Tyler, P. C.; Hartley, O.; Winchester, B. G. *Tetrahedron* **1995**, 51, 12611. (c) Furneaux, R. H.; Mason, J. M.; Tyler, P. C. *Tetrahedron Lett.* **1994**, 35, 3143.

[158] In monocyclic systems the conversion of pyrrolidines into sterically less strained piperidines has been reported, where in the course of these reactions aziridinium intermediates are included. For examples see: (a) Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante P. R.; Reider, P. J. *Tetrahedron Lett.* **2001**, 42, 6223-6225. (b) Cossy, J.; Dumas, C.; Pardo, D. G. *Eur. J. Org. Chem.* **1999**, 1693-1699. (c) Calvez, O.; Chiaroni, A.; Langlois, N. *Tetrahedron Lett.* **1998**, 39, 9447.



Scheme 38 Assumed mechanism of indolizidinone rearrangement during iodide-nitrate exchange

As a potential application of this new reaction, the synthesis of new hydroxy indolizidines should be pointed out. In a first test it was shown that the nitrate group in **[32]** can be selectively cleaved by a reductive method to generate the 6-hydroxy-indolizidinone **[34]** (Scheme 39). During this reaction the configuration of C-3 at the α-chloro atom was maintained.



Scheme 39 Formation of five-membered hydroxy indolizidinone **[34]** by nitro group reduction

However, the desired formation of six-membered hydroxy indolizidinones by substitution reactions of transannular cyclisation products was not successful. With the intention to convert azoninones into hydroxy indolizidinones further efforts were focused on cycloaddition reactions.

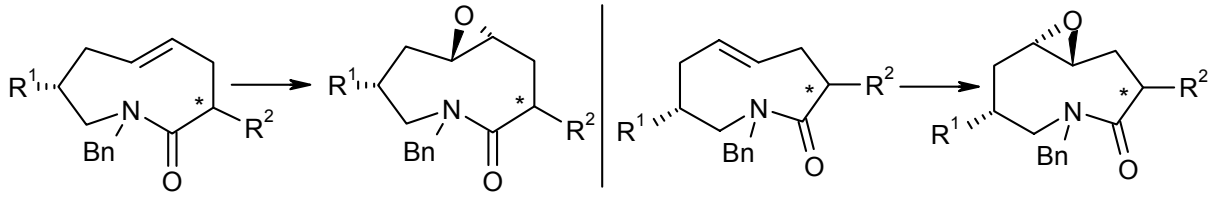
2.4 Cycloaddition Reactions of Optically Active Azoninones

The structure and the planar chiral properties of azoninones substantially influence the course of cycloaddition reactions. In analogy to transannular ring contractions the sterically shielding of one side of the (*E*)-double bond should lead to a stereospecific cycloaddition at the unshielded face. Considering the symmetrical substitution pattern of the double bond in the periphery, non-symmetrical cycloaddition reactions (1,3-dipolar cycloadditions) should cause the formation of a mixture of regioisomers. Since the investigation of stereospecific reactions with respect to the planar chiral properties of azoninones was desired, only symmetrical cycloadditions have been investigated. Furthermore, X-ray structures of azoninones revealed an additional important aspect for the course of cycloaddition reactions. The obvious deviation of the double bond from planarity (dihedral angles 153° instead of 180°) indicated the presence of a sterically strained reactive bond. This represents an important structural feature as it is known that strained double bonds often undergo cycloaddition reactions that are not observable with the unstrained analogues.[159]

In the following chapters the results of cycloaddition reactions with various azoninones are summarised.

2.4.1 Epoxidation Reactions

The epoxidation of the azoninones *pS* **[12a]-[17a]** and *pR* **[12b]-[14b]** in a buffered solution of m-chloroperbenzoic acid (mCPBA) succeeded with fairly high yields resulting in 5,6-epoxy azonanones (Table 10). The cycloaddition was always found to be diastereoselective because of an efficient and fast reaction, even at low temperatures (0-5°C) that mostly suppressed epimerisation (*pS*/*pR*).



[159] For a review on transition metal-mediated cycloaddition reactions see : (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, 96, 49-92.

Table 10 Results of epoxidation reactions

azoninone	scale	R^1	R^2	yield	azonanones (ratio) from *pS*	azonanones (ratio) from *pR*
***pS*-[12a]**	p	OTBS	Cl (β)	92%	**[35a]** - 1	-
***pS*-[13a]**	p	OTBS	Ph (β)	100%	**[36a]** - 1	-
***pS*-[16a]**	p	H	Cl (β)	90%	**[38a]** - 1	-
***pS*-[17a]**	p	H	Cl (α)	100%	**[39a]** - 1	-
***pR*-[12b]**	p	OTBS	Cl (β)	86%	[32a] - 1	**[35b]** - 20
***pR*-[13b]**	p	OTBS	Ph (β)	95%	[33a] - 1	**[36b]** - 6
***pR*-[14b]**	p	OTBS	OBn (β)	91%	-	**[37b]** - 1

The thermal isomerisation of planar chiral azoninones always provided mixtures of both isomeric forms, similarly the epoxidation of *pR*-azoninones also yielded mixtures of epoxy azonanones. In some cases a separation of the diastereomeric epoxides was difficult, although some purification could be achieved by HPLC or by recrystallisation of the products.[160] For the preparation of diastereomerically pure epoxides of *pR*-azoninones, a separation by HPLC of *pR* azoninones after the thermal isomerisation would be recommendable.

The relative configuration of the protons at C-5 and C-6 was always found to be *trans*, as proved beyond doubt by NOE analyses. The correct absolute configuration was confirmed independently by X-ray analyses of some azonanones (Fig. 19 and Fig. 20).[161]

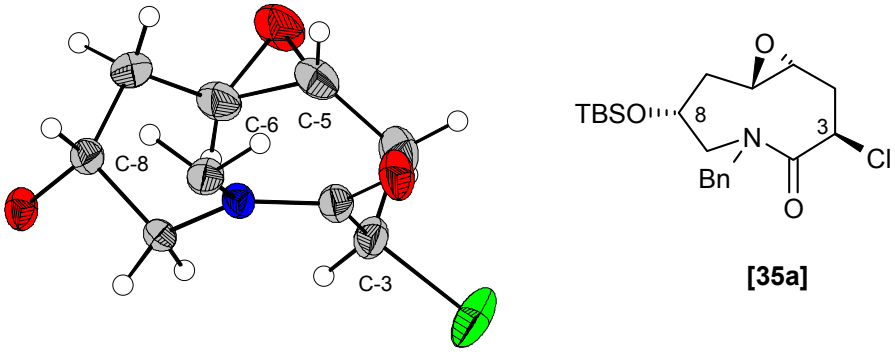


Fig. 19 Crystal structure of epoxy azonanones **[35a]**[162]

[160] HPLC separation or crystallisation was in some cases complicated by broadening of HPLC peaks or low crystallisation abilities due to the occurrence of amide-isomers.

[161] The absolute configuration was determined using the anomalous X-ray dispersion of the Cl or Si atoms located directly at the stereogenic centre C-2 and C-8 respectively. For a detailed discussion of anomalous X-ray dispersion see : Massa, W. *Kristallstrukturbestimmung*, 2. Aufl.; Teubner, Stuttgart, **1996**, p. 168-176.

[162] N-Bn and TBS-groups are omitted for clarity, for crystal data see Appendix; CCDC ref. code no. 145066 **[35a]**.

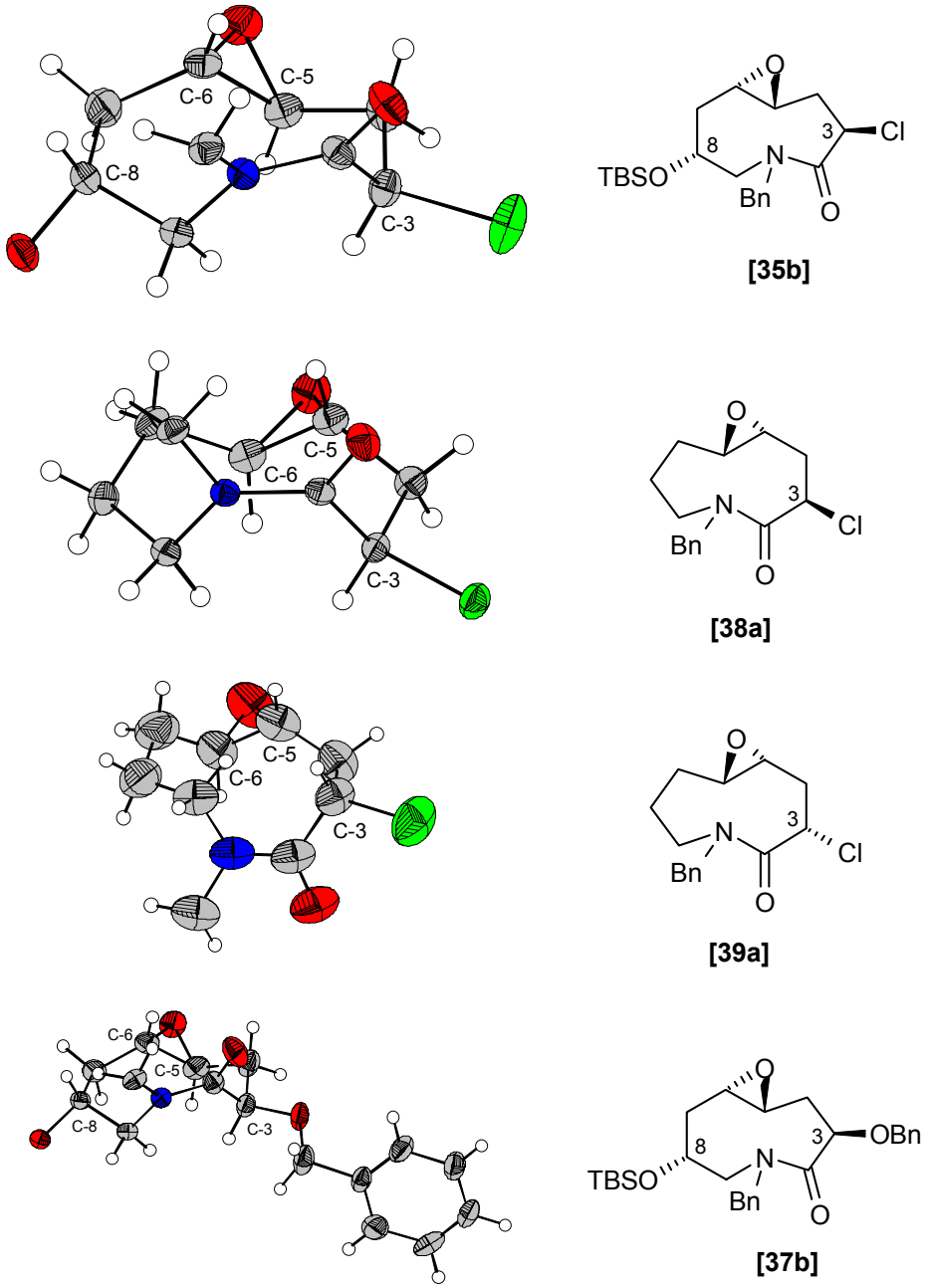


Fig. 20 Crystal structures of epoxy azonanones **[35b]**, **[38a]**, **[39a]** and **[37b]**[163]

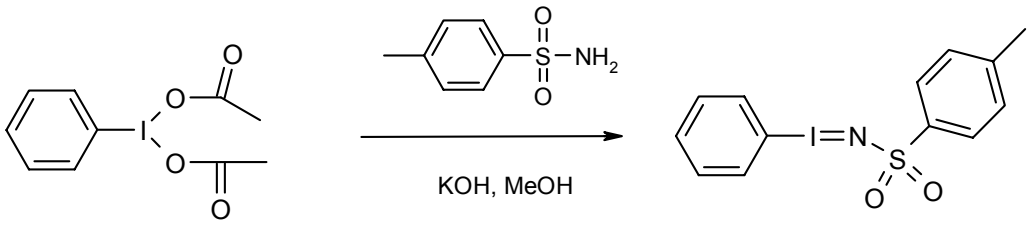
In analogy to unsaturated azoninones some epoxy azonanones showed the presence of amide isomers in solution. Particularly, the 3-chloro epoxy azonanone **[38a]** is characterised by the coexistence of two conformeric forms exhibiting a fast interconversion at room temperature. In the solid state only a single conformation is found. NOE measurements indicated the similarity of both conformations to conformations **A** and **B** (see 2.2.3) of the corresponding azoninones. Compared to the unsaturated

[163] In compound **[35b]** and **[37b]** the N-Bn and the TBS-group are omitted for clarity, for crystal data see Appendix; CCDC ref. code no. 145067 **[35b]**, 172936 **[38a]**, 172937 **[39b]**, 145068 **[37b]**.

precursor **[16a]**, the epoxide **[38a]** showed a different ratio of conformers (60% **A'**, 40% **B'**).[164] These conformations differ in transannular distances between N-C5 and C6 in analogy to unsaturated azoninones, respectively. From the X-ray structure of **[38a]** (example for conformation **A'**) a close proximity of N and C-5 was determined (N-C5 3.07 Å; N-C6 3.19 Å) whereas the X-ray structure of **[39a]** (example for conformation **B'**) showed a short distance between N and C-6 (N-C5 3.42 Å; N-C6 3.12 Å). Considering a desired epoxide opening reaction for the synthesis of hydroxy indolizidinones, these conformational equilibria have to be carefully considered, since an influence of amide isomers on the regioselectivity of transannular ring contractions is indicated by prior described studies.

2.4.2 Aziridination Reactions

In comparison to epoxidation, the preparation of 5,6-aziridino azonanones was found to be more difficult. The best reagent for the introduction of the nitrogen at low temperatures was found to be (N-(p-toluenesulfonyl)imino)-phenyl iodinane[165] as reported by Yamada.[166] During the investigation of aziridination reactions using this hypervalent iodine reagent[167] it was found that a successful reaction course strongly depends on the quality of the prepared imino phenyl iodinane. The reagent was freshly prepared by reaction of diacetoxy iodosobenzene with potassium p-toluenesulfonate in methanol (modification of the original procedure) as outlined in Scheme 40.[168]



Scheme 40 Preparation of N-(p-toluenesulfonyl)imino-phenyl iodinane

[164] Energy acc. MM-Plus optimisation for conformation A: 167. 26kcal/mol (N-C5 3. 21Å, N-C6 3. 23 Å); for conformation B: 169. 59 kcal/mol (N-C5 3. 41Å, N-C6 3. 07 Å) calculated for **[38a]**.

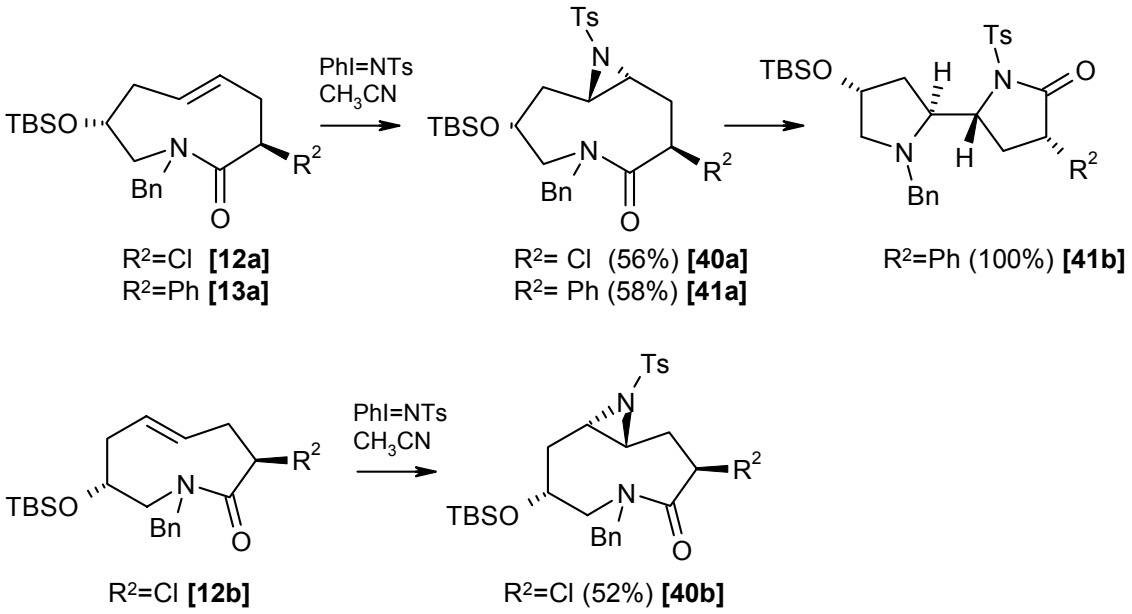
[165] For structural investigations of the reagent see: (a) Cicero, R. L.; Zhao, D.; Protasiewicz J. D. *Inorg. Chem.* **1996**, 35, 275-276. (b) Boucher, M.; Macikenas, D.; Ren, T.; Protasiewicz, J. D. *J. Am. Chem. Soc.* **1997**, 119, 9366-9376.

[166] (a) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361-362. (b) Besenyei, G.; Nemeth, S.; Simandi, L. I. *Tetrahedron Lett.* **1993**, 34, 6105. (c) Södergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1997**, 38, 6897.

[167] Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 8, 1271-1287.

[168] Reaction course strongly depended on the amount of methanol used, if the amount was too small the reactants did not dissolve, if the amount of methanol was too large (see Exp. Part) the product could not be precipitated by addition of ice water. Instead a hydrolysis of the iodinane to iodobenzene and tosylamide was observed. The instability of the reagent in methanol has also been reported by (a) Schardt, B. C.; Hill, C. L. *Inorg. Chem.* **1983**, 22, 1563-1565. (b) White, R. E. *Inorg. Chem.* **1987**, 26, 3916-3919.

The lactams ***pS*-[12a]**,**[13a]** and ***pR*-[12b]** were treated with the reagent in the presence of catalytic amounts of copper(II)triflate[169] resulting in the aziridines **[40a]**, **[40b]** and **[41a]**, respectively, as single diastereomers (Scheme 41). Although the reaction was found to be complete after 0.5-3 h according to TLC analyses, the yields obtained after aqueous workup were only moderate (50-60%). The N-tosyl aziridines were found to be unstable: azonanone **[41a]** decomposed completely after overnight storage at room temperature overnight; the major product generated was a five-membered ring lactam **[41b]**, which indicated a reorganisation of the bicyclic skeleton.



Scheme 41 Aziridination of azoninones

2.4.3 Cyclopropanation Reactions

Cyclopropanations were carried out using the procedure first described by Vorbrüggen *et al.*[170] The unsaturated olefins were treated with diazoalkanes in the presence of catalytic amounts of palladium(II)-acetate. Other catalysts ($Rh_2(OAc)_4$, $Cu(OTf)_2$) as well as other cyclo-propanation methods[171] (Simmons-Smith reactions) failed. The results of cyclopropanation reactions are summarised in Table 11.

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[169] (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, 56, 6744. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, 116, 2742. (c) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, 115, 5326. (d) Li, Z.; Quan R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, 117, 5889. (e) Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, 50, 11827.

[170] (a) Mende, U.; Radüchel, B.; Skuballa, W.; Vorbrüggen, H. *Tetrahedron Lett.* **1975**, 629-632. (b) Kottwitz, J.; Vorbrüggen, H. *Synthesis* **1975**, 636. (c) Suda, M. *Synthesis* **1981**, 714.

[171] For a review on metal catalysed cyclopropanation methods see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, 96, 49-92. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, John Wiley & Sons (New York), **1998**. (c) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, 54, 7919-7946.

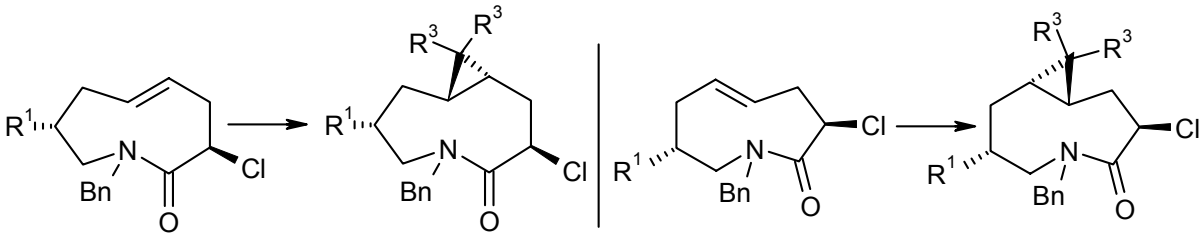


Table 11 Results of cyclopropanation reactions

entry	azoninone	reagent	scale	R^3	yield	azonanones - ratio	
						from *pS*	from *pR*
a	***pS*-[12a]**	CH_2N_2	p	H	92%	**[42a]** - 1	-
b	***pR*-[12b]**	CH_2N_2	p	H	96%	[42a] - 1	**[42b]** - 9
c	***pR*-[12b]**	$C(CO_2Et)_2N_2$	a	CO_2Et	30%	**[43a]** -2	**[43b]** - 3

The reaction of azoninones with diazomethane (entry *a*, *b*) and a catalyst proceeded with complete transformation of planar chirality into central chirality of the corresponding cyclopropanes. Epimerisation (*pS* ⇔ *pR*) did not occur, although the reaction time required was longer than in the epoxidation reactions (usually 1d, reaction temperature 23°C). A possible explanation for this stability[172] results from the TLC control of the reaction. Immediately after addition of the catalyst to reaction solution, the formation of an intermediate nonpolar product was observed that was completely transformed into the cyclopropane after 1 d reaction time. Presumably, the cycloaddition of diazomethane at first gave a pyrazoline that underwent rearrangement to a cyclopropane under loss of nitrogen.[173]

In contrast, the analogous cyclopropanation with diethyl diazomalonate[174] (entry *c*) as carbenoid precursor required a significantly higher reaction temperature of 65°C. The reaction of azoninone ***pS*-[12a]** led to formation of a mixture of diastereomeric 5,6-cyclopropano azonanones **[43a]** and **[43b]** in a 2:3 ratio. This indicated a partial epimerisation of ***pS*-[12a]** into ***pR*-[12b]** during the course of the reaction.

In the resulting methano-azonanones the relative configuration of the protons at C-5 and C-6 was always found to be *trans*, as proven by NOE analyses. These results were confirmed by X-ray analysis of **[42a]** (Fig. 21).

[172] Pure *pS*-azoninones showed a measurable epimerisation during storage at room temperature.

[173] Usually, these products are obtained in cycloadditions of unsaturated alkenes. For literature examples see: (a) Muray, E.; Alvarez-Larena, A.; Piniella, J. F.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2000**, 65, 388-396. (b) March, J. *Advanced Organic Chemistry*, J. Wiley & Sons, 4th ed. **1992**, p. 1045-1046 and references therein.

[174] Prepared from diethyl malonate and tosyl azide in acetonitrile acc. to : Regitz, M.; Liedhegener, A. *Chem. Ber.* **1966**, 99, 3128.

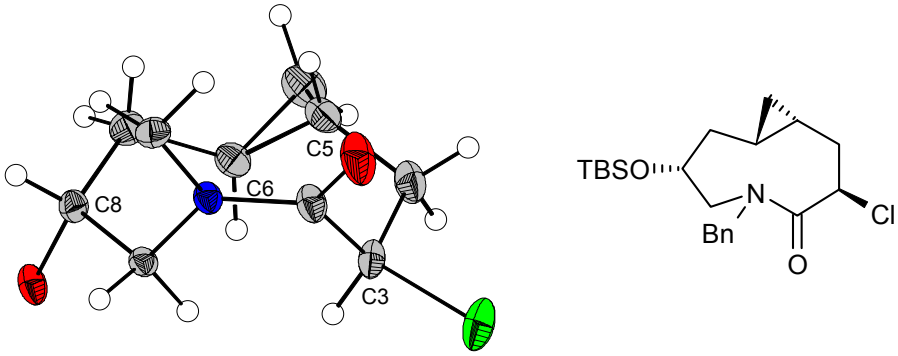
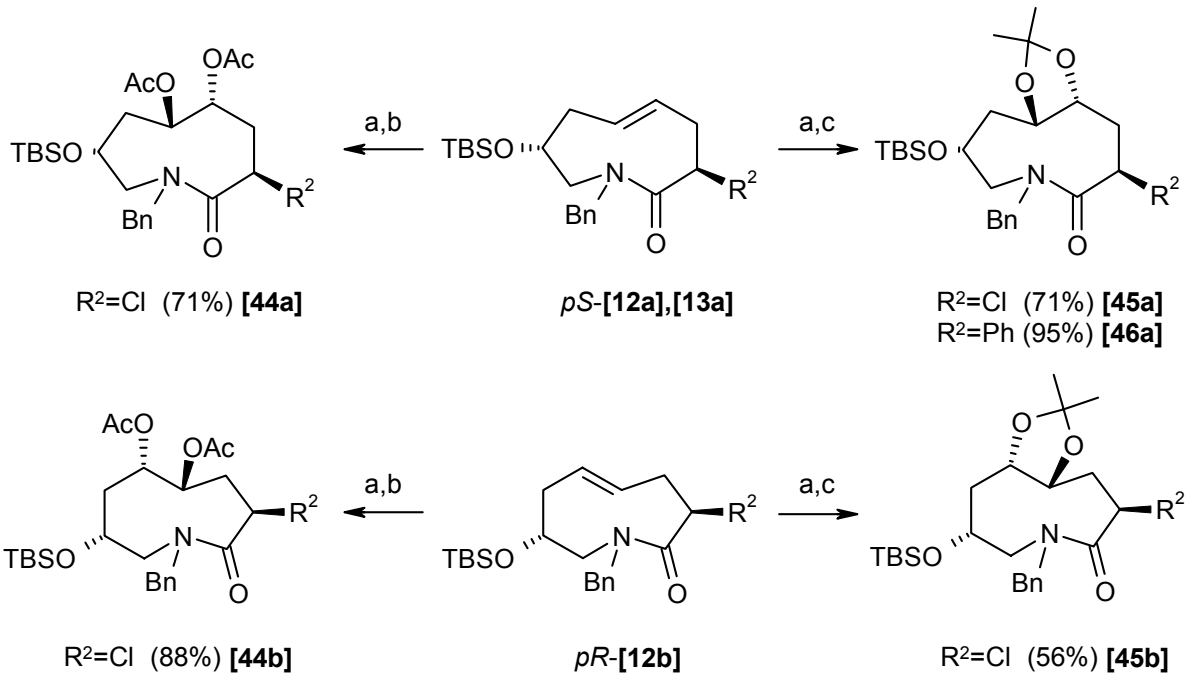


Fig. 21 Crystal structure of methano-azonanone **[42a]**[175]

2.4.4 Dihydroxylation Reactions

Furthermore, the conversion of planar chiral azoninones into dihydroxylated azonanones was investigated.[176] The introduction of two adjacent OH groups was performed by a procedure published by Shing.[177] Azoninones ***pS*-[12a]**, **[13a]** and ***pR*-[12b]** were treated with $NaIO_4$ in the presence of catalytic amounts of $RuCl_3$. After a short reaction time (5 min, 0 °C) dihydroxy azonanes were obtained diastereoselectively (Scheme 42). A purification of the polar diols and consecutive proof of their stereochemical properties by spectral analyses was difficult. Thus, the crude diols were immediately protected under standard basic conditions with Ac_2O resulting in 5,6-bisacetates **[44a]** and **[44b]**, and with dimethoxypropane in the presence of catalytic amounts of p-TsOH resulting in 5,6-acetonides **[45a]**, **[46a]** and **[45b]**, respectively.[178]

[175] N-Bn and TBS-group are omitted for clarity.
[176] Although during the course of a dihydroxylation a cycloadduct appears only as intermediate, this reaction type is discussed at this point.
[177] (a) Shing, T. K. M.; Tam, E. K. W.; Tai, V. W.-F.; Chung, I. H. F.; Jiang, Q. *Chem. Eur. J.* **1996**, 2, 50. (b) Shing, T. K. M.; Tai, V. W.-F.; Tam, E. K. W. *Angew. Chem.; Int. Ed. Engl.* **1994**, 33, 2312. (c) Shing, T. K. M.; Wan, L. H. *J. Org. Chem.* **1996**, 61, 8468-8479. (d) Shing, T. K. M.; Tam, E. K. W. *J. Org. Chem.* **1998**, 63, 1547-1554.
[178] (a) G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, 90, 602. (b) *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 569. (c) P. Garner, J. M. Park, *Org. Synth. Coll.* **1998**, 9, 300.



Scheme 42 Dihydroxylation reactions : (a) $RuCl_3$ cat., $NaIO_4$, H_2O, MeCN, EtOAc, 5 min, 0°C; (b) Ac_2O, Py, DMAP cat., CH_2Cl_2, RT, 3h; (c) $Me_2C(OMe)_2$, pTsOH cat., Me_2CO, RT, 3 h

Both protective-group insertions proceeded with moderate to high yields, the resulting products were easily to handle with regard to isolation and purification. Their spectroscopic behaviour strongly depended on the substitution pattern of the 5,6-dioxo-azonanones. The acetonides **[45a]** and **[46a]** and the diacetoxy-azonanone **[44a]** gave sharp signals in the ^{1}H-NMR spectra although the presence of different conformers was detected by NOE measurements. The extraordinary increase of flexibility that is achieved when the double bond in azoninones is converted to a single bond became evident in case of the azonanones **[44b]** and **[45b]**. At room temperature the NMR spectra were characterised by very broad peaks, which indicated a conformational mobility whereas at lower temperatures (T< -10°C) a double set of signals was observed.

The relative configuration of one of the conformations could be determined by NOE analysis, proving the complete diastereoselectivity of the dihydroxylation.

2.4.5 Conclusions

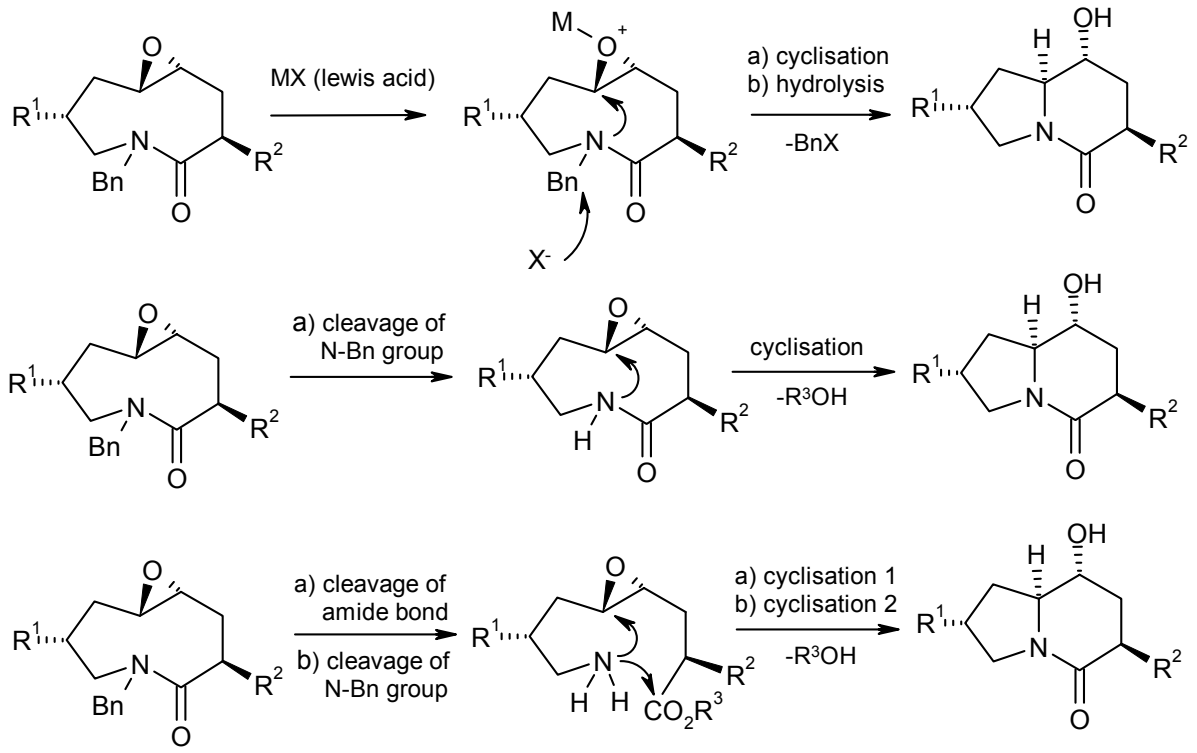
In addition to the investigated transannular ring contractions, cycloaddition reactions can also be applied to transform planar chirality of azoninones into central chirality. Low temperature methods for epoxidation, cyclopropanation, aziridination and dihydroxylation allowed this conversion with high diastereoselectivities. The resulting azonanones can be useful building blocks in organic synthesis, since the amide unit can be hydrolytically opened, providing a bifunctional aliphatic chain bearing a chiral epoxide, cyclopropane or two adjacent dihydroxy groups within the chain. Moreover, the stereoselective epoxidation of azoninones provides an access to the hydroxy indolizidinone core if an intramolecular epoxide opening by the amide nitrogen can be achieved.

The studies towards a synthetic method that allows the large scale preparation of bicyclic hydroxy indolizidinones as key compounds for total syntheses of indolizidines are introduced and discussed in the following chapter.

2.5 Synthesis of Hydroxy Indolizidinones by Ring Opening Reactions of Epoxy Azonanones

The two prior described studies have shown that planar chiral azoninones are versatile intermediates for the generation of new chiral centres. They can be stereospecifically converted into various indolizidinones or epoxy azonanones. Since all attempts to generate six-membered hydroxy indolizidinones by substitution reactions of suitable bicyclic products were unsuccessful, epoxide opening reactions of epoxy azonanones were investigated.

Three main strategies to generate hydroxy indolizidinones from epoxy azonanones are outlined in Scheme 43.

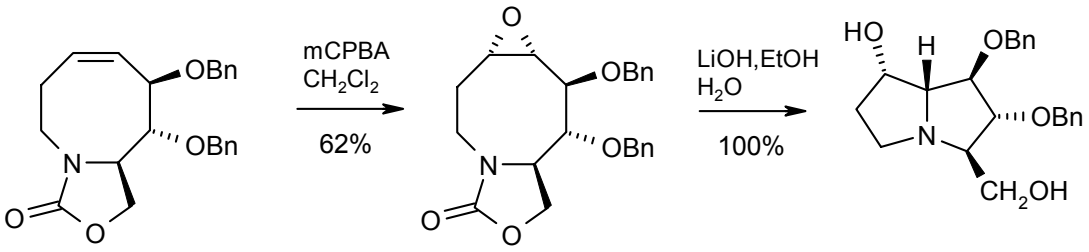


Scheme 43 Synthesis of hydroxy indolizidinones from epoxy azonanones

The first synthetic pathway involves the epoxide activation by a lewis acid (MX) generating an oxonium ion. The increased electrophilicity should lead to an intramolecular attack of the nitrogen atom and generation of an N-benzyl acylammonium intermediate. Then, the N-Bn group is cleaved by a nucleophilic substitution of the counterion X^-. This strategy is very similar to ring contraction reactions of azoninones, thus the factors that control regioselectivity of the cyclisation should be valid.

The second strategy starts with the removal of the N-protecting group preferentially by a reductive method. The nucleophilicity of the resulting secondary amide should be sufficient for an intramolecular epoxide opening without an additional activation. A promising evidence for the

generation of hydroxylated pyrrolizidine alkaloids starting from epoxy aza-cyclooctanes has recently been described by White.[179] An unsaturated aza-cyclooctene was stereoselectively converted into the epoxide.[180] After cleavage of the oxazolidinone group the nucleophilic nitrogen induces the transannular epoxide ring opening (Scheme 44).



Scheme 44 Epoxide opening reaction during the synthesis of australine by White [179]

The third synthesis envisioned to build-up hydroxy indolizidinones proceeds via a cleavage of the amide bond and a consecutive reduction of the N-Benzylamine. Numerous examples reported in the literature confirm a regioselective opening of the oxirane ring by the intermediately primary amine as expected from the Baldwin rules[195] (preference for a 5-exo-tet attack). After the initial cyclisation the pyrrolidine undergoes a second ring-closure to form an indolizidinone. This sequential strategy is one of the main methods applied for the construction of hydroxy indolizidinones starting from a primary amine.[181]

2.5.1 Lewis Acid Promoted Epoxide Opening

Due to the diastereoselective and regioselective course of transannular ring contractions of azoninones with electrophiles (PhSeBr, I_2, Br_2), a range of epoxy azonanones were treated with lewis acids with the intention to synthesise 5-hydroxy-azabicyclo[4.3.0]-nonan-2-one (8-hydroxy-indolizidin-5-one) compounds. Similar to numerous methods described for metal assisted enantioselective epoxide opening,[182] the synthetic conception included the activation of the epoxide with an electrophile

[179] (a) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, 120, 7359-7360. (b) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, 65, 9129-9142.

[180] The aza-cyclooctene adopts a half-chair conformation, in which one side of the double bond is shielded by the oxazolidinone group and the benzyloxy groups.

[181] (a) Nemr, A. E. *Tetrahedron* **2000**, 56, 8579-8629. (b) Kim, Y. G.; Cha, J. K. *Tetrahedron Lett.* **1989**, 30, 5721-5724. (c) Setoi, H.; Takeno, H.; Hashimoto, M. *J. Org. Chem.* **1985**, 50, 3948-3950. (d) Kim, N.-S.; Choi, J.-R.; Cha, J. K. *J. Org. Chem.* **1993**, 58, 7096-7099. (e) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, 61, 5546-5556.

[182] For a recent review on the enantioselective ring opening of symmetrical epoxydes, see (a) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, 52, 14361-14384. (b) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, 114, 2768. (c) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, 117, 5897. (d) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, 277, 936. (e) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem.; Int. Ed. Engl.* **1996**, 35, 1668. (f) Bonini, C.; Righi, G. *Synthesis* **1994**, 225.

(various lewis acids) to induce the intramolecular attack of the nitrogen atom. The results of lewis-acid mediated epoxide opening reactions are presented in Table 12.

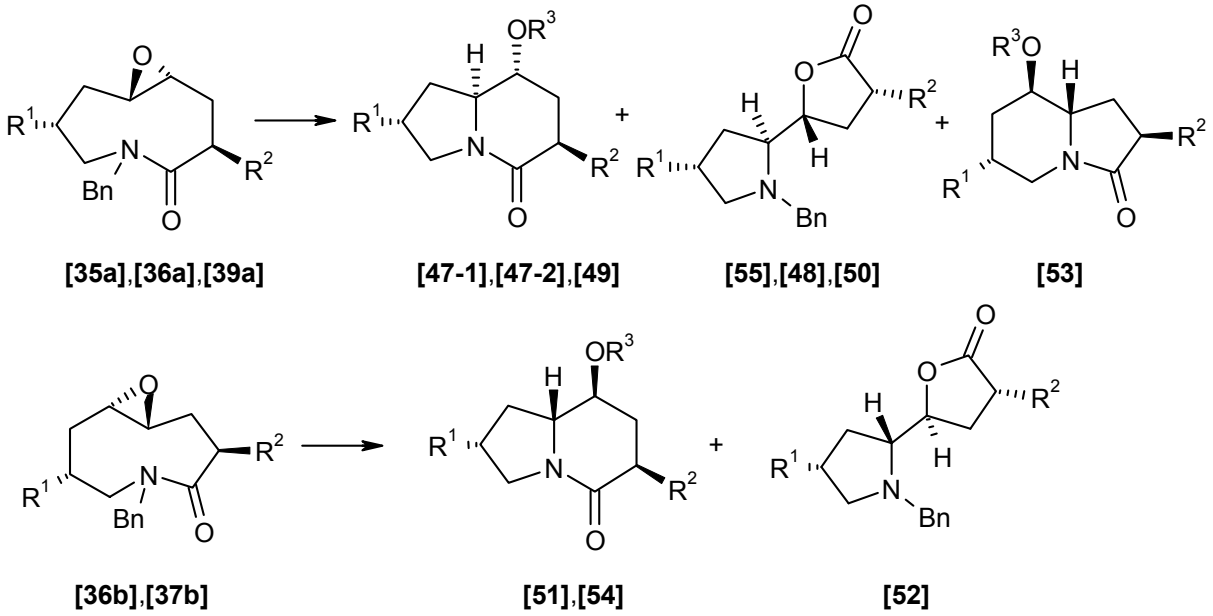


Table 12 Results of lewis acid epoxide opening reactions

entry compound		sc.	reaction conditions (lewis acid M-X)	R^1	R^2	R^3	product ratio (yield) indolizidinone lactone	(educt)	regioisomer
a	**[36b]**	a	a) BF_3*OEt_2,LiCl	TBSO	Ph	-	-	**[52]**	-
			b) Me_3Al, LiCl				-	**[52]** (**[36b]**)	
			c) LiCl				-	**[52]** (**[36b]**)	
			d) $TiCl_4$				-	**[52]**	
			e) $MgBr_2$*OEt_2				-	**[52]** (**[36b]**)	
			f) 10% HCl				-	**[36b]**	
			g) $AlCl_3$				-	-	
			h) Me_2AlCl				-	**[52]**	
b	**[35a]**	p	TMSCl, CH_2Cl_2, rt, 2h	TBSO	Cl	-	-	**[48]** (100%)	-
c	**[39a]**	p	TMSCl, CH_2Cl_2, rt, 2h	H	Cl	-	-	**[55]** (100%)	-
d	**[35a]**	p	TMSI, LiI, CH_2Cl_2, rt, <90s	TBSO	Cl	H	**[47-1]** (32%)*	**[48]** (>30%)	-
e	**[35a]**	a	TMSI, various reaction times and solvents	TBSO	Cl	OTMS	**[47-2]** (up to 47%)*	**[48]** (20-50%)	-
f	**[36a]**	p	TMSI, LiI, $CHCl_3$, rt	TBSO	Ph	H	**[49]** (28%)	**[50]** (15%)	-
g	**[36b]**	p	TMSI, LiI, $CHCl_3$, rt	TBSO	Ph	H	**[51]** (32%)	**[52]** (18%)	-
h	**[36a]**	p	TMSI, LiI, $CHCl_3$, -10°C	TBSO	Ph	H	-	-	**[53]** 19%
i	**[37b]**	p	TMSI, LiI, $CHCl_3$, -10°C	TBSO	OBn	H	**[54]** (57%)	(n.d.)	-

* C-3 chloro atom partially exchanged by iodide

In a first series of epoxide opening reactions various metal halogenides were used to activate the epoxy azonanones (entry *a*). Despite widely varying solvents, temperatures and reaction times,

mixtures of unreacted epoxy azonanones and lactones were always obtained. Although the formation of lactones indicated the desired epoxide opening, the removal of the N-benzylic group failed completely. Due to the known instability of epoxy azonanones under weak lewis acidic conditions[183] and the recovery of starting material in many cases, a slow decomposition reaction of epoxy azonanones under the reaction conditions was assumed to be responsible for the lactone formation. The formation of lactones indicated the existence of a nucleophilic oxygen during the course of the reaction (either O···Lewis acid or O-H formed during the workup). With the intention to exclude any lactone formation by trapping the nascent oxygen nucleophile as a TMS ether, the reaction of epoxy azonanones with trimethylsilyl halides was investigated (entries *b*-*i*). The reaction of epoxides with silyl halides normally results in the formation of halohydrines as reported in literature[184] due to a free intermediate halogenide ion. In the present case the halogenide ion should remove the N-benzylic group in a von-Braun type cleavage. However, the reaction with trimethylsilyl chloride (TMSCl) resulted in a fast and complete conversion of epoxy azonanones into the corresponding lactones (entry *b* and *c*). The use of trimethylsilyl iodide (in some cases combined with an additional iodide ion source such as LiI) finally resulted in the desired formation of hydroxy indolizidinones (entries *d*-*i*). The regioselectivity of the transannular epoxide opening should be influenced by factors similar to that observed in transannular ring contraction reactions (see 2.3). Indeed, using reaction conditions similar to method A (thermodynamic control, see chapter 2.3.1, page 59) the transannular epoxide opening reactions gave six-membered lactams as major products whereas under reaction conditions similar to method B (kinetic control) the formation of an regioisomer hydroxy indolizidinone (compound **[53]** entry *h*) was found. Although the amount of lactones formed in these reactions was lower, their formation could not be completely suppressed neither by changing the reaction conditions nor by additional ion sources.

Furthermore, the exhaustive use of halide ions caused some new side reactions. Particularly, the use of 3-chloro azonanones (entry *d*, *e*) led to a chloro-iodo-exchange reaction. In other cases (entry *i,* R^2= OBn) a cleavage of benzyl ethers occurred.[185]

In analogy to the transannular ring contractions of azoninones (chapter 2.3) the indolizidinones obtained by epoxide opening reactions are characterised by *trans* configurations of the protons at C-5 and C-6 (NOE). These results were confirmed by X-ray analysis of **[54]** (Fig. 22).

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[183] Some epoxy azonanones showed decomposition to the corresponding lactones during chromatographic purification on silica gel.

[184] (a) Andrews G. C.; Crawford T. C.; Contillo L. C. *Tetrahedron Lett.* **1981**, 22, 3803-3806. (b) Naruse, Y.; Esaki, T.; Yamamoto, H. *Tetrahedron* **1988**, 44, 4747. (c) Srebnik, M.; Joshi, N. N.; Brown, H. C. *Isr. J. Chem.* **1989**, 29, 229. (d) Joshi, N. N.; Srebnik, M.; Brown, H. C. *J. Am. Chem. Soc.* **1988**, 110, 6246. (e) Denmark, S. E.; Barsanti, P. A.; Wong, K. T.; Stavenger, R. A. *J. Org. Chem.* **1998**, 63, 2428. (f) For a review, see: Bhat, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249. (f) Bruns, S.; Haufe, G. *Tetrahedron* : *Asymmetry* **1999**, 10, 1563. (g) Reymond, S.; Brunel, J. M.; Buono, G. *Tetrahedron*: *Asymmetry* **2000**, 11 4441-4445. (h) Garrett, C. E.; Fu, G. C. *J. Org. Chem.* **1997**, 62, 4534-4535.

[185] These side reactions often prevented an upscaling of the reaction or required careful optimisation for changed reaction scales.

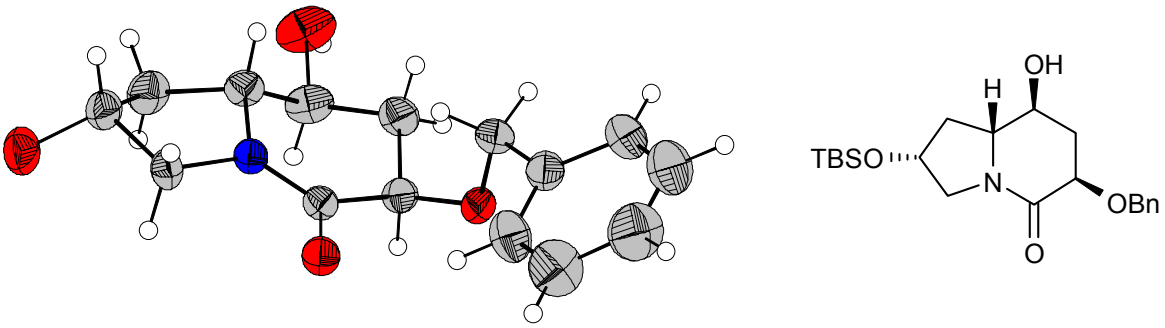
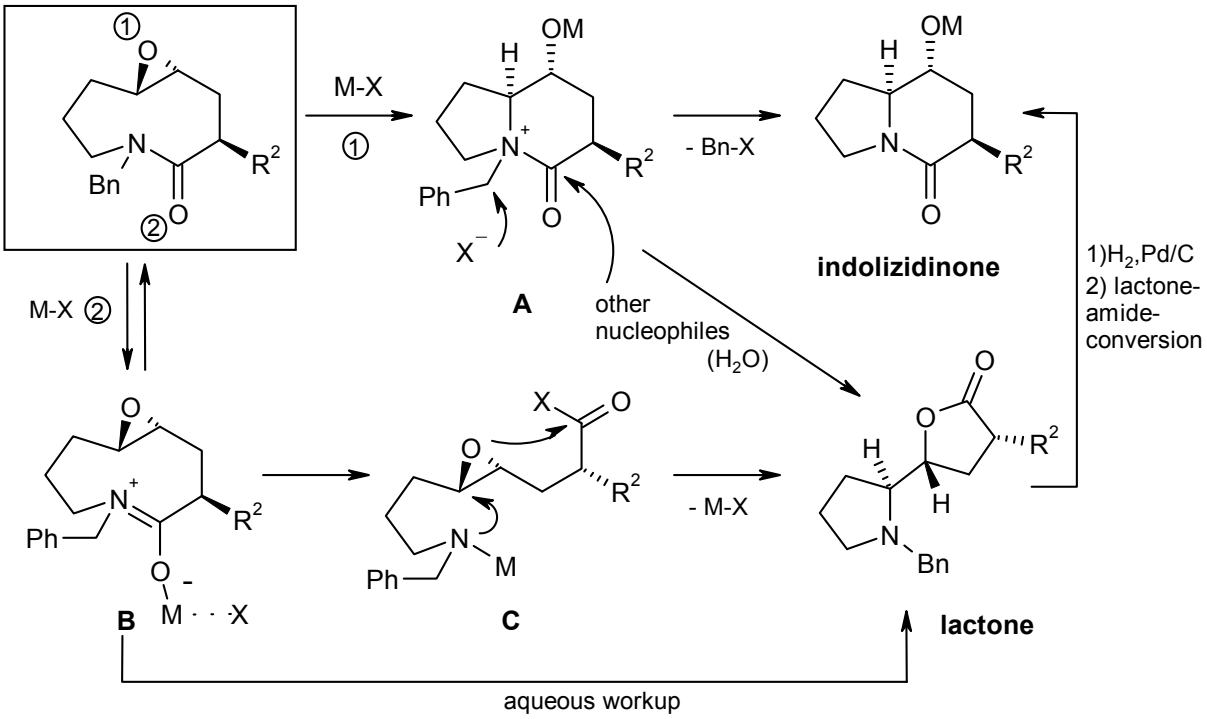


Fig. 22 Crystal structure of **[54]**[186]

Mechanistic discussion

A mechanistic model that explains both the formation of hydroxy indolizidinones and lactones during the reaction with lewis acids, is presented in Scheme 45.



Scheme 45 Mechanism of epoxide opening in azoninones by lewis acids

One potential reaction pathway includes the activation of the epoxide by a lewis acid (pathway 1) leading to an intramolecular attack of the nitrogen atom. If the intermediate acylammonium salt **A** is attacked by the nucleophile counterion at the benzylic position the hydroxy indolizidinone and a benzyl halide are formed. An alternative attack of a nucleophile (counterion X^- or oxygen atom of a different intermediate A) at the carbonyl group proceeds with formation of an acid halide. This acid

[186] The TBS group is omitted for clarity, for crystal data see Appendix.

halide easily reacts with the unprotected oxygen atom at C-5 leading to formation of the lactone and the lewis acid. The different reactivity with TMSCl and TMSI is observed due to the different strengths of Si-X bonds (Si-Cl: 406 kcal/mol,[187] Si-I: 293 kcal/mol[188]). The Si-I bond is quickly cleaved releasing the nucleophilic iodide ion, followed by the rapid cleavage of the N-benzylic group by a nucleophilic substitution reaction. In contrast, silyl chlorides caused no formation of chloride ions since no benzyl chloride was detectable. Instead, a stable intermediate may be formed that generates a N-benzyl lactone during the subsequent aqueous workup.

In addition to the desired epoxide activation by the lewis acid another important pathway that has to be included in mechanistic considerations is the reaction of the amide group with the lewis acid.

Although not completely proven yet, an alternative reaction mechanism may be considered for the formation of lactones: The nucleophilicity of the amide leads to a competing attack of the amide oxygen at the lewis acid[189] generating an iminium ion. A lactam opening by the corresponding nucleophile results in the formation of compound **C** containing a secondary amine and an acyl halide. The attack of the amine at the epoxide leads to the 5-exo ring opening and the formation of the lactone. Alternatively, an aqueous workup of the intermediate **B** also leads to the lactone via the hydrolysis of the activated amide. The observed quantitative formation of lactones from epoxy azonanones with TMSCl (entry *b*, *c*) supports the assumption that during this reaction no free chloride ions are present and silylation of the amide followed by hydrolysis represents a major pathway.

Summarising these results, transannular epoxide opening reactions employing lewis acids produced only low to moderate yields of the desired hydroxy indolizidinones. The competing formation of lactones and various other side reactions could not be suppressed. Although a stereoselective transformation could be developed that allowed an exclusive formation of pyrrolidine-lactones in high yields, a further utilisation of these lactones for the preparation of indolizidinones[190] would require additional steps (see Scheme 45). Since the cleavage of the benzylic group represents the crucial step during the epoxide opening, the attention was focused on reactions removing the N-Bn group prior to an epoxide opening. As discussed in chapter 2.5, a hydrogenolytic cleavage of the benzylic group would generate an amine that should be able to open the epoxide constructing the hydroxy

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[187] (a) Rajamanickam, N.; Dhuvaragaikannan, N.; Raja Mohamed, K.; *Acta Physica Hungarica* **1994**, 74, 385. (b) Venkataramanaiah, M.; Lakshman, S. V. J. *J. Quant. Spectrosc. Radiat. Transfer* **1981**, 26, 11.

[188] Huber, K. P.; Herzberg, G. *Molecular Spectra and Molecular Structure Constants of Diatomic Molecules*, Van Nostrand, New York, **1979**.

[189] This behaviour can be used for cleavage of amide bonds as reported by (a) Malpass, J. R.; Hemmings, D. A.; Wallis, A. L. *Tetrahedron Lett.* **1996**, 37, 3911-3914. (b) Kaiser, E.; Tam, J. P.; Kubiak, T. M.; Merrifield, R. B. *Tetrahedron Lett.* **1988**, 29, 303-306. (c) Lee, S. G.; Yoon, Y. J.; Shin, S. C.; Lee, B. Y.; Cho, S. D.; Kim, S. K.; Lee, J. H. *Heterocycles* **1997**, 45, 701-706. (d) Schmidt, A. H. *Aldrichim. Acta* **1981**, 14, 31-38. (e) Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc. Chem. Commun.* **1979**, 495-496. (f) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, 38, 2225. (g) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, 115, 3030. (h) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, 59, 2685.

[190] The intramolecular lactone opening represents a well established synthetic approach to indolizidinones. For literature see: (a) Nemr, A. E. *Tetrahedron* **2000**, 56, 8579-8629. (b) Rassu, G.; Carta, P.; Pinna, L.; Lucia B.; Zanardi, F.; Acquotti, D.; Casiraghi G. *Eur. J. Org. Chem.* **1999**, 1395-1400. (c) Hanessian, S.; McNaughton-Smith, G. *Bioorg. & Med. Chem. Lett.* **1996**, 6, 13, 1567-1572. (d) Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, 55, 8905-8914.

indolizidinone core. Employing such a sequence would allow the difficult nucleophilic substitution reaction to be skipped.

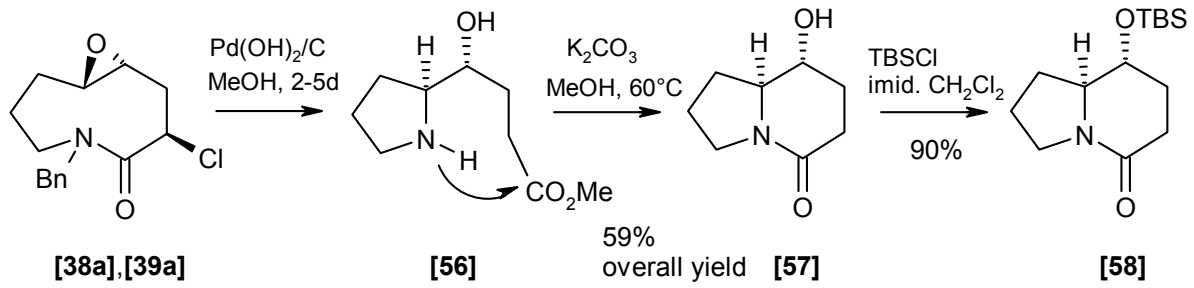
A hydrogenolytic approach towards hydroxy indolizidinones starting from epoxy azonanones is discussed in the following chapter.

2.6 Total Syntheses of Pumiliotoxins (Part I) - Preparation of the Bicyclic Core

2.6.1 Synthesis of Hydroxy Indolizidinones via Hydrogenation of Epoxy Azonanones

The removal of a lactam-N-benzyl group requires carefully chosen conditions. Generally, sequences using N-PMB (para-methoxybenzyl) protecting groups allow their easy removal by hydrogenation or oxidation with ceric ammonium nitrate (CAN)[191] and have been described in the literature. In the present case any access to the suitable epoxy azonanones turned out to be impossible. Such lactams were found to be very labile. A fast reorganisation generating the corresponding pyrrolidine lactones was observed (see preceding chapter).[192]

Thus, N-benzyl lactams were subjected to a range of hydrogenation conditions. Unfortunately, nearly all attempts to achieve the direct hydrogenolytic cleavage of the N-benzyl group failed. Only the hydrogenation performed in methanol with palladium(II)-hydroxide as catalyst caused the disappearance of the benzylic group as detected by ^{1}H-NMR spectroscopy. A very polar intermediate compound **[56]** was formed that additionally showed the presence of a methyl ester group and complete removal of the 3-chloro-substituent (Scheme 46).



Scheme 46 Synthesis of hydroxy indolizidinone **[57]** via hydrogenation method

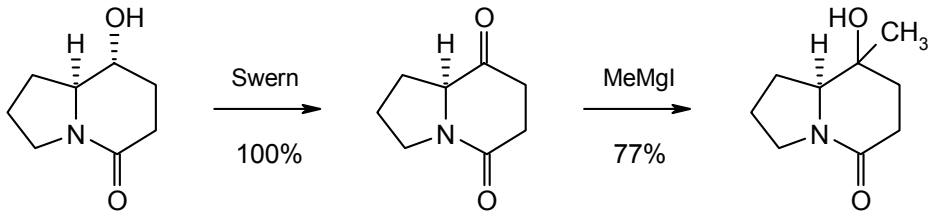
Heating of the intermediate pyrrolidine in the presence of potassium carbonate in methanol led to a cyclisation and the formation of the bicyclic hydroxy indolizidinone **[57]**. Protection of the hydroxy group provided the 5-TBSO substituted indolizidinone **[58]** with a high yield. Although the 3-chloro-substituent was reductively removed, this synthesis offered the advantage of being applicable in large scale preparations.[193] Crude epoxy azonanones[194] could be used without further purification and workup of the reaction required only filtration of solid reactants and catalyst. Additionally, the

[191] (a) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, **1999**.
[192] The preparation and epoxidation of N-PMB-azoninones are not described in this work, the procedures are identical to the preparation of N-Bn-azoninones.
[193] Epoxy azonanones can be used in 20g scale reactions.
[194] Usually, diastereomeric mixtures (substituent at C-3) of azoninones were subjected to epoxidation; in large scale preparations after epoxidation some chlorobenzoic acid remained in the crude product mixture.

intermediate lactam ring opening solved the problem of regioselectivity, because the nucleophilic epoxide opening reaction favours *5-exo-tet* processes rather than *6-endo-tet* cyclisations.[195]
The relative configuration of C-5 and C-6 of the hydroxy indolizidinone **[57]** was undoubtedly proven by NOE analysis.

2.6.2 Introduction of the Tertiary Stereogenic Centre

The formal total synthesis of pumiliotoxin alkaloids was completed by introducing the lacking methyl group at C-5. An oxidation-alkylation sequence appeared to be the method of choice to achieve this goal in a large scale reaction. The hydroxy indolizidinone **[57]** was converted to the tertiary alcohol **[60]** by an initial Swern oxidation to the ketone **[59]** followed by a Grignard-type nucleophilic introduction of the C-5 methyl group (Scheme 47). Although both reactions are standard transformations the reaction workup of the products required optimisation due to their high polarity (for details see Experimental Part).



[57] **[59]** **[60]**

Scheme 47 Synthesis of the tertiary alcohol **[60]** by Grignard addition

The Grignard reaction proceeded with a low diastereoface selectivity presumably due to the almost planar structure of the amido ketone **[59]**. A change in the methyl transferring reagent led to an inverted stereoselectivity of the addition which could be caused by different chelating abilities of MeMgI and MeLi (precomplexation of the magnesium at the amide or ketone moiety). The change of the reaction temperature did not influence the diastereoselectivity (Table 13). Unfortunately, the Grignard reaction (MeMgBr) was found to be incomplete. In all tests performed varying amounts of the ketone **[59]** were re-isolated that could be separated only after the final silylation step via HPLC.

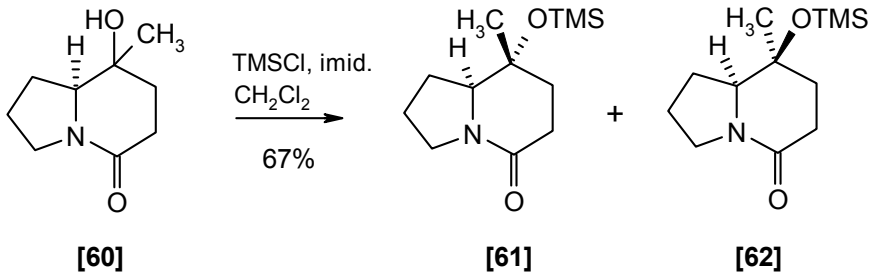
[195] (a) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734-738. (b) Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, 38, 2939.

Table 13 Diastereoselectivity of the C-5 methyl group insertion at various reaction conditions

entry	reactant	conditions	*syn* : *anti* *
a	MeMgBr (1eq)	4°C, THF	1.1:1
b	MeLi (5 eq)	-78°C, 3h, THF	1 : 1.6
c	MeMgI (5 eq)	-78°C, THF	2 : 1
d	MeMgI (6 eq)	0°C, THF	1.86 : 1

* determined by NMR analysis of small scale test reactions (50-100mg), the yields were not determined

Because of the high polarity the isomeric hydroxymethyl indolizidinones **[60]** were converted into the TMS-ethers, which could be separated by HPLC (Scheme 48). The correct relative configuration of **[61]** and **[62]** was proven by NOE analysis.



[60] **[61]** **[62]**

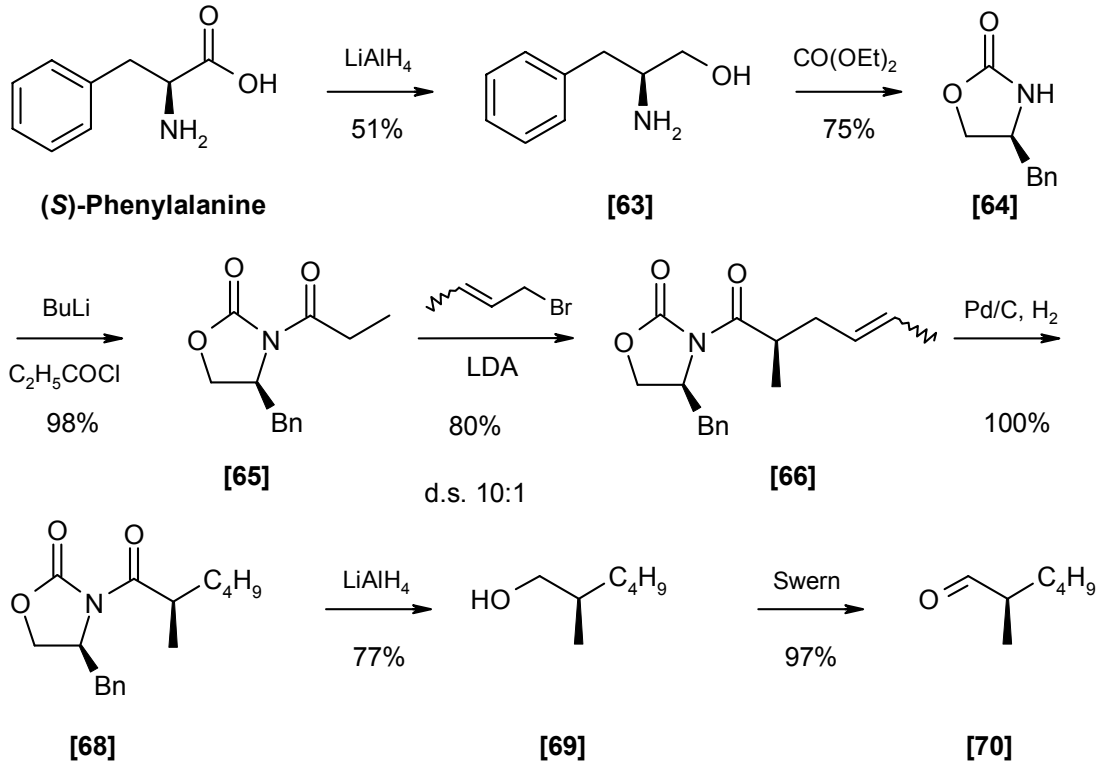
Scheme 48 Silylation of tertiary hydroxy indolizidinones

Considering the problems of the alkylation step (high polarity of the products, low diastereoselectivity), an alternative method for the C-5 introduction should be developed in the future. A synthesis proposal is outlined in the outlook (see 2.10, page 108).

2.7 Total Syntheses of Pumiliotoxins (Part II) - Synthesis of the Side Chain subunit

Focussing on the convergent total synthesis of (+)-pumiliotoxin 251D the second key fragment (*R*)-2-methyl hexanal has to be supplied. The Evans method has been described in the literature as the sequence of choice to generate aldehyde **[70]** in sufficient amounts (Scheme 49).[196] Originally, (*D*)-phenylalanine was used for the preparation of (*R*)-2-methylhexanol.[197] Since *D*-Phenylalanine is very expensive, an inversion of the alkylation sequence was necessary (introduction of C_1 unit preceding to the C_4 unit).

Starting with (*S*)-phenylalanine the acylated oxazolidinone **[65]** was prepared according to the literature over 3 steps.[198] The reduction of (*S*)-phenylalanine to **[63]** was followed by cyclisation to **[63]**. Acylation with propionyl chloride provided the acyl oxazolidinone **[65]** with a high yield.



Scheme 49 Synthesis of (*R*)-2-methylhexanal

Then, imide **[65]** was subsequently deprotonated with LDA and treated with butyliodide to obtain the alkylated oxazolidinone. Unfortunately, this alkylation failed because of the low nucleophilicity of the

[196] Evans, D. A.; Ennis, M.; Mathre, D. *J. Am. Chem. Soc.* **1982**, 104, 1737–1739.
[197] (a) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, 110, 2506. (b) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, 57, 1179. (c) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, 104, 1737. (d) Evans D. A.; Weber A. E. *J. Am. Chem. Soc.* **1986**, 6757-6761.

propionimide enolate and the weak acceptor character of the alkyl halide. Other attempts involving the more reactive butyl triflate[199] also proved unsuccessful. Finally, use of the more reactive crotyl bromide[200] resulted in the desired introduction of the C-4 chain with a good yield and a high diastereoselectivity (d.e. 10:1). The additional hydrogenation step was acceptable since this step to achieve **[66]** proceeded quantitatively. Reduction of **[68]** with $LiAlH_4$ provided (*R*)-2-methyl hexanol in a good yield. The spectral and optical data for **[69]** (α_D = +13.98°, c = 1.18, MeOH) were in accordance with that reported earlier.[201] (*R*)-2-methyl hexanal was prepared by Swern oxidation with a high yield in analogy to Overman *et al*.,[202] obtaining identical optical data for **[70]** (α_D = -19.95°, c = 1.12, $CHCl_3$).

[198] Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, 68, 77-82 and 83-89.

[199] (a) Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, 58, 7195-7203. (b) Williams D. R.; McGill J. M. *J. Org. Chem.* **1990**, 3457-3459. (c) Roeder *et al*. *Tetrahedron*: *Asymmetry* **1999**, 841-853. (d) Decicco C. P.; Grover P. *J. Org. Chem.* **1996**, 3534-3541.

[200] Many literature examples point out that unsaturated alkyl halogenides possess a higher reactivity towards the imide anion than the saturated derivatives. For examples see: (a) Santini, C.; Ball, R. G.; Berger, G. D. *J. Org. Chem.* **1994**, 59, 2261. (b) Evans D. A. *J. Am. Chem. Soc.* **1991**, 7615-7631. (c) Evans D. A.; Ennis M. D.; and Mathre D. J. *J. Am. Chem. Soc.* **1982**, 104, 1737-1739. (d) White J. D.; Johnson A. T. *J. Org. Chem.* **1994**, 3347-3358.

[201] (a) α_D = +13.2° (2.34, methanol) Karlsson, S.; Hedenstroem, E. *Acta Chem. Scand.* **1999**, 53, 620-630. (b) α_D = +14.5° (2.25, methanol) Mori, K.; Horikiri, H. *Liebigs Ann. Org. Bioorg. Chem.* **1996**, 4, 501-506.

[202] (a) Caderas, C.; Lett, R.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; *J. Am. Chem. Soc.* **1996**, 118, 9073-9082. (b) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, 57, 1179-1190. α_D = -19.7° (c = 5.8, $CHCl_3$).

2.8 Total Syntheses of Pumiliotoxins (Part III) - Aldol approach

After the preparation of the bicyclic core of pumiliotoxin alkaloids and the side chain, two remaining synthetic problems had to be solved:

- introduction of the side chain controlling exocyclic alkene geometry
- removal of the lactam C=O group

The first objective was to introduce the basic carbon framework of the side chain and the use of a stereospecific elimination step to control the alkene geometry. Finally, the lactam unit should be selectively reduced. Since the introduction of the C-5 methyl group only proceeded with a low diastereoselectivity, an alternative approach was investigated. Starting from a bicyclic lactam with the established alkylidene side chain the conversion of the C-5-OH group into the tertiary alcohol via an oxidation-alkylation approach was explored concerning a higher stereoselectivity.

Compared to the syntheses of α,β-unsaturated acid derivatives such as esters, reports regarding the preparation of α,β-unsaturated amides are scarce. Some synthetic strategies for the generation of α,β-unsaturated amides from cyclic amides are summarised in Scheme 50.

Since the target is the thermodynamically disfavoured (*Z*)-alkylidene lactam, highly efficient reactions are required to control the alkene geometry.

Unfortunately, the loss of the α-chlorine substituent during the reductive cyclisation of epoxy azonanones **[38a]** and **[39a]** resulted in the initially envisaged Boord-[203] and Darzens[204] reactions being less efficient. The re-introduction of the C-3 halide would have been necessary for the stereospecific elimination generating the double bond.

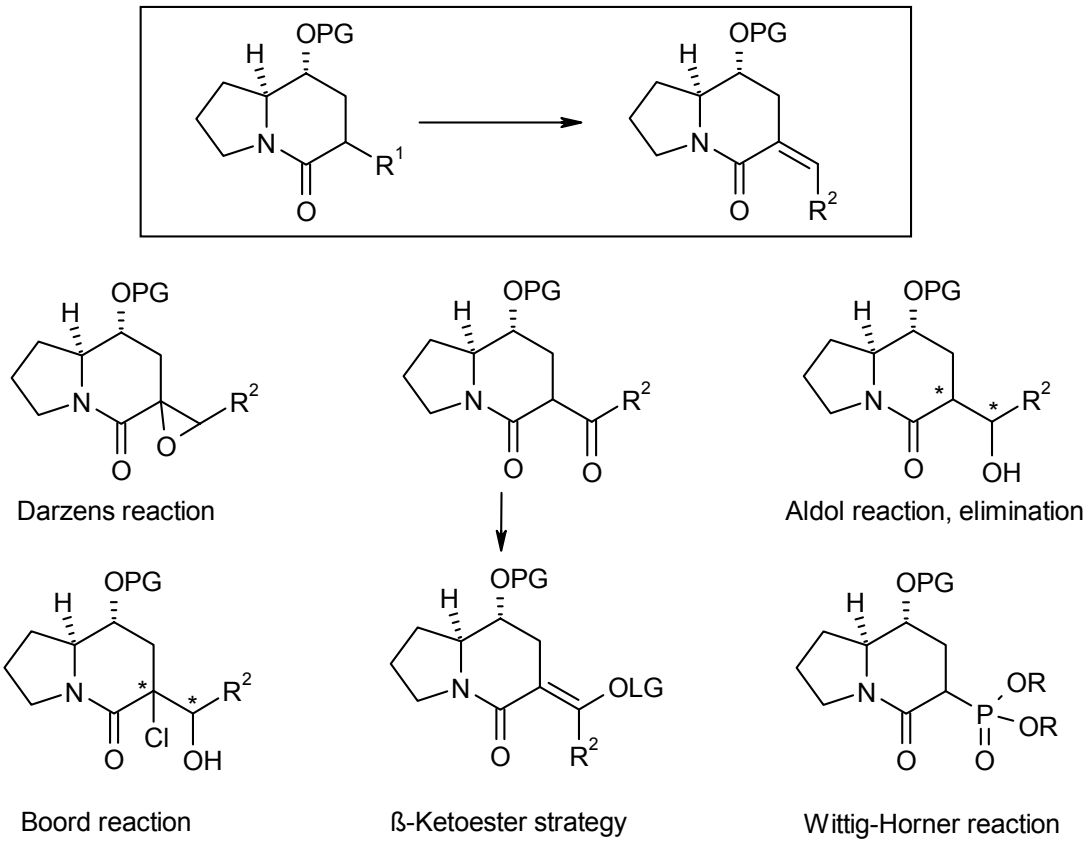
Alternatively, the introduction of the side chain can be achieved by the condensation of an amide enolate and an ester generating a β-keto amide. Transformation of the β-keto function into an enolate bearing the correct double bond geometry can be performed using phosphoric esters (OLG = $OP(OR)_2$).[205] In such reactions the formation of the (*E*)-enol phosphate enolate is favoured due to a steric strain between the amide carbonyl group and the substituent at the enolate. Furthermore, a reductive removal of the leaving group should lead to the generation of the correct (*Z*)-alkylidene framework.

---

[203] (a) SmI_2 induced elimination of α-chloro-β-hydroxy ketones: Concellôn, J. M.; Pérez-Andrés, J. A.; Rodríguez-Solla, H. *Chem. Eur. J.* **2001**, 7, 14, 3062-3068.

[204] for a review see: Arai, S. *Tetrahedron* **1999**, 55, 6375-6386.

[205] (a) Kozenasheva, L. Y.; Balaev, A. N.; Krylova, T. O.; Vasyanina, L. K.; Kurkovskaya, L. N. *J. Gen. Chem. USSR (Engl. Transl.)//Zh. Obshch. Khim.* **1992**//**1992**, 62//62, 1471-1476//1790-1796. Kozenasheva, L. Y.; Smirnova, T. V.; Kolesova, V. A.; Virin, L. I.; *J. Gen. Chem. USSR (Engl. Transl.)//Zh. Obshch. Khim.* **1983** //**1983**, 53//53, 830-831//943-944.



Scheme 50 Strategies and intermediates for the synthesis of α,β-unsaturated amides

The aldol methodology offered another approach to establish the (*Z*)-alkylidene geometry. The efficient construction of the exocyclic alkene requires the diastereoselective formation of *syn* or *anti* aldol adducts. The stereospecific *syn* or *anti* elimination, depending on the aldol products, results in a selective formation of the (*Z*)-alkylidene unit if an isomerisation of the exocyclic double bond could be excluded under the reaction conditions. In the particularly case of *anti* eliminations this prerequisite is difficult to achieve because these reactions are known to be less efficient (see Scheme 5, page 8).

Furthermore, the use of α-phosphono amides to introduce the alkene unit via a Horner type reaction is promising. The olefin could be directly build-up without the formation of intermediates with two additional stereogenic centres. In the literature one example of such a reaction is described[206] delivering an equimolar mixture of *cis* and *trans* olefins. Considering the progress in synthesising olefin units employing special phosphonates described by Ando[207] and Still,[208] an investigation into the applicability of a such reaction type appeared to be most practical.

[206] Tay, M. K.; About-Jaudet, E.; Collignon, N.; Savignac, P. *Tetrahedron* **1989**, 45, 4415-4430.
[207] (a) Ando, K. *J. Org. Chem.* **1997**, 62, 1934-1939. (b) Ando, K. *Tetrahedron Lett.* **1995**, 36, 4105-4108. (c) Ando, K. *J. Org. Chem.* **1998**, *63,* 8411-8416.
[208] Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 24, 4405-4408.

2.8.1 Attachment of the Side Chain by Aldol Addition

The first attempt to introduce the side chain was performed according to the aldol methodology. The disadvantage of the aldol attachment described by Gallagher[214] (see Scheme 5, page 8) was the obtainment of a mixture of three different aldol adducts. One isomer (27% yield) was separated and subjected to a *syn* elimination using DCC and Cu(I)Cl. The (*Z*)-alkylidene product was obtained in a yield of 98%. The remaining inseparable mixture was incorporated in an *anti* elimination sequence (CH_3SO_2Cl, KOH) leading to a 2.6:1 mixture of (*E*)- and (*Z*)-isomers (73% combined yield). Since the configuration of the aldol adducts was not determined, any stereospecifity of the *anti* elimination sequence remains speculative. However, a comparison of several studies concerning the stereospecifity of elimination reactions with cyclic amides indicated that a smooth *anti* elimination is difficult to achieve.[209] Most of the reaction conditions (TsOH-benzene, DBU-benzene, MsCl-DMAP, DMAP-Ac_2O-Py, DBU-MsCl, NaOMe, NaOAc-DMF) provided the thermodynamically stable (*E*)-alkenes independent of the *anti* or *syn* aldol reactants involved. A stereospecific *anti* elimination has been reported only for $NaHCO_3$-MeOH.[210] In contrast, efficient dehydration reactions including a stereospecific *syn* elimination are well-known, the mostly used reaction conditions are $CuCl_2$ - DCC[211] or $CuCl_2$ - EDC.[212] Thus, the prospects for a selective generation of the (*Z*)-alkylidene side chain primarily depended on the stereocontrol of the aldol reaction.

A thorough analysis of the reaction performed by Gallagher allowed the following benchmarks to be set. For the aldol reaction employing tertiary alcohol **D-3**, 2 eq of LDA were required do generate the dianion. This excess of base is unfavourable because of a potential epimerisation of the chiral aldehyde applied. Furthermore the obtained dianionic aldol intermediate potentially caused a retro-aldol reaction as detected by a decreased conversion of the reactant **D-3** (only 70%) into the aldol-adducts **D-4**. Finally, the mixture of *syn* and *anti* aldol products **D-4** obtained required an additional separation step, to isolate the *syn*-diastereomer. The majority of the remaining aldol products could only be nonselectively transformed into the corresponding alkylidene products **D-5** providing a mixture of the (*E*)- and (*Z*)-alkenes.

In view of these results the bicyclic amide **[58]** was chosen as reactant for the aldol reaction. Since the hydroxy group at C-5 was protected as silyl ether only 1 eq of base should be sufficient to effect the required transformation. Additionally, because of the different substrate structures[213] of indolizidin-

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[209] Usually, addition-elimination reactions led to a complete conversion into the (*E*)-isomer. For references see : (a) Norman, B. H.; Kroin, J. S. *Tetrahedron Lett.* **1995**, 36, 4151-4154. (b) Norman, B. H.; Kroin, J. S. *J. Org. Chem.* **1996**, 61, 4990-4998.

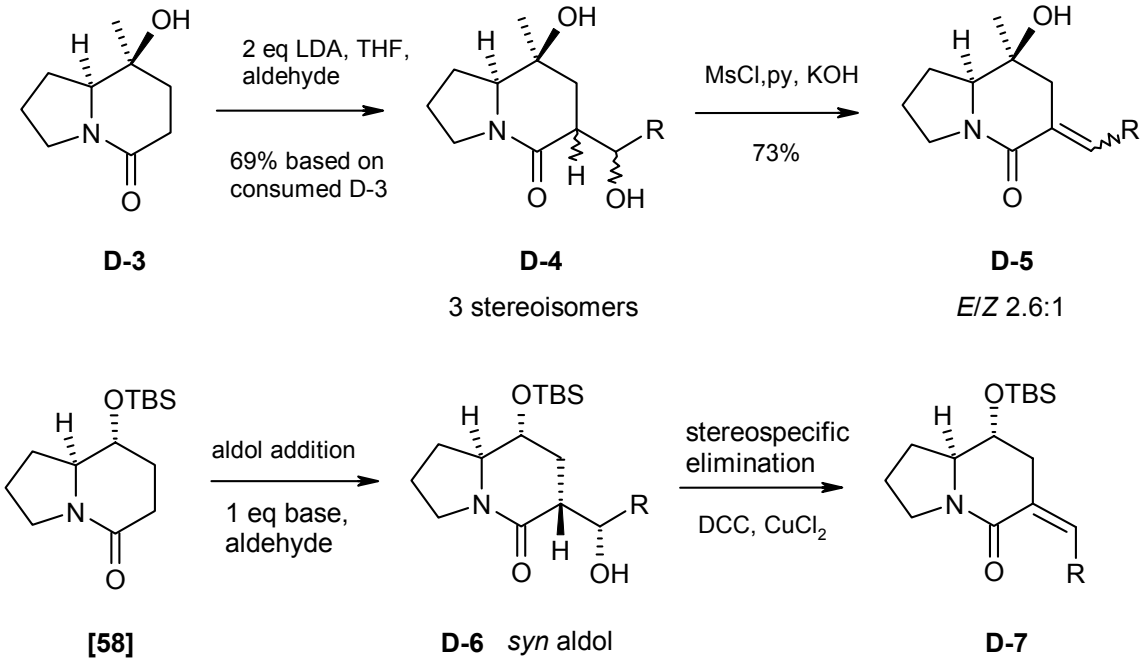
[210] (a) Bouffard, F. Aileen; Johnston, David B. R.; Christensen, Burton G. *J. Org. Chem.* **1980**, 45, 1130-1135. (b) Sunagawa, M.; Matsumura, H.; Enomoto, M.; Inoue, T.; Sasaki, A. *Chem. Pharm. Bull.* **1991**, 39, 1931-1938. (c) Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, 109, 1129-1135.

[211] (a) Corey E. J.; Andersen N. H.; Carlson, R. M.; Paust, J.; Vedejs, E.; Vlattas I.; Winter, R. E. K. *J. Am. Chem. Soc.* **1968**, 90, 3245-3247. (b) Alexandre C.; Rouessac F. *Bull. Soc. Chim. Fr.* **1971**, 1837. (c) Corey, E. J.; Letavic, M. A. *J. Am. Chem. Soc.* **1995**, 117, 9616-9617.

[212] Sai, H.; Ohmizu, H. *Tetrahedron Lett.* **1999**, 40, 5019-5022.

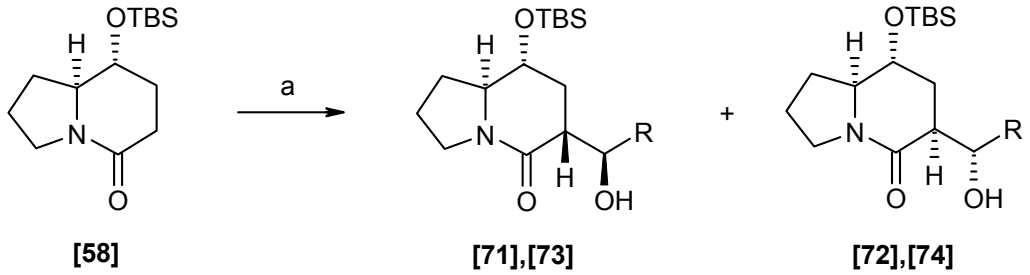
[213] Compound **[58]** represents a less sterically demanding alcohol (equatorial position of the TBSO group).

one **[58]** and the hydroxy indolizidinone **D-3** used by Gallagher *et al.*[214] it was speculated that a different stereochemical course of the aldol reaction could be observed. This could provide the necessary *syn*-aldol **D-6** (Scheme 51) that should be stereospecifically converted into the (Z)-alkylidene amide **D-7**.



Scheme 51 Planned synthesis for the side chain introduction by aldol addition-elimination compared to the approach of Gallagher *et al.*

With the intention to test the aldol sequence, reactions of **[58]** with isobutyraldehyde and (*R*)-2-methyl hexanal were investigated (Scheme 52). The results of aldol additions are summarised in Table 14.



Scheme 52 Aldol addition: (a) 1 eq LDA -78°C, THF, aldehyde

[214] Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, 113, 2652-2656 (same reference as ref. [25]).

Table 14 Test aldol reactions performed on an analytical scale

entry	R	formation of enolate	reaction time with aldehyde	isolated yield	product ratio **[product]**	educt
a	$CH(CH_3)_2$	1 eq LDA, 1h -78°C	3h, -78°C to -60°C (4 eq aldehyde)	27%	1.4:1 **[71]**,**[72]**	58%
b	$CH(CH_3)_2$	1 eq LDA, 3h -78°C	3h, -65°C to -30°C (4 eq aldehyde)	17%	1.5:1 **[71]**,**[72]**	n.d.
c	$CH(CH_3)_2$	1.5 eq NaHMDS, 3h -30°C to -20°C	3h, -78°C to rt (4 eq aldehyde)	-	-	n.d.
d	$CH(CH_3)_2$	1.5 eq LiHMDS, 3h -78°C	3h, -78°C to rt (4 eq aldehyde)	16%	1.3:1 **[71]**,**[72]**	n.d.
e	$CH(CH_3)C_4H_9$	1.1 eq LDA, 30min -78°C	20min -78°C (2eq aldehyde)	32%	1:1:0.5 **[73]**,**[74]**,**[75]**	60%
f	$CH(CH_3)C_4H_9$	1.1 eq LDA 15min -78°C	20min -78°C (2eq aldehyde)	45%	1.1:1:0.16 **[73]**,**[74]**,**[75]**	n.d.
g	$CH(CH_3)C_4H_9$	1.1 eq LDA 1h -78°C	20min -78°C (2 eq aldehyde)	31%	1:1:0.5 **[73]**,**[74]**,**[75]**	n.d.

n.d. = not determined

In all cases the isolated yields were low and varying amounts of the educt indolizidinone **[58]** was re-isolated. Neither changes of reaction time and reaction temperature nor a variation of the base applied led to an increased yield of aldol adducts. Since the incomplete formation of the amide enolate can be excluded (kinetic deprotonation, excess of base), the *retro* aldol reaction appears to be responsible for the re-isolation of the educt.

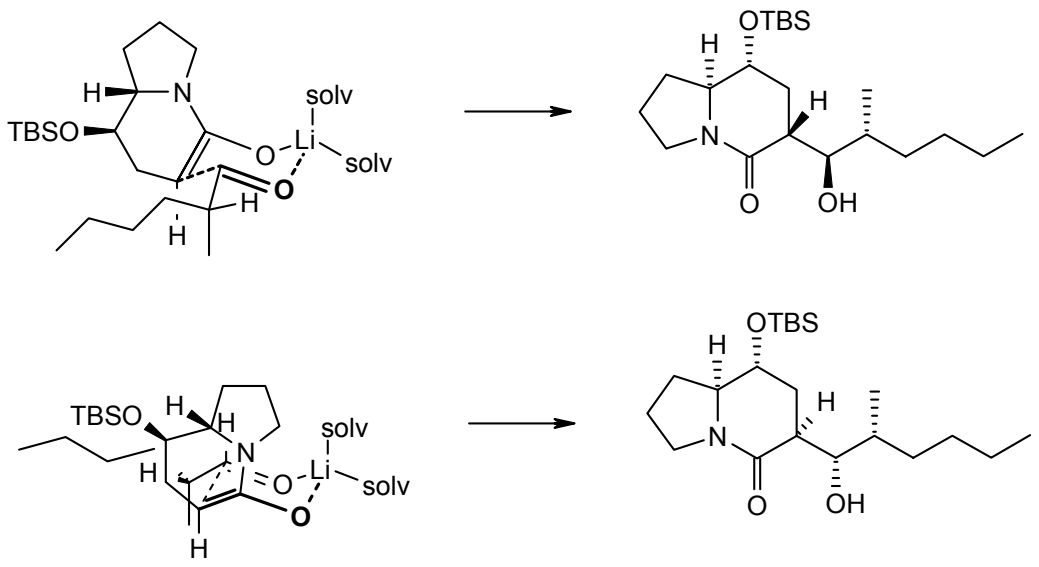
Considering the stereochemical course of the reaction, all tests performed showed the exclusive formation of two *anti*-aldol products. In the case of reactions employing (*R*)-2-methyl hexanal as aldehyde a third minor diastereomer was isolated, the exact configuration could not be determined.[215]

A plausible reaction mechanism to explain the formation of the *anti*-isomers is given in Scheme 53. Deprotonation of the cyclic amide **[58]** build-up the (*E*)-enolate, which undergoes aldol-addition via a Zimmermann-Traxler[216] chairlike transition state. The lack of diastereoface selectivity arose from the planarity of the bicyclic amide and the weak stereodirecting properties of the TBSO group adopting an equatorial position.[217]

[215] NOE enhancements of **[75]** suggest that the configuration of **[75]** and **[73]** are identical but with an inverted methyl group in **[75]**.

[216] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, 79, 1920.

[217] For an analogous observation, where a large Ph substituent had no effect of the diastereoface selectivity in an aldol reaction see : Beard, M. J.; Bailey, J. H.; Cherry, D. T.; Moloney, M. G.; Shim, S. B.; Statham, K.; Bamford, M.; Lamont, R. B. *Tetrahedron* **1996**, 52, 3719-3740 and corrigenda *Tetrahedron* **1997**, 53, 1177.



Scheme 53 Mechanism of aldol addition with (*R*)-2-methyl hexanal

The *anti*-configuration of the aldol products **[71]-[74]** was proven beyond a doubt via NOE analyses since the strong hydrogen-bridge between the carbonyl group and the hydroxy group reduces the conformational flexibility of the side chain.[218]

At this point further investigations or optimisation of the aldol-pathway were stopped because of the reasons given below:

- In all test reactions the aldol reaction - *retro* aldol equilibrium was trapped with low conversion of the reactant resulting in unacceptable low yields of the aldol products.
- The exclusive formation of *anti*-aldol products reduces the prospects for a successful preparation of the (*Z*)-alkylidene subunit by a subsequent stereospecific elimination because *anti*-eliminations are reported to be problematic.
- The strong basic reaction conditions resulted in a partial epimerisation involving the chiral aldehyde.

Recently, Santos and Pilli have described the application of a Mukayiama aldol reaction to introduce the side-chain in the Homopumiliotoxin series (see also Scheme 6 page 9).[219] The aldol reaction of a N,O-silylketene acetal **E-4** and isobutyraldehyde catalysed by TMSOTf resulted in a 3:1 mixture of *syn*/*anti* aldol products. The preferred formation of the *syn*-isomers[220] arose from the "open" transition state in the Lewis acid-mediated Mukayiama aldol reaction as depicted in Scheme 54.[221]

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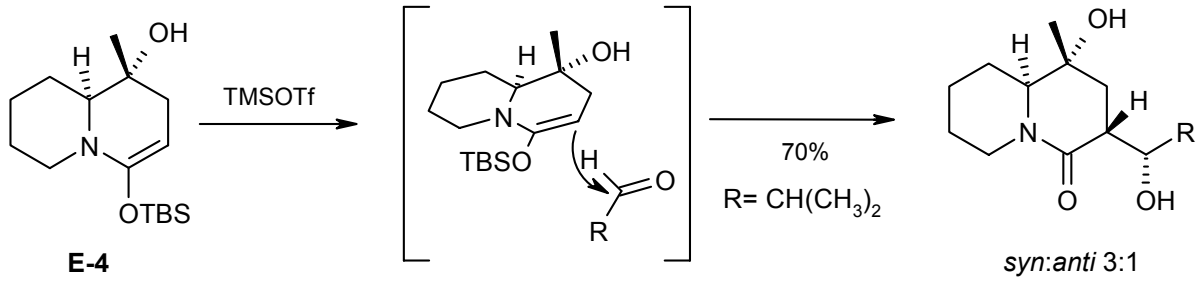
[218] This observation was also made by others in similar cyclic aldol compounds. For references see : Amoroso, R.; Cardillo, G.; Mobbili, G.; Tomasini, C. *Tetrahedron*: *Asymmetry* **1993**, 4, 2241-2254.
[219] Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, 42, 6999–7001 (same reference as ref. [30]).
[220] The diastereoface selectivity or the ratio of the two possible *syn*-isomers was not reported.
[221] for a review of the diastereoselection in Lewis-Acid-Mediated Aldol Additions see : Mahrwald, R. *Chem. Rev.* **1999**, 99, 1095-1120.

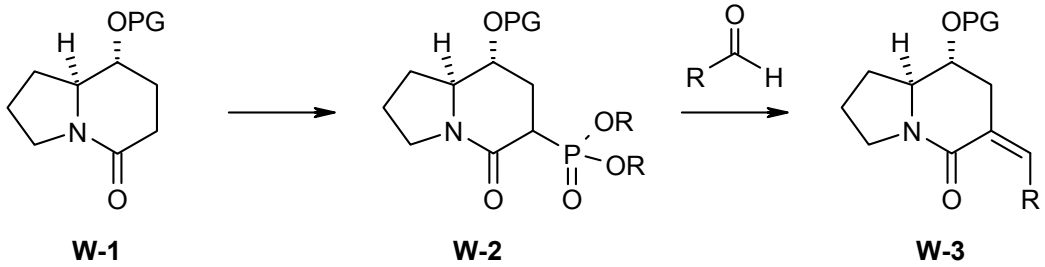
This result was published after the completion of the total synthesis of (+)-Pumiliotoxin 251D and offered no advantage with respect to the shorter Horner-Wittig path introduced in the following chapter.



Scheme 54 Formation of *syn*-aldol products in the Mukayiama aldol reaction

2.9 Total Syntheses of Pumiliotoxins (Part IV) - Horner Approach

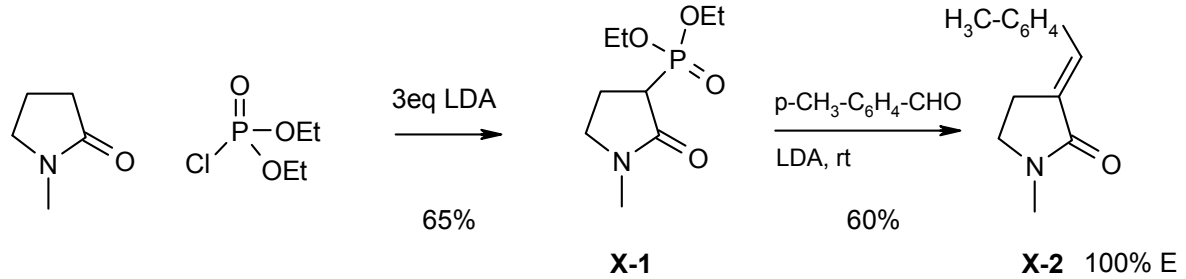
With the intention to circumvent the problems associated with the aldol strategy (formation of two additional stereogenic centres, stereospecific elimination necessary), the employment of a Horner-Wittig reaction was investigated to introduce the side-chain (Scheme 55).



Scheme 55 Synthesis plan for the introduction of the side chain via a Horner-Wittig reaction

Starting from the bicyclic amide **W-1** a suitably constructed phosphono amide **W-2** had to be prepared. A final Horner-Wittig reaction with an aldehyde generates the α,β-unsaturated amide **W-3**. Generally, the Horner-Wittig reaction of an α-amido diethyl phosphonate would build-up (*E*)-olefins. In contrast, diarylphosphonates or bis-(trifluoroethyl)phosphonates lead to the predominant formation of the (*Z*)-olefins, as recently reported by Ando[222] and Still.[223] The potential variability of the phosphonate substituent should allow the generation of either the (*E*)- or the (*Z*)-olefins.

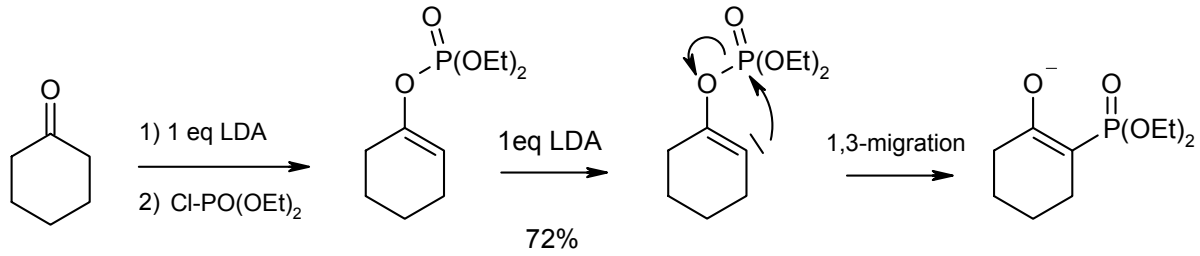
However, in contrast to the well known chemistry of cyclic β-ketophosphonates,[224] the preparation and Horner-Wittig conversion of cyclic β-amidophosphonates has been sparsely investigated. A single example was reported by Savignac *et al.*[225] who obtained the amido-phosphonate **X-1** after treatment of 1-methyl-pyrrolidine-2-one with diethyl chlorophosphate and LDA. The Horner-Wittig reaction of **X-1** yielded the pure (*E*)-olefin **X-2** with a moderate yield (Scheme 56).



Scheme 56 Horner-Wittig reaction of a cyclic amido phosphonate by Savignac *et al.* [225]

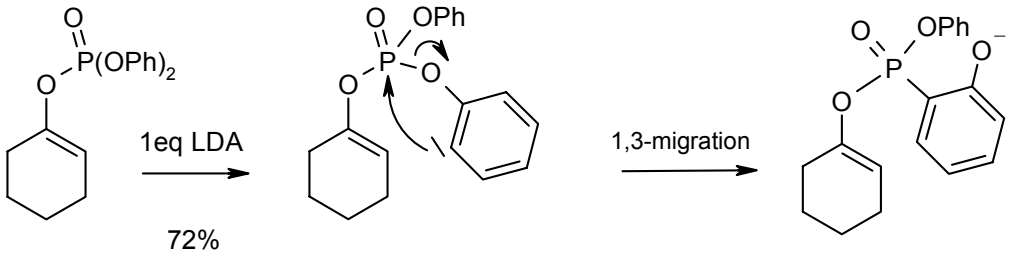
[222] (a) Ando, K. *Tetrahedron Lett.* **1995**, 36, 4105-4108. (b) Ando, K. *J. Org. Chem.* **1997**, 62, 1934-1939. (c) Ando, K. *J. Org. Chem.* **1998**, 63, 8411-8416. (d) Ando, K. *J. Org. Chem.* **1999**, 64, 6815-6821. (e) Ando, K. *J. Org. Chem.* **1999**, 64, 8406-8408. (f) Ando, K. *Synthesis* **2001**, 8, 1272-1274.
[223] Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 24, 4405-4408.
[224] for reviews see: (a) Eymery, F.; Iorga, B.; Savignac, P. *Tetrahedron* **1999**, 55, 13109-13150. (b) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 24, 4405-4408. (c) Wiemer D. F. *Tetrahedron* **1997**, 53, 16609-16644.
[225] Tay, M. K.; About-Jaudet, E.; Collignon, N.; Savignac, P. *Tetrahedron* **1989**,45, 4415-4430.

Considering the first step of this reaction, the preparation of a β-amidophosphonate starting from a cyclic amide is not trivial since a deprotonation of the amide leads to an amide enolate. Due to the ambident nucleophilic character of this anion the phosphorylation can occur either at the C- or the O-atom leading to mixtures of amido phosphonates and enol phosphates. A very elegant solution to this problem, the preparation of cyclic β-ketophosphonates, was developed by Wiemer.[226] The sequential treatment of a cyclic ketone with LDA, diethyl chlorophosphate and then LDA led to the exclusive formation of β-ketophosphonates with high yield (Scheme 57).



Scheme 57 Formation of β-ketophosphonates by base induced phosphorus migration of enol phosphates

In the initial step the reaction of diethoxy chlorophosphate with the enolate results in the clean formation of an enol phosphate. The deprotonation of the enol phosphate with LDA produces an intermediate vinyl anion which undergoes a 1,3-phosphorus migration to generate the highly stabilised ketophosphonate anion. The reaction is limited to cyclic substrates with the exception of the diphenyl enol phosphate of cyclohexanone which did not give the analogous result after treatment with LDA.[227] Instead, an aryl-o-anion is formed, inducing a migration leading to an aryl phosphonate (Scheme 58). In acyclic ketones the phosphate elimination predominates resulting in the formation of alkynes or allenes.[228]



Scheme 58 Side reaction during the generation of β-ketophosphonates from aryl phosphates

Despite of these limitations, the scope of the vinyl phosphate/β-ketophosphonate rearrangement was

[226] (a) Hammond, G. B.; Calogeropoulou, T.; Wiemer, D. F. *Tetrahedron Lett.* **1986**, 4265-4268. (b) Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, 52, 4185-4190.

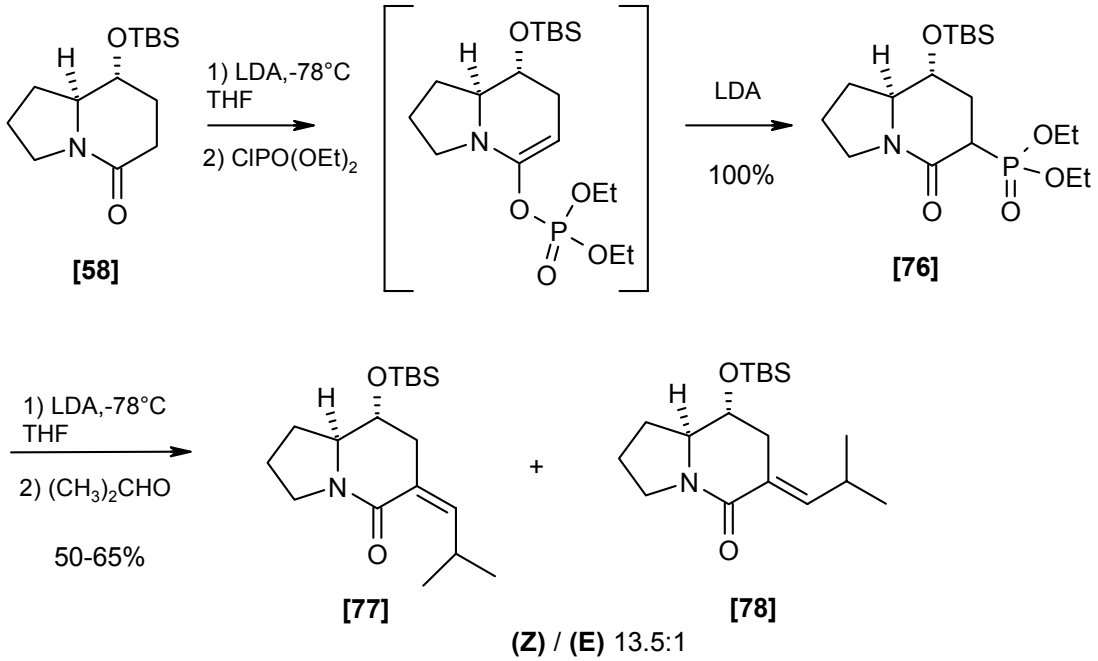
[227] This aryl anion rearrangement was used in the preparation of o-hydroxy aryl diphosphonic acids. For references see: Dhawan, B.; Redmore, D. *J. Org. Chem.* **1984**, 49, 4018-4021.

[228] (a) For the rearrangement of the acetophenone enolphosphate to phenylacetylene see : Negishi, E.; King, A. O.; Klima, W. L.; Patterson, W.; Silveira Jr.; A. *J. Org. Chem.* **1980**, 45, 2526. (b) for the examination of the formation of allenes by LDA induced elimination of enol phosphates, see : Brummond, K. M.; Dingess, E. A.; Kent, J. L. *J. Org. Chem.* **1996**, 61, 6096-6097.

broadly extended during the last years[229] and the analogous transformation of a cyclic amide into a β-amido phosphonate appeared to be reasonable.

2.9.1 Introduction of the Side Chain via Horner-Wittig Reaction

In the first series of experiments the indolizidinone **[58]** was treated with LDA and diethoxy chlorophosphate according to the sequence described by Wiemer (Scheme 59).



Scheme 59 Preparation and Horner-Wittig reaction of amidophosphonate **[76]**

Directly after workup of the reaction mixture the amido phosphonate **[76]** could be isolated in an excellent yield as a 1:1 mixture of both C-3 isomers. The reaction could be performed on a multigram scale. Furthermore, the isolation of the hydrolysis sensitive intermediate enolphosphate was not necessary.[230]

The structure of the mixture of amidophosphonates **[76]** with the newly formed C3-P bonds was unambiguously determined by ^{31}P-NMR spectroscopy (202.5 MHz, $CDCl_3$, δ= 22.72 and 22.32)[231] and by analysis of ^{13}C-^{1}H-HMQC and ^{31}P-^{1}H-HMQC spectra.

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[229] (a) For the regioselectivity of P-migration in cyclic systems see: An, Y.-Z.; Wiemer, D. F. *J. Org. Chem.* **1992**, 57, 317-321. (b) For diastereoselective Vinyl Phosphate rearrangements see: An, J.; Wilson, J. M.; An, Y.-Z.; Wiemer, D. F. *J. Org. Chem.* **1996**, 61, 4040-4045. (c) Baker, T. J.; Wiemer, D. F. *J. Org. Chem.* **1998**, 63, 2613-2618.

[230] For the generation of enolphosphates of cyclic amides and esters see: (a) Nicolaou, K. C.; Shi, Guo-Qiang; Namoto, Kenji; Bernal, Federico *Chem. Commun.* **1998**, 1757-1758. (b) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gaertner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, 119, 5467-5468. (c) Jiang, J.; DeVita, R. J.; Doss, G. A.; Goulet, M. T.; Wyvratt, M. J. *J. Am. Chem. Soc.* **1999**, 121, 593-594.

[231] For comparison : δ = +23.07 ppm (β-ketophosphonate) and-4.24 ppm (enolphosphate) of cyclopentane (taken from ref. [226]).

The amidophosphonate **[76]** was then deprotonated with LDA and subsequently treated with isobutyraldehyde at -78°C. After a short reaction time, the conversion was found to be completed. The Horner-Wittig reaction of the amidophosphonate was exceptional for generating the target (*Z*)-olefin **[77]**, exhibiting both with a high selectivity (13.5:1) and acceptable yields. This result was in total contrast to the Horner-Wittig reaction of amidophosphonates described earlier. Moreover, the reaction could also be performed as a one-pot reaction starting from **[58]** without any intermediate isolation of the amidophosphonate in good yields and high (*Z*)-selectivity (12.5:1). Both (*Z*)- and (*E*)-olefins could be easily analysed and separated since they exhibit distinct physical and spectroscopic properties (R_f^{cis} = 0.55 and R_f^{trans} = 0.30 with ethyl acetate 1:1, ^{1}H-NMR: $\delta^{cis\text{-olefin}}$ = 5.60 ppm $\delta^{trans\text{-olefin}}$ = 6.60 ppm due to the anisotropic effect of the amide carbonyl moiety).

Mechanistic considerations:

With the intention to develop a preliminary model to explain the unexpected formation of (*Z*)-olefins in the Horner-Wittig reaction of diethoxyphosphono amide **[76]** with isobutyraldehyde, the actual mechanistic concepts for such a reaction have to be discussed. A characteristic feature of the general Horner-Wittig reaction performed with the common (dialkylphosphono)acetates is the predominant formation of the thermodynamically favoured *trans*-olefins. Furthermore, several attempts have successfully been made to prepare *cis*-olefins by careful choose of the cation, temperature, solvent and special phosphonate reagents[232] such as ethyl(diarylphosphono)acetates.[222] In a recent mechanistic study, the electronic effects of phosphor substituents on the stereochemical course of the Horner-Wittig reaction were examined by ab-initio calculations.[233] In Scheme 60 a stereochemical model of the Horner-Wittig reaction is presented that includes experimental findings and theoretical calculations. The stereoselectivity of the HWE reaction is a result of both kinetic and thermodynamic control of the reversible formation of the *cis* and *trans* adducts and their decomposition to olefins. Considering the addition of the phosphonate enolate to the aldehyde the calculations indicated an energetic preference for the *cis*-adduct due to a lower steric strain (pathway 1a). In the second step- the formation of the oxaphosphetane - the cyclisation of the *trans*-adduct is energetically favoured (pathway 2b). In the usual Horner-Wittig reaction this step is thought to be rate-determining. Since the addition step 1 might be reversible, the *cis*-adduct can be equilibrated back into the *trans*-adduct. The elimination affords the (*E*)-olefin. Additionally, a direct conversion pathway of the *cis*- into the *trans*-adduct via a deprotonation-reprotonation reaction is plausible due to the high acidity of the α-hydrogen in the ketophosphonate.

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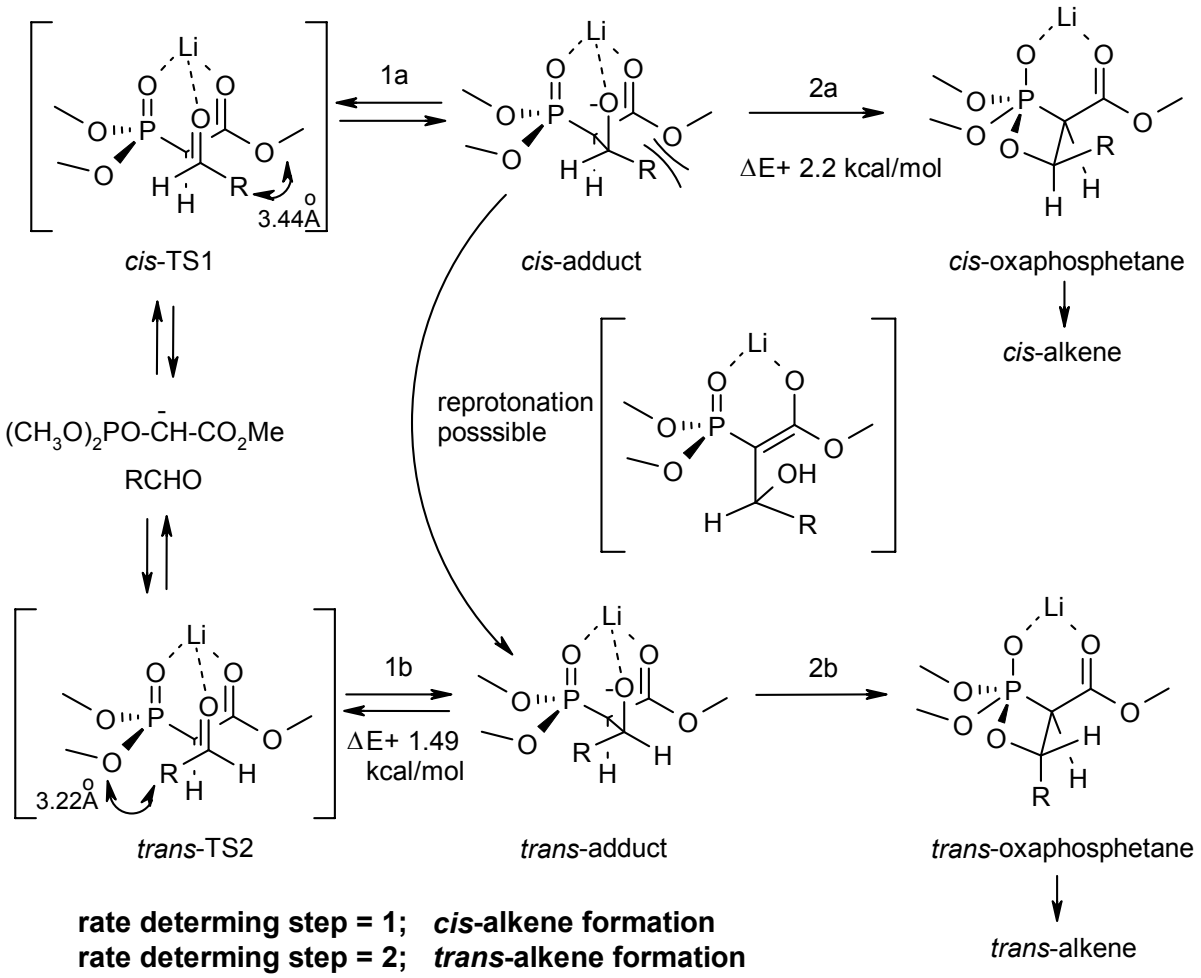
[232] (a) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, 37, 3873-3888. (b) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 24, 4405-4408. (c) Breuer, E. Bannet, D. M. *Tetrahedron Lett.* **1977**, 1141-1144. (d) Patois, C.; Savingnac, P. *Tetrahedron Lett.* **1991**, 32, 1317-1320. (e) Kokin, K.; Motoyoshiya, J.; Hayashi, S.; Aoyama, H. *Synth. Commun.* **1997**, 27, 2387-2392. (f) Zhang, T. Y.; O'Toole, J. C.; Dunigan, J. M. *Tetrahedron Lett.* **1998**, 39, 1461-1464.

[233] The mechanism of the Horner-Wadsworth-Emmons (HWE) reaction has been investigated using ab initio calculations (RHF/6-31+G*, calculated for the gas phase and for the solvent dimethyl ether) by Ando, K. *J. Org. Chem.* **1999**, 64, 6815-6821.

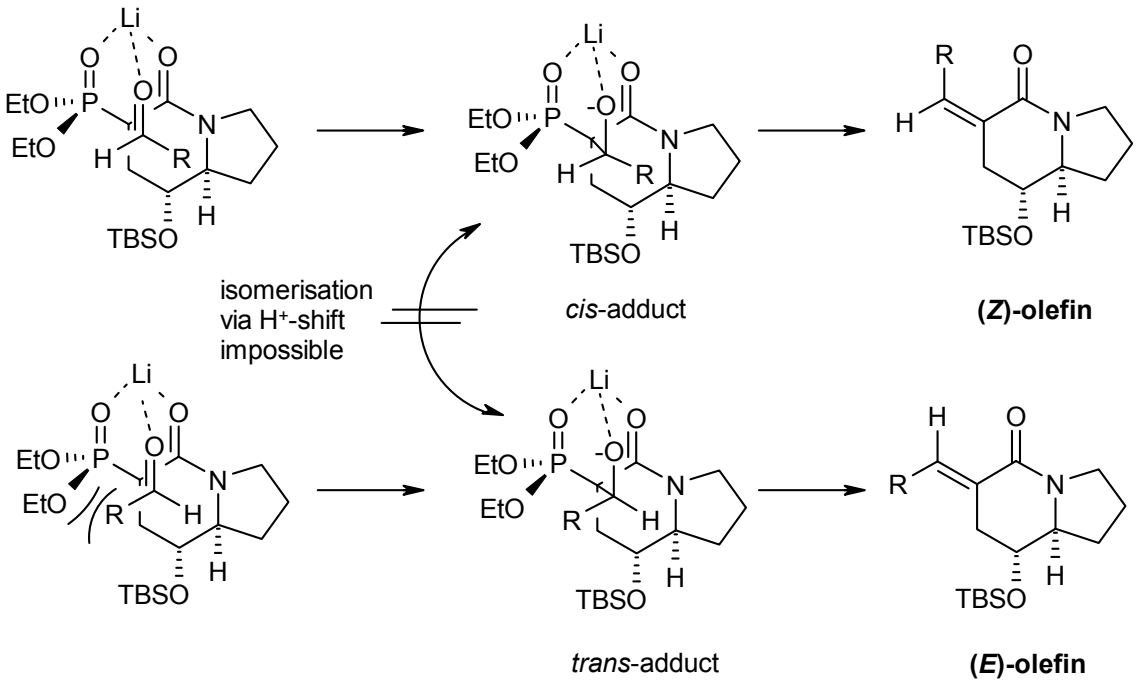


Scheme 60 Stereochemical course of the Horner-Wittig reaction

The predominant formation of (*Z*)-olefins via diarylphosphono- and bis(trifluoroethyl)phosphono reagents can be rationalised as a result of the predominant formation of *cis*-adducts, which then irreversibly collapse to the *Z*-olefins. Due to the electron-withdrawing character of the aryloxy group ($pK_a(PhOH) = 10.0$ vs $pK_a(CH_3CH_2OH) = 16$) and the trifluoroethyl group ($pK_a(CF_3CH_2OH) = 12.5$), the electrophilicity of the phosphor in the intermediate *cis*-adducts should be enhanced and thus the activation energy for the oxaphosphetane formation substantially lowered. Consequently, the rate-determining step of the phosphonates is the first addition step.

Compared to the Horner-Wittig reaction of acyclic β-ketophosphonates, the olefination of cyclic amidophosphonates requires the consideration of two structural differences in the preliminary reaction mechanism. On the one hand, the phosphonate group and the bicyclic ring represent two bulky fragments which might direct the preorientation of the attacking aldehyde (Scheme 61). Assuming a complexation of the aldehyde oxygen with the amide enolate the bulky isopropyl group is positioned *anti* to the phosphorus atom of the amidophosphonate or *anti* to the amide C=O group leading to the

cis- and the *trans*-adduct.[234] The decreased steric interaction of the aldehyde hydrogen with the phosphorus atom in contrast to the isopropyl group is presumably responsible for the preference of an attack leading to the *cis*-adduct.[235] On the other hand, an isomerisation of the *cis*-adduct into the *trans*-adduct via the well-known deprotonation-reprotonation reaction can be excluded due to the lack of an α-proton in the intermediate. Thus the stereochemical outcome of the Horner-Wittig reaction must be a result of the kinetic control in the first addition step.



Scheme 61 Potential mechanism of the Horner-Wittig reaction of cyclic amidophosphonates

Comparing these experimental findings with the contrasting result of Savignac (100% *E*) in a similar reaction (see Scheme 56, page 95) the different reaction temperature (-78°C vs. room temperature) is probably the crucial factor in the reaction.[236]

In summary the Horner-Wittig reaction of cyclic amidophosphonates allowed the smooth and selective synthesis of (*Z*)-configured alkylidene indolizidinones. The precursor amidophosphonates could easily be prepared by the application of a procedure for cyclic ketones described by Wiemer *et al*.[226] Due to the high degree of (*Z*)-selectivity of the coupling reaction further changes of the phosphonate substituents were unnecessary.

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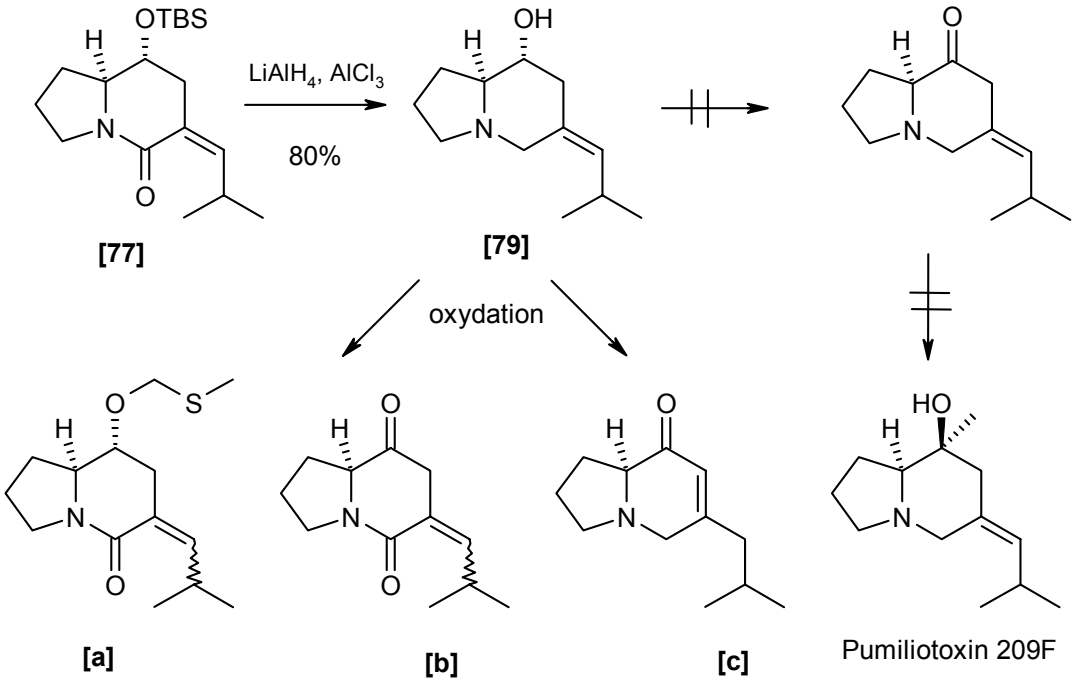
[234] MMPlus calculations of both adducts indicate that an *anti*-periplanar arrangement of the phosphorus atom and the bulky isopropyl group of the aldehyde is favoured. Assuming an orientation of the aldehyde oxygen that allows a complexation the *cis* adduct exhibit a lower energy than the *trans* adduct (*cis*: 49.79kcal/mol, *trans*: 51.38 kcal/mol, MM+ calculation with the Hyperchem Conformational Search module in analogy to chapter 2.2.4).

[235] Since both possible diastereoface additions of the aldehyde onto the deprotonated amidophosphonate result in the same olefin geometry (identical arrangement of aldehyde) only one addition is presented in Scheme 61.

[236] (Z)-configured α,β-unsaturated amides readily isomerise under basic conditions into the more stable (*E*)-olefins at ambient temperature. This could explain the exclusive formation of (*E*)-alkylidene compounds as reported by Savignac *et al*. (ref. [225]). Own experiments indicated that aqueous workup had to be performed at -78°C. If the reaction mixture was allowed to reach room temperature over a few hours a diminished stereoselectivity was observed due to isomerisation reactions.

2.9.2 Attempts for the Introduction of the C-5 Methyl Group

After the successful construction of the (*Z*)-alkylidene chain, the introduction of the remaining methyl group was investigated. Because of the low diastereoselectivity in the alkylation of the keto amide **[59]** (see Scheme 47, page 84) the reduction of the amide **[77]** should be performed prior to the oxidation-alkylation sequence. The lactam unit was selectively reduced with $LiAlH_4/AlCl_3$. Additionally, these reaction conditions caused the complete cleavage of the silyl group resulting in the formation of amino alcohol **[79]** with a high yield. The C-5 alcohol was then oxidised to a ketone. A final reaction with MeMgI[237] should lead to pumiliotoxin 209 F (Scheme 62). This Grignard reaction could proceed with a higher selectivity due to the chair-like structure of the amine and the shielding effect of the ring junction.



Scheme 62 Attempts for the introduction of the C-5 methyl group via an oxidation-alkylation method

However, all oxidation attempts (DMSO-oxalyl chloride-Et_3N, DMSO-Ac_2O, Dess-Martin reagents,[238] Jones oxidation, Collins oxidation) failed to generate the desired amino ketone. The Swern reaction yielded a mixture of the unreacted educt and the isomerised ketone **[c]**. Oxidation with chromium reagents[239] led to the oxidised amide **[b]** while attempts with the Dess-Martin periodinane showed no reaction. Finally, an attempted oxidation of the secondary alcohol in the presence of a tertiary amine

[237] in the literature this Grignard reaction with the alkylidene free indolizidine proceeds with a good selectivity due to the shielding effect of the ring junction. see: Tan, C.-H.; Stork, T.; Feeder, N.; Holmes, A. G. *Tetrahedron Lett.* **1999**, 40, 1397-1400.
[238] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, 48, 4155.
[239] (a) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39. (b) Mueller, R. H.; Thompson, M. E.; DiPardo, R. M. *J. Org. Chem.* **1984**, 49, 2217.

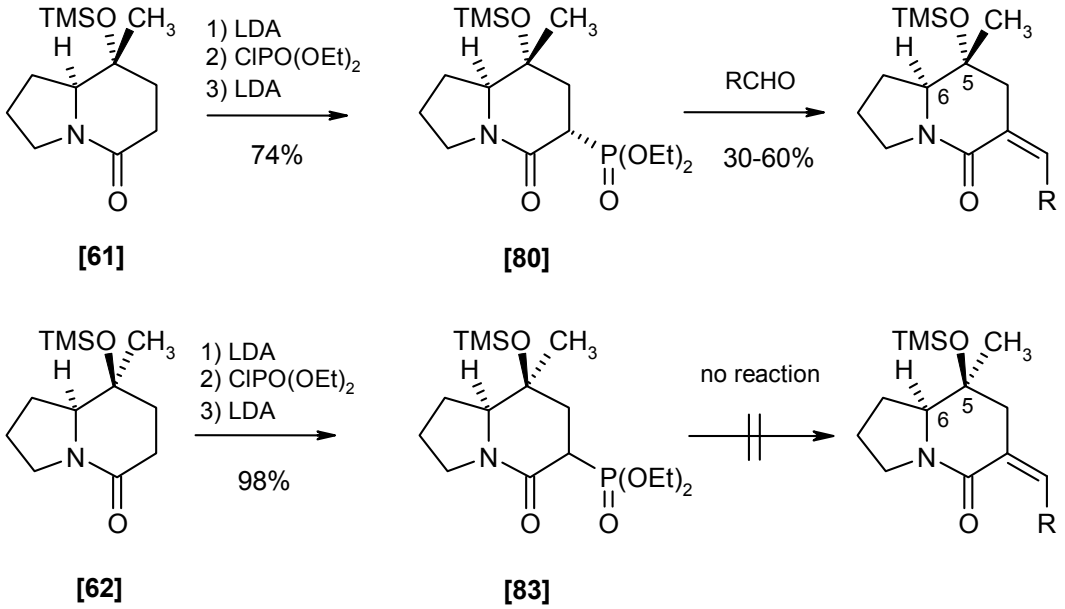
employing the Albright-Goldman protocol,[240] resulted in the formation of the methylthio-methylether **[a]** of the reactant **[79]**.

The oxidation reactions revealed the difficulties resulting from this synthesis plan. The basicity of the tertiary amine and the lability of the β,γ-unsaturated ketone framework leads to a strongly reduced stability of the intermediate amino ketone. Thus, the indolizidinones **[61]** and **[62]** had to serve as the building blocks of choice to complete the total synthesis of pumiliotoxins.

2.9.3 Total Synthesis of *epi*-Pumiliotoxin 209F and Pumiliotoxin 209F-amide [85]

The silyl protected tertiary hydroxy indolizidinones **[61]** and **[62]** should be used to complete the total synthesis of the pumiliotoxins *epi*-209F and (+)-251D in analogy to the reaction of the desmethyl indolizidinone **[58]** (described in chapter 2.9.1). Compared to indolizidinone **[58]**, the Horner-Wittig sequence with the more sterically hindered substrates **[61]** and **[62]** revealed new problems.

The amidophosphonates **[80]** and **[83]** could be prepared in good yields by the sequential addition of LDA, diethyl chlorophosphate and LDA to the amides **[61]** and **[62]** (Scheme 63).



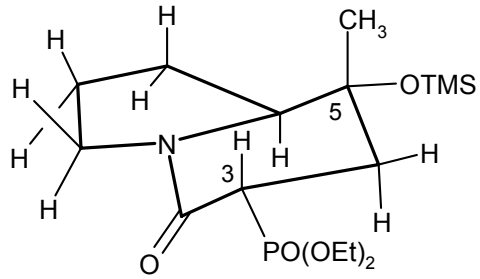
Scheme 63 Horner-Wittig introduction of the alkylidene side chain in the TMS protected amides **[61]** and **[62]**

The reaction of the phosphonates **[80]** and **[83]** exhibited large differences in reactivity with isobutyraldehydes. The 5*R*-configured phosphonate **[80]** could be successfully converted into the desired (*Z*)-alkylidene indolizidinone. The analogous reaction involving the 5*S*-configured

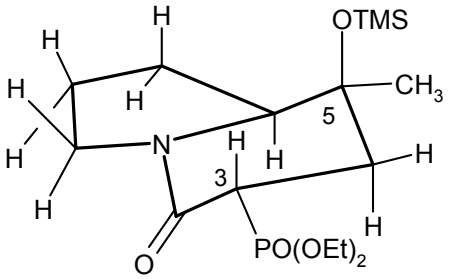
[240] (a) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, 89, 2416. (b) exp. description from: Broka, C. A. ; Gerlits, J. F. *J. Org. Chem.* **1988**, 53, 2144-2150.

phosphonate **[83]** failed. Neither a change of the reaction temperature nor the use of an excess of aldehyde led to an enhancement of the low reactivity. A potential explanation for this unexpected behaviour was provided by NOE and ^{1}H-NMR analysis of both phosphonates. Analysing the amidophosphonate **[80]**, the TMSO group adopts an equatorial position. In compound **[83]** this group is found to be axially arranged. Thus, a steric shielding at C-3 by the axial TMSO group in the deprotonated amidophosphonate **[83]** is reasonable. This steric hindrance could prevent the attack of the aldehyde and consequently the formation of the (*Z*)-olefin.

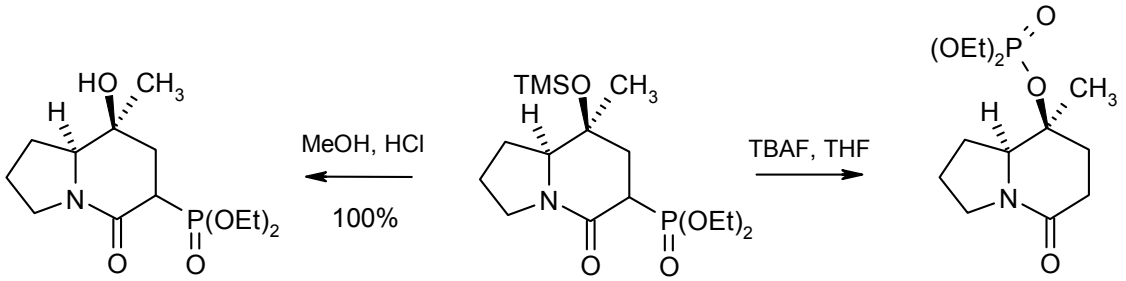
structure of **[80]** according to NOE



structure of **[83]**[241]



With the intention to reduce the steric influence of the axial substituent, a cleavage of the silyl group of the amidophosphonate **[83]** was performed. First attempts using TBAF were unsuccessful, instead of the desired deprotected alcohol **[84]** a rearrangement of the phosphonate group to the hydroxy group was observed resulting in the formation of **[86]**.[242] Finally, the silyl ether cleavage was successfully achieved in a high yield using methanolic HCl (Scheme 64).



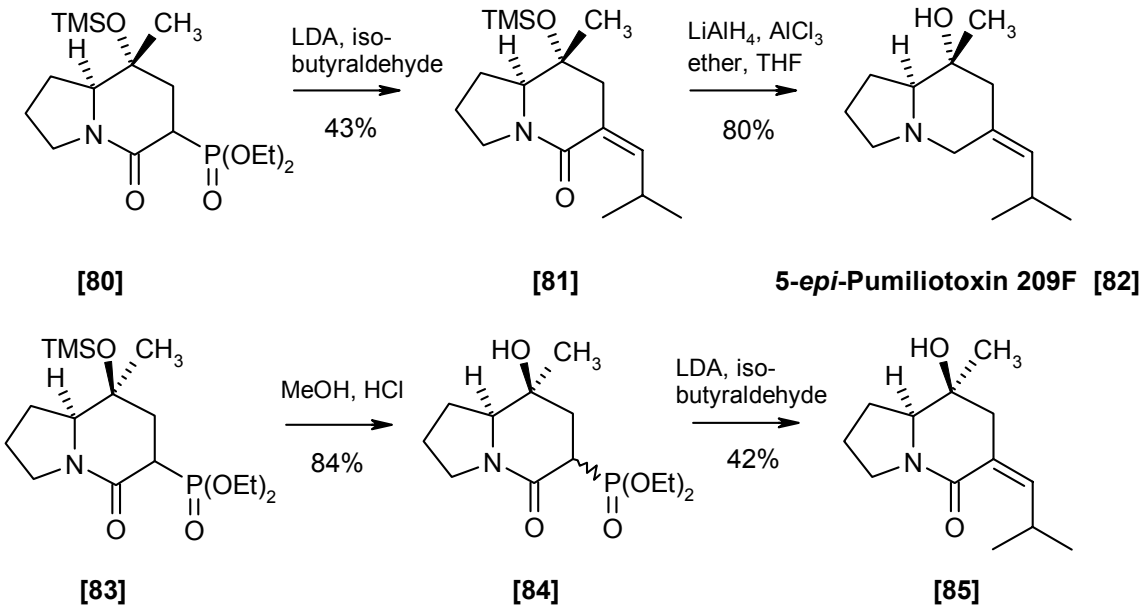
[84] **[83]** **[86]**

Scheme 64 Desilylation of the amidophosphonate **[83]**

The final steps of the synthesis of *epi*-pumiliotoxin 209F and the precursor of the naturally occurring pumiliotoxin 209F are outlined in Scheme 65. The amidophosphonate **[80]** was deprotonated with 1eq LDA at -78°C and subsequently treated with isobutyraldehyde to give the (*Z*)-alkylidene indolizidinone **[81]** in a 43% yield (*Z*/*E* 6:1). Reduction of the amide group and cleavage of the TMS

[241] The configuration of **[83]** at C-3 is based on comparison with the ^{1}H-NMR spectra of **[80]**. Force field calculations (HyperChem v. 6.0 MM+] indicated the strong preference of the TMSO group for the axial position as also found in the C-3 unsubstituted compound **[62]**.

ether was carried out by a reaction with AlH_3, in situ prepared from $LiAlH_4$ and $AlCl_3$.[243] The 5-*epi*-pumiliotoxin 209F **[82]** was obtained in an 80% yield.



[80] **[81]** **5-*epi*-Pumiliotoxin 209F [82]**

[83] **[84]** **[85]**

Scheme 65 Synthesis of *epi*-pumiliotoxin 209F and derivative - final steps

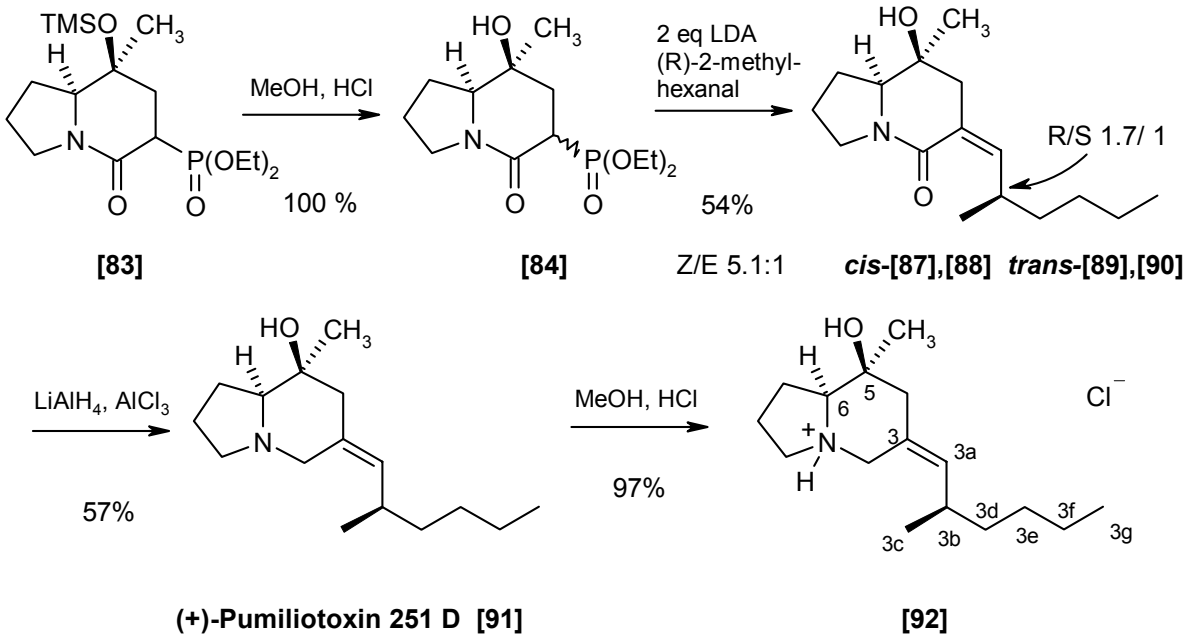
In contrast, the amidophosphonate **[83]** was initially deprotected using methanolic HCl. The obtained indolizidinone **[84]** was subjected to the Horner-Wittig reaction resulting in (*Z*)-alkylidene indolizidinone **[85]** with a 42% yield and a high (*Z*)-selectivity (10:1).

[242] The strong nucleophilicity of the alkoxide ion formed during the TBAF cleavage led to the phosphonate rearrangement since the amide enolate produced is the less basic species.

[243] (a) Yoon, N. M; Brown, H. C. *J. Am. Chem. Soc.* **1968**, 90, 2927-2938. (b) Jorgenson, M. G. *Tetrahedron Lett.* **1962**, 13, 559-562.

2.9.4 Total Synthesis of (+)-Pumiliotoxin 251D

With the selective cleavage of the bulky TMS group, suppressing any phosphonate rearrangement, it was possible to complete the total synthesis of natural (+)-Pumiliotoxin 251D using the Horner-Wittig method. The reaction proceeded with a 54% yield and a *Z*/*E* selectivity of 5:1 (Scheme 66).



Scheme 66 Total synthesis of (+)-Pumiliotoxin 251D final steps

Although the ^{1}H-NMR-spectrum of the (*Z*)-alkylidene indolizidinone appeared to be pure, HPLC analysis revealed the presence of a minor impurity. After separation of both compounds and structural assignment by NOE spectroscopy it was ascertained that the minor compound possesses the (*S*)-configuration of the side chain stereogenic centre. Presumably, an epimerisation of the chiral aldehyde had taken place prior to the Horner-Wittig coupling reaction. This epimerisation could be effected by the use of two equivalents of LDA during the course of the reaction, which was found to be necessary for the deprotonation of the tertiary alcohol position. A test experiment showed that the epimerisation rate was substantially lower when only 1 mol.-eq of LDA was used (Fig. 23). However, in this reaction the yield was decreased since the phosphonate rearrangement, generating **[86]** (Scheme 64), re-occurred.[244]

[244] with the use of two eq. of LDA the phosphonate and the hydroxy group are deprotonated, thus no rearrangement takes place.

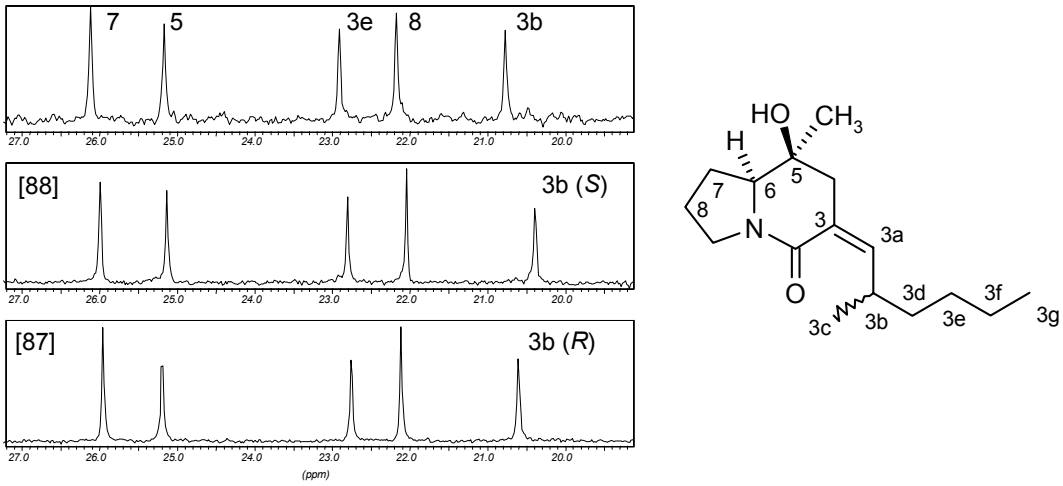


Fig. 23 Epimerisation rate in test Wittig reaction (1 eq of base) in comparison to the pure 3b-isomers (*S* / *R*)

The comparison of the optical rotations for the isomers **[87]** and **[88]** and the value reported by Gallagher *et al.*[245] revealed that the aldol addition (see Scheme 51) potentially suffered from the analogue epimerisation. The large difference in the optical rotation of the 3*R* and the 3*S* isomer which exhibit nearly identical ^{1}H-NMR and ^{13}C-NMR spectra (a small difference in the shifting for the 3b-^{13}C resonance signal is the only indicator for the existence of a mixture of diastereomers), allowed the conclusion to be drawn that the amide and thereby the pumiliotoxin 251D (no further purification steps) reported by Gallagher *et al*. was not diastereomerically pure, but rather a mixture of the C-3b isomers (see Table 15).

After HPLC separation, the 3*R*-(*Z*)-alkylidene indolizidinone **[87]** was reduced with AlH_3 resulting in (+)-pumiliotoxin 251 D with a 57% yield.

Table 15 Comparison of optical properties of synthetic pumiliotoxin 251D and derivatives[246]

compound	optical rotation $[\alpha]_D^{20}$	mp
[87]	- 67.58° (c=1.644, $CHCl_3$)	135-140°C
[88]	+ 55.02° (c=1.79, $CHCl_3$)	150-153°C
synthetic amide[245] (Gallagher)	- 28.0° (c=0.40, $CHCl_3$)	135-138°C
[91] (+) pumiliotoxin 251D	- 8.47° (c=1.05, $CHCl_3$)	-
[92] (+) pumiliotoxin 251 D hydrochloride	+ 27.98° (c=1.09, CH_3OH)	203-205°C
synthetic (+) pumiliotoxin 251 D hydrochloride[245]	+ 23.6° (c= 0.11, CH_3OH)	200-201°C
synthetic (+) pumiliotoxin 251 D hydrochloride[247]	+ 28.0° (c= 0.62, CH_3OH)	206-206.5°C
synthetic (+) pumiliotoxin 251 D hydrochloride[248]	+ 31.4° (c= 0.62, CH_3OH)	205-206°C

[245] Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, 113, 2652-2656 (same reference as ref. [25]).
[246] The comparison of mp and optical rotation must await the isolation of additional natural ptx 251D.
[247] Overman, L. E.; Bell, K. L. Ito, F. *J. Am. Chem. Soc.* **1984**, 106, 4192-4201.
[248] Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, 103, 1851-1853.

Finally, the free base was converted into the (+)-pumiliotoxin 251D hydrochloride using methanolic HCl. The physical properties of the synthetic compound **[92]** were in accordance with that reported in the literature (see Table 15). Recrystallisation of the hydrochloride from dichloromethane/ethyl acetate yielded colourless needles (mp 203-205°C) that were used for X-Ray analysis (Fig. 24).

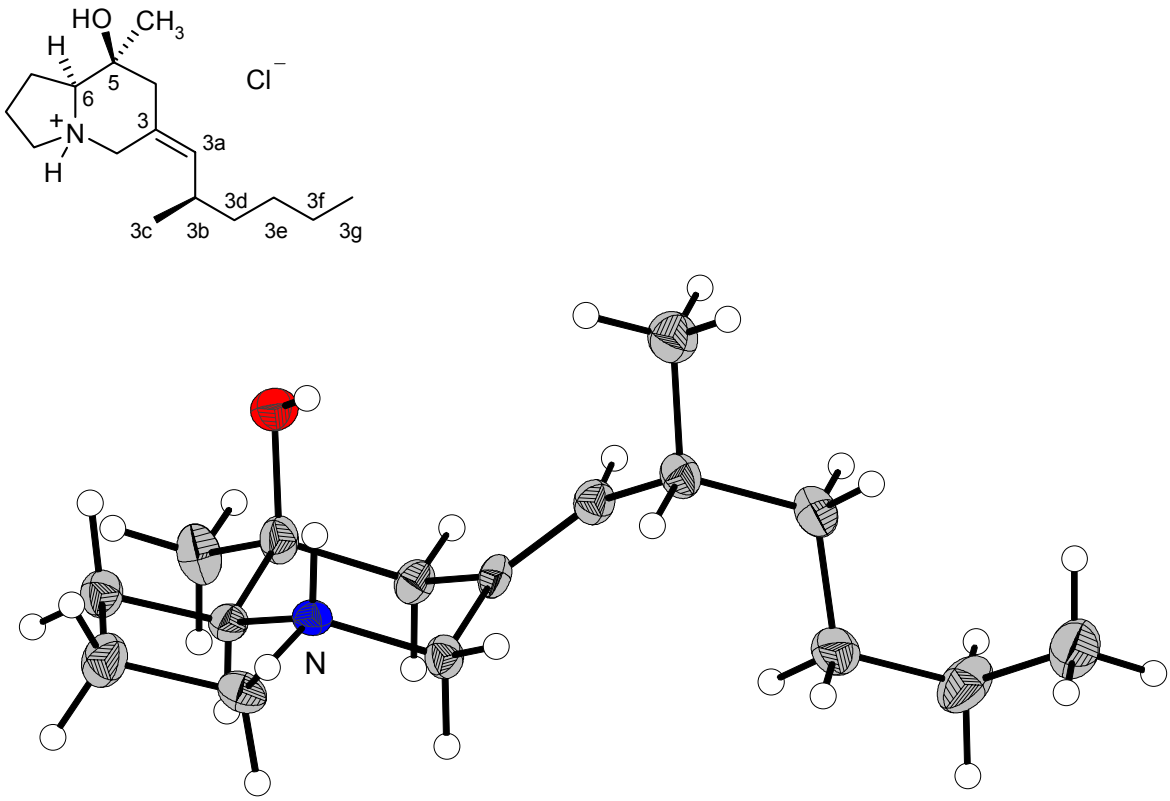


Fig. 24 Crystal structure of (+)-pumiliotoxin 251D hydrochloride **[92]**[249]

The crystal structure was identical to that published for the hydrochloride of the natural product.[250] The correct absolute configuration of the synthesised product was also confirmed.

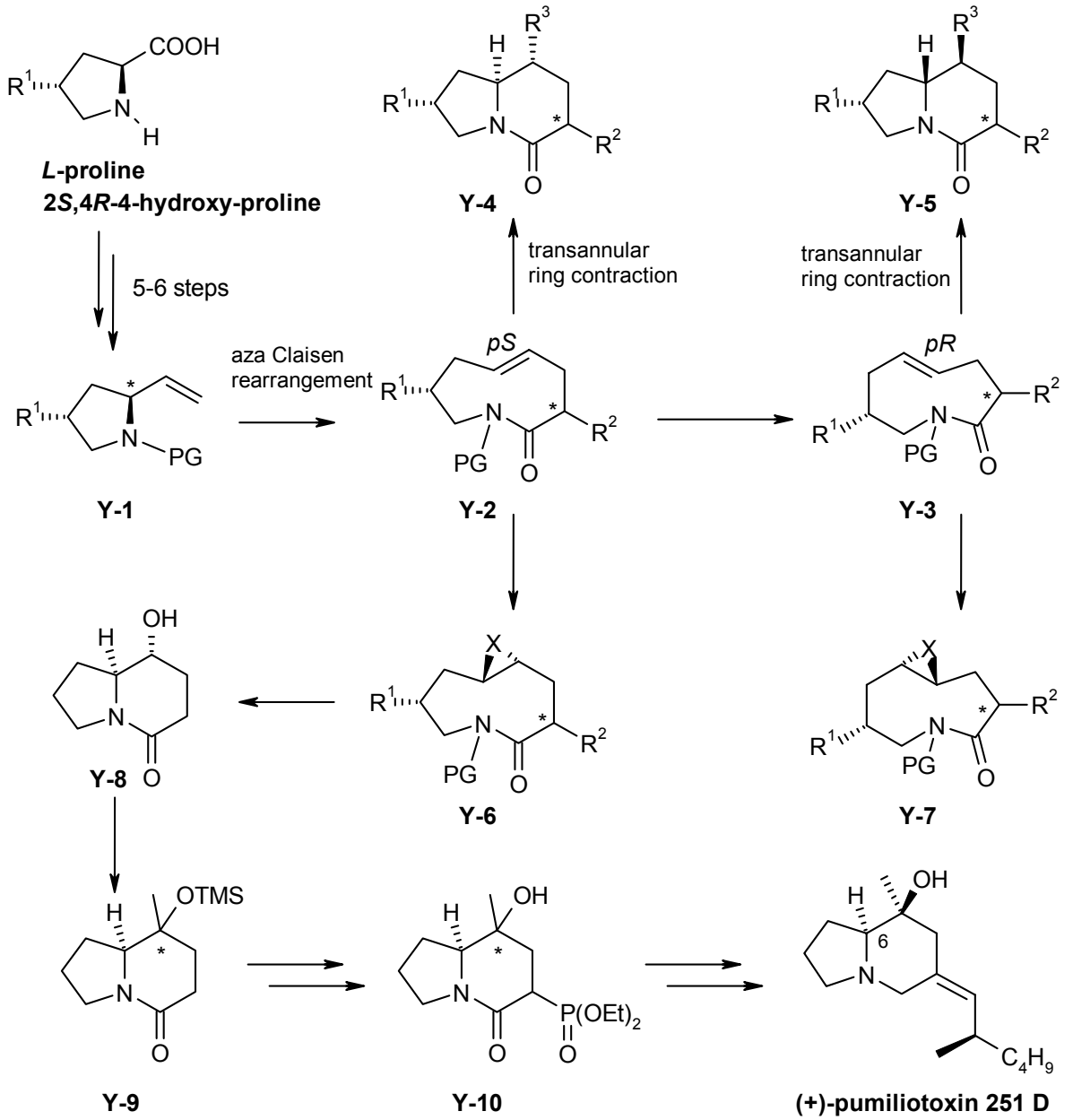
The synthetic sequence reported here provides a highly convergent, concise and practical route for the synthesis of the pumiliotoxin alkaloids. The stereoselective total synthesis of (+)-pumiliotoxin 251D was achieved in 9 total steps from N-Benzyl vinyl pyrrolidine **[11]** and 2-(*R*)-hexanal **[70]**. The overall yield was ~ 3% from vinyl pyrrolidine **[11]**.

[249] The chloride atom is located between the OH group and the NH-proton and was omitted for clarity. The absolute configuration could be determined using the anomalous X-ray dispersion of the chlorine atom.

[250] Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. J.; Karle I. L. *J. Am. Chem. Soc.* **1980**, 102, 830, CCDC-code HMHXZB.

2.10 Summary and Outlook

Indolizidine alkaloids are characterised by a variety of interesting biological activities such as the inhibition of glycosidases, specific binding to ion channels in nerve and muscle cells or the ability to act as trail pheromones. The breadth of biological activities arises from the defined substitution pattern at the azabicyclo[4.3.0]nonane core and the configuration at the bridgehead position. The *D*-proline derived hydroxylated indolizidinone castanospermine and the *L*-proline derived pumiliotoxin alkaloids serve as examples. Total syntheses of such alkaloids developed earlier have always focused on the generation of a single absolute configuration of the bicyclic core, depending on the desired target. In this work, a new synthetic concept has been introduced that allows the easy access to optically active indolizidines with both absolute configured bicycles (Scheme 67).



Scheme 67 Summary

Starting from commercially available prolines, 2-vinyl pyrrolidines **Y-1** were generated in 5-6 steps with a high overall yield (chapter 2.1.1, page 22). This allowed the preparation of 50-100g of vinyl pyrrolidines with almost complete exclusion of chromatographic separations (R^1= OTBS one chromatographic separation included).

In the first key step the 2-vinyl pyrrolidines were converted into azoninones **Y-2** via a zwitterionic aza-Claisen rearrangement (chapter 2.1.2, page 24). The employment of acid fluorides during the rearrangement suppressed any von-Braun degradation reaction and substantially increased the yields in comparison to the earlier performed rearrangements with acid chlorides. Analysing the stereochemical outcome of the aza-Claisen rearrangement, the defined enolate geometry and the defined chair- and boat-like transition state led to a high degree of 1,4-chirality transfer. The generation of azoninones bearing a *trans* double bond led to the formation of medium-sized rings with an additional planar chiral information. In the present case the 2*S*-vinyl pyrrolidines **Y-1** gave rise to the formation of *pS*-azoninones **Y-2**, the *pS* arrangement was found to be of an outstanding stability. The *pS*-azoninones **Y-2** were converted into thermodynamically stable *pR*-azoninones **Y-3** by means of heating. The planar chiral isomerisation needed an activation energy of ~25 kcal, as determined by calculations and kinetic measurements (chapter 2.2, page 36). The *pS* and *pR* conformations can be handled as discrete compounds. Depending on the substitution pattern several kinetically generated *pS*-azoninones could be completely converted into the thermodynamically stable *pR*-analogs.

In the second key step the azoninones were converted into indolizidinones and azonanones. The transannular cyclisation of **Y-2** and **Y-3**, using soft electrophiles, gave indolizidinones **Y-4** and **Y-5** with high yields and stereoselectivities (chapter 2.3, page 58). The planar chiral information of the *pS* and *pR* azoninones could be completely transferred into new stereogenic centres, respectively. By the choice of the reaction processing two defined oppositely configured products **Y-4** and **Y-5** could be obtained from the same reactant azoninone.

Employing cycloaddition reactions, defined azonanones **Y-6** and **Y-7** were obtained depending on the reactant azoninones. Again, a complete transfer of planar chirality into central chirality was achieved (chapter 2.4, page 67).

Focussing on the synthesis of pumiliotoxin alkaloids, the generation of 5-hydroxy indolizidinone **Y-8** was required. The method of choice was found to be the ring-closure of epoxy azonanones via a hydrogenation approach (chapter 2.6, page 83). The construction of the pumiliotoxin core was completed by the generation of hydroxymethyl indolizidinones **Y-9** via an oxidation-alkylation sequence that suffered from a low diastereoselectivity.

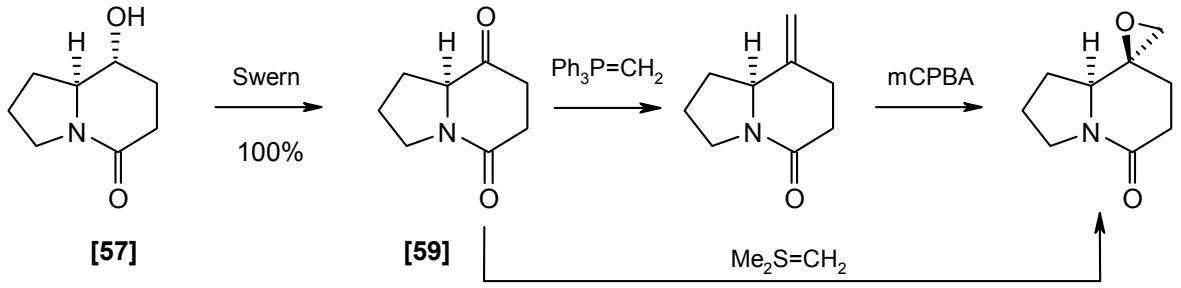
The total synthesis of **(+)-pumiliotoxin 251D** had to be completed by the introduction of the side chain generating a defined trisubstituted (*Z*)-double bond. Initial approaches employing the aldol reaction failed to generate a suitable β-hydroxy amide (chapter 2.8, page 88). Actually, the selective generation of (*Z*)-alkylidene compounds via a Horner-Wittig olefination is a promising approach to generate exocyclic double bonds. Such a process requires the efficient generation of amido

phosphonate **Y-10**, which was successfully performed adopting a Wiemer-Savignac method of an enolphosphate-ketophosphonate rearrangement (chapter 2.9, page 95). The consecutive Horner reaction gave a smooth reaction in the 5-*nor* methyl and the 5-*epi* series, some difficulties were encountered in the natural series by the bulky C-5 TMSO group. Finally, the successful reductive removal of the amide C=O group completed the highly convergent total syntheses of **(+)-pumiliotoxin 251D** and **5-*epi*-pumiliotoxin 209F**. The identity of the synthetic (+)-pumiliotoxin 251D and the naturally occurring compound was confirmed by X-ray analysis of its hydrochloride.

The interesting properties of planar chiral lactams offer many perspectives for future research. On the one hand the exploration of pathways concerning oxygen substituted indolizidines in this work revealed many concepts for the conversion of azoninones into other biologically active molecules like new hydroxy indolizidines. Particularly, syntheses starting from hydroxyproline could give access to new aminosugar compounds with interesting biological activities (new glycosidase inhibitors ?). On the other hand the restricted rotation of a (*E*)-double bond in medium-sized rings, including steric strains, is a synthetically challenging field which is far from being well explored. Some of the new questions are : How can the advantage of the switchable chirality in unsaturated nine-membered rings be extended to larger cyclic systems ? Which type of steric strains have to be incorporated into the cyclic system to increase the activation barrier for the double bond rotation ? Which further reactions can be carried out using the constrained double bond (such as Diels-Alder-, [2+3]- or [2+2]-cycloadditions) ?

In view of the total synthesis of pumiliotoxins further research should focus on the enhancement of the diastereoselectivity of reactions introducing the C-5 stereogenic centre in the bicyclic hydroxymethyl indolizidinone **Y-9**. As already discussed in the preceding chapters, an advantage of the employment of planar chiral nine-membered lactams is the adjustable chirality of the C-6 stereogenic centre, which enables access to *D*- and *L*-proline derived natural products. Therefore, an alternative synthesis should proceed via the readily available bicyclic hydroxy indolizidinone **[56]** that can be prepared by the method developed in this work.[251] Some suggestions to solve this problem are given in Scheme 68.

[251] Other synthetic approaches for the synthesis of hydroxy indolizidinone **[62]** have been described by Gallagher *et al*., Barrett *et al*. and Cossy *et al*. However, in these methods the configuration of the C-6 junction is fixed by the use of *L*-proline as ex-chiral pool starting material. For references see: (a) ref. [25] and ref. [26].



Scheme 68 Alternative synthetic strategy for the formation of the C-5 tertiary group

After conversion of **[57]** into the ketone **[59]** a methylenation of the keto group using $Ph_3P=CH_2$ should provide an alkylidene indolizidinone.[252] Epoxidation of the alkene results in the formation of a spiro epoxide. Alternatively, the ketone can be directly converted into the spiro epoxide using the Corey-Chaykovski reagent ($Me_2S=CH_2$).[253] Due to the absence of a free hydroxy group in this intermediate epoxide no hydroxy-protective step is necessary. Furthermore, the consecutive Horner-Wittig reaction requires only 1 eq of base since no deprotonation of the tertiary hydroxymethyl group is needed which should suppress the isomerisation of the introduced chiral aldehyde. Additionally, in this spiro-epoxide the steric hindrance should be reduced, in comparison to the bulky TMS protected hydroxy methyl indolizidinone **Y-9**.
After the side chain introduction, the epoxide moiety is opened to reinstall the tertiary alcohol function in the final lactam reduction step.

Last but not least several of the applied reactions have to be explored in detail for a potentially broader application.

- The selective generation of (*Z*)-alkylidene compounds via the Horner-Wittig olefination is a promising reaction to generate exocyclic double bonds (chapter 2.9).
- The iodide-nitrate exchange in iodo-indolizidinones, suffering from an intermediate ring rearrangement, should allow the generation of an additional series of chiral indolizidinones thus extending the potential of the method developed (chapter 2.3.4).

Such perspectives point out that the field of azoninones and indolizidine syntheses should gain an increase in importance.

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[252] Jefford, C. W.; Sienkiewicz, K.; Thornton, S. R. *Helv. Chim. Acta* **1995**, 78, 1511-1524.
[253] (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, 87, 1353-1364. (b) Childers, W. E.; Furth, P. S.; Shih, M.-J.; Robinson, C. H. *J. Org. Chem.* **1988**, 53, 5947.