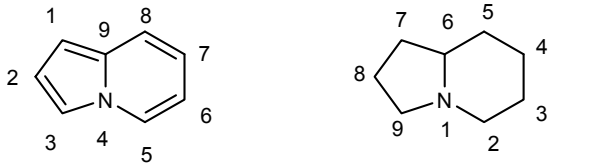
1 Introduction

1.1 Indolizidines as Natural Products

Indolizidines are widely distributed in nature – in plants as well as in many animals. Their structures can be described either as derivatives of the aromatic bicyclic indolizine or as azabicyclo[4.3.0]-nonanes.[1]



Indolizine Azabicyclo[4.3.0]nonane

Fig. 1 The bicyclic core of indolizidine alkaloids

The indolizidine alkaloids display a wide range of biological activities[2] and have been the subject of numerous synthetic studies.[3] The development of general methods for the synthesis of racemic and enantiopure indolizidines remains an area of active investigation. Most of the naturally occurring indolizidines have been isolated from species of the genus *Dendrobates* (poison-arrow frogs); *Monomorium* (ants), *Dendrobium* (orchids), *Tylophora* and the *Leguminosae* family (plants). The classification of the indolizidines according to their natural sources is difficult due to the structural diversity within these species. Nevertheless some characteristic structural motives are unique for the species and often linked to the high biological activities of the compounds. Among them the lipophilic pumiliotoxins and hydrophilic polyhydroxy indolizidines are the two most important classes of compounds.

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[1] In this work the azabicyclo[4.3.0]nonane nomenclature was used in order to maintain clarity and consistency when comparing different heterocyclic systems

[2] For leading references to the biological activity of indolizidine *Alkaloids*, see: (a) Michael, J. P. *Nat. Prod. Rep.* **1997**, 14, 21-41. (b) Takahata, H.; Momose, T. In *The Alkaloids*; Cordell, G. A.; Ed.; Academic Press, Inc. : San Diego, **1993**; Vol. 44, Chapter 3.

[3] For recent examples of and leading references to the synthesis of natural indolizidines, see: (a) Angle, S. R.; Breitenbucher, J. G. in *Studies in Natural Products Chemistry; Stereoselective Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: New York, **1995**; Vol. 16, Part J, page 453-502. (b) Okano, T.; Sakaida, T.; Eguchi, S. *Heterocycles* **1997**, 44, 227-236. (c) Comins, D. L.; Zhang, Y. M. *J. Am. Chem. Soc.* **1996**, 118, 12248-12249. (d) Michael, J. P.; Gravestock, D. *Synlett* **1996**, 981-982. (e) Thanh, G. V.; Célérier, J.-P.; Lhommet, G. *Tetrahedron*: *Asymmetry* **1996**, 7, 2211-2212. (f) Chan, C.; Cocker J. D.; Davies, H. G.; Gore, A.; Green, R. H. Bioorg. Med. Chem. Lett. **1996**, 6, 161-164. (g) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, 118, 707-708. (h) Takahata, H.; Bandoh, H.; Momose, T. *Heterocycles* **1996**, 42, 39-42. (i) Muraoka, O.; Zheng, B-Z.; Okumura, K.; Tabata, E.; Tanabe, G.; Kubo, M. *J. Chem. Soc. Perkin Trans.* 1 **1997**, 113-119. (j) Lee, E.; Kang, T.; Chung, C. Bull. Korean Chem. Soc. **1996**, 17, 212-214. (k) Solladié, G.; Chu, G.-H. *Tetrahedron Lett.* **1996**, 37, 111-114. (l) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, 117, 5399-5400.

1.1.1 Pumiliotoxins

A wide variety of structurally unique and pharmacologically active compounds are obtained from amphibians. One unique source is the skin secretions of certain brightly coloured frogs native to the rain forests of western Colombia and Panama. Likely, since pre-Columbian times, these frogs have been employed by the Noanamá and Emberá Indians to prepare poison blow darts.[4] The first description of darts envenomed with skin secretions of poison frogs dates from 1825 and described the use of a single frog to charge at least 20 blow darts. The chemistry and pharmacology of "poison dart" frogs of the family *Dendrobatidae* was pioneered by Witkop, Daly and co-workers.[5] To date, more than 300 organic compounds have been isolated from this amphibian family, the vast majority of which are unique to Dendrobatid frogs.[6] The pumiliotoxin A and allopumiliotoxin classes of dendrobatid alkaloids are a group of ~ 40 alkylidene indolizidine alkaloids that display particularly significant pharmacological activities.[7] Pumiliotoxins A and B were the second and third dendrobatid alkaloids to be isolated and were initially obtained in 1967 from skin of the Panamanian poison frog *Dendrobates pumilio*.[8] Elucidation of the structure of these alkaloids was complicated by their instability in acid, likely due to their allylic hydroxyl group. The structure of these toxins remained unknown until 1980 when a simpler alkaloid, pumiliotoxin 251D, was isolated as the major alkaloid component of skin extracts of the ecuadorian poison frog, *Dendrobates tricolour (Epipedobates tricolour)*. Single-crystal X-ray analysis of pumiliotoxin 251D hydrochloride finally provided the key for revealing the constitution of the pumiliotoxin A alkaloids.[9]

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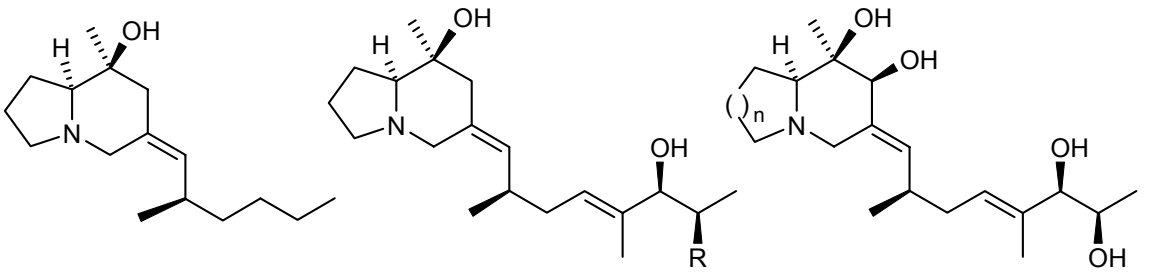
[4] (a) Myers, C. W.; Daly, J. W. *Sci. Am.* **1983**, 248, 120. (b) Märki, F.; Witkop, B. *Experentia* **1963**, 19, 329.
[5] For recent reviews, see: (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. *Alkaloids* **1993**, 43, 185. (b) Daly, J. W.; Garaffo, H. M.; Spande T. F. In *Alkaloids: Chemical and Biological Perspectives*; Vol. 13; Pelletier, S. W.; Ed.; Elsevier Science Ltd. : Oxford, **1999**; page 1.
[6] For a discussion of the possibility that the skin *Alkaloids* of dendrobatid frogs may have a dietary origin, see: Daly, J. W.; Secunda, S. I.; Garraffo, H. M.; Spande, T. F.; Wisnieski, A.; Cover, J. F. *Jr. Toxicon* **1994**, 32, 657.
[7] For recent general reviews, see: (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. *Alkaloids* **1993**, 43, 185. (b) Daly, J. W.; Spande, T. F. In *Alkaloids*: Chemical and Biological Perspectives; Pelletier, S. W.; Ed.; Wiley: New York, **1986**; Vol. 4, Chapter 1.
[8] Daly, J. W.; Myers, C. W. *Science* (Washington, D. C.) **1967**, 156, 970.
[9] Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. J.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, 102, 830.



(+)-Pumiliotoxin 251D

(+)-Pumiliotoxin A (R =H)
(+)-Pumiliotoxin B (R= OH)

n= 1 (+)-Allopumiliotoxin 339B
n= 2 (+)-Homopumiliotoxins

Fig. 2 Representative pumiliotoxin and allopumiliotoxin alkaloids.

The pumiliotoxin alkaloids are characterised by the bicyclic 8-hydroxy-8-methyl-6-alkylidene-indolizidine ring system (Fig. 2). The allopumiliotoxins contain an additional hydroxy group at C-7. Beside these two main classes another bicyclic alkaloid, namely homopumiliotoxin 223G, has been isolated in small quantities from the Panamanian poison frog Dendrobates pumilio and its structure analysed.[10] In this compound the indolizidine moiety is replaced by a quinolizidine ring.

Due to the great number of pumiliotoxins only a few have been given a common name. Instead a numbering system consisting of a bold faced number, corresponding to the nominal mass of the compound, plus a bold faced letter to distinguish compounds of the same mass, is used.

Pumiliotoxins A and B are relatively toxic and a subcutaneous dose of pumiliotoxin B of 20 μg can cause death in mice.[8] Recent studies indicate that pumiliotoxin B binds to an unique modulatory site on the voltage-dependent sodium channel and enhances sodium influx.[11] This ion flow stimulates phosphoinositide breakdown, which is believed to be ultimately expressed as cardiotonic and myotonic activities. Structure-activity studies of natural alkaloids and synthetic analogs have shown that the structure of the side chain is critical for these pharmacological activities.[11,12]

The intriguing pharmacological properties and the low availability of the compounds from their natural sources has led to the development of numerous syntheses of the pumiliotoxins. Important synthetic contributions have been made by the groups of Overman[13] and Trost[14] which have synthesised key members of the class of pumiliotoxins.

When contemplating the design of a total synthesis strategy for the pumiliotoxin alkaloids, attention is immediately drawn to the (Z)-alkylidene side chain. This unit presents particular problems, since

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[10] (a) Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, 43, 643-652. (b) Kibayashi, C.; Aoyagi, S.; Wang, T.-C.; Saito, K.; Daly, J. W.; Spande T. F. *J. Nat. Prod.* **2000**, 63, 1157-1159. (c) Tokuyama, T.; Tsujita, T. *Tetrahedron* **1991**, 47, 5415-5424.

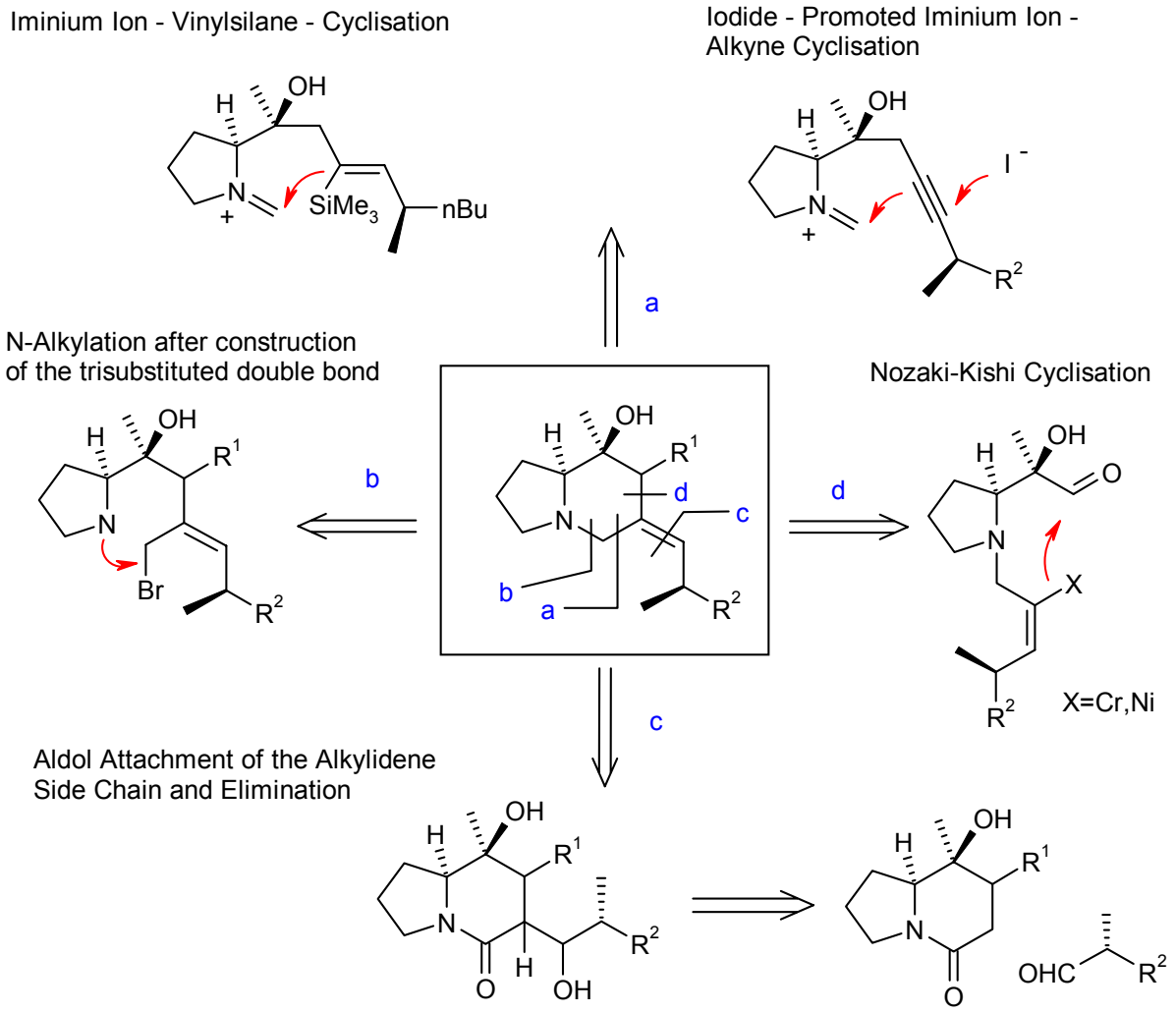
[11] (a) Gusovsky, F.; Padgett, W. L.; Creveling, C. R.; Daly, J. W. *Mol. Pharmacol.* **1992**, 42, 1104 and references cited therein. (b) Daly, J. W.; Nishizawa Y.; Padgett, W. L.; Tokuyama, T.; Smith A. L.; Holmes A. B.; Kibayashi C.; Aronstam R. S. *Neurochem. Res.* **1991**, 16, 1213.

[12] (a) Daly, J. W.; McNeal, E. T.; Overman, L. E.; Ellison, D. H. *J. Med. Chem.* **1985**, 28, 482. (b) Daly, J. W.; McNeal, E. T.; Gusovsky, F.; Ito, F.; Overman, L. E. *J. Med. Chem.* **1988**, 31, 477. (c) Daly, J. W.; Gusovsky, F.; McNeal, E. T.; Secunda, S.; Bell, M.; Creveling, C. R.; Nishizawa, Y.; Overman, L. E.; Sharp, M. J.; Rossignol, D. P. *Biochem. Pharmacol.* **1990**, 40, 315. (d) Siegl, P. K. S.; Overman, L. E. *Abstracts International Union of Physiological Science*s, Vancouver, Canada, July **1986**.

[13] For a recent review see: Overman L. E.; Franklin A. S. *Chem. Rev.* **1996**, 96, 505-522.

stereocontrolled synthesis of exocyclic alkenes is difficult to achieve. The prospects for the selective generation of the (*Z*)-side chain by a Wittig type functionalisation of a suitable precursor indolizidine ketone are low. Therefore, the majority of synthetic approaches have focused on the selective generation of an acyclic configurational stable alkene fragment that was used in a cyclisation to generate the pumiliotoxin framework.

The most applied strategies for the construction of the pumiliotoxin core are summarised in Scheme 1.

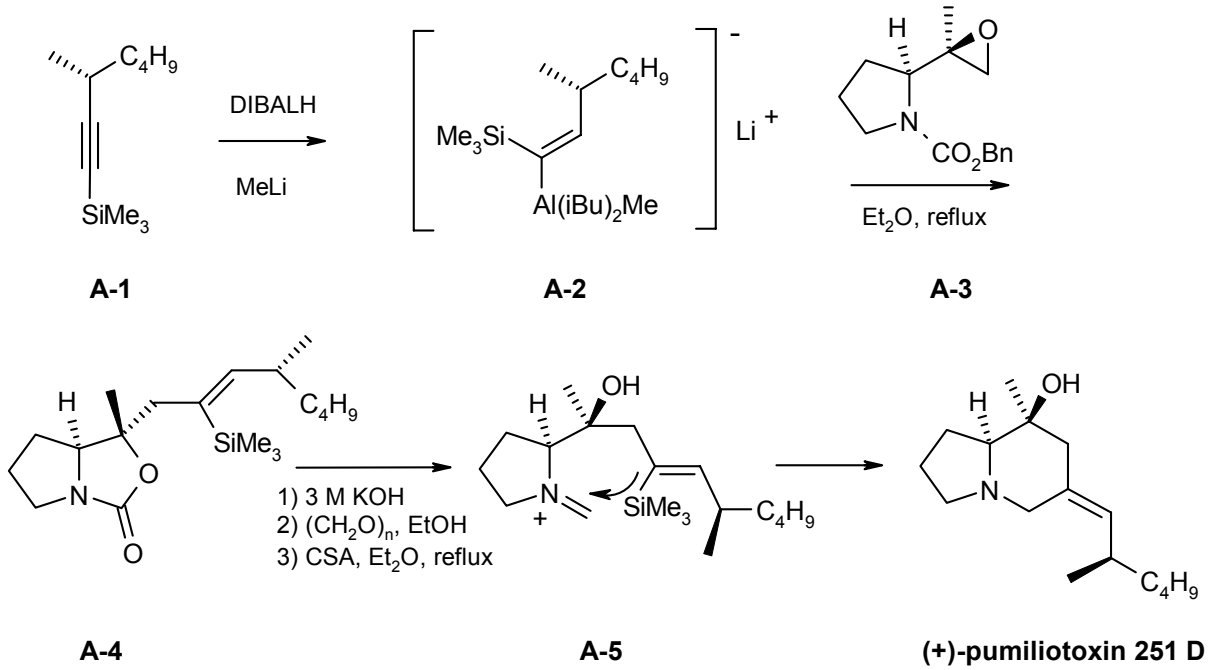


Scheme 1 Synthetic pathways to the alkylidene side chain of the pumiliotoxins

The *Iminium Ion - Vinylsilane - Cyclisation* strategy (a) was developed by Overman *et al*. based on the observation that bimolecular substitution reactions of vinylsilanes with electrophiles had recently been shown to proceed with retention of alkene configuration.[15] The vinylsilanes, despite their weak nucleophilic character, were found to be reactive in intramolecular cyclisation reactions with iminium ions as electrophiles. This synthetic pathway was successfully applied for the total synthesis of

[14] Trost, B. M.; Scanlan, T. S. *J. Am. Chem. Soc.* **1989**, 111, 4988.
[15] For first unambiguous reports, see: (a) Koenig, K. E.; Weber, W. P. *J. Am. Chem. Soc.* **1973**, 95, 3416. (b) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic: London, **1988**.

pumiliotoxin 251 D,[16] pumiliotoxin B[17] and pumiliotoxin A.[18] The total synthesis of pumiliotoxin 251D according to Overman *et al*. is depicted in Scheme 2.



Scheme 2 Total synthesis of pumiliotoxin 251D according to Overman *et al*.[16]

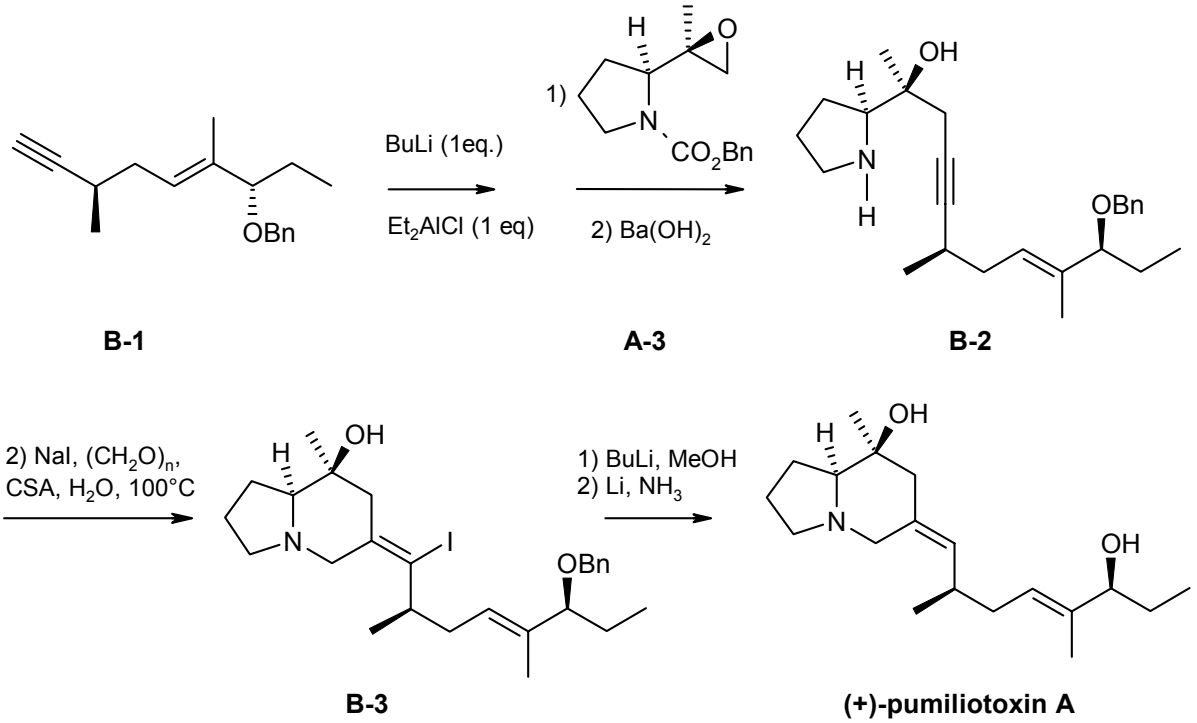
As part of this synthetic work (*R*)-silylalkyne **A-1** was converted into the vinylalanate **A-2** following a procedure introduced by Eisch.[19] This intermediate alanate reacted with the epoxide **A-3** to the bicyclic carbamate **A-4**. Although variable substituents at the vinylalanate could be used for this transformation this step required special optimisation for each side chain nucleophile and was often low yielding. After hydrolysis of **A-4** to the corresponding amino alcohol with ethanolic KOH and a reaction with paraformaldehyde, a cyclopentaoxazolidine was obtained. Subsequent heating in ethanol in the presence of 1 equiv of camphorsulfonic acid (CSA) generated the iminium ion **A-5** that directly yielded (+) pumiliotoxin 251D by cyclisation.

The major drawback to the iminium ion - vinylsilane cyclisation route to the pumiliotoxin alkaloids is the coupling of the vinylsilane side chain and pyrrolidine epoxide fragments. An alternative, conceptually simpler approach to the pumiliotoxin alkaloids, is the *Iodide-Promoted Iminium Ion-Alkyne Cyclisation* (a). The applicability of this method for the selective construction of the (*Z*)-alkylidene chain arises from the stereoelectronic preference for electrophile-nucleophile pairs to add to alkynes in an antarafacial fashion.[20] The intramolecular Mannich cyclisation of alkynyl amines in the

[16] Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, 103, 1851.
[17] Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, 104, 4192.
[18] Overman, L. E.; Lin, N.-H. *J. Org. Chem.* **1985**, 50, 3669.
[19] (a) Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, 36, 3520. (b) Eisch, J. J.; Damasevitz, G. A. *J. Org. Chem.* **1976**, 41, 2214.
[20] Patai, S. *Chemistry of the Carbon-Carbon Triple Bond*; Wiley: New York, **1978**.

presence of reactive external nucleophiles was discovered in 1988 by Overman *et al*.[21] This reaction proceeded under aqueous conditions with high yields and afforded exclusively the (*E*)-1-iodoalkylidene stereoisomer that can be reduced with retention of the double bond geometry. The mechanistic studies of this new method were followed by their successful application in the total syntheses of (+)-pumiliotoxins A and B and allo-pumiliotoxin 339[22] and later in the total synthesis of (+)-pumiliotoxin 251 D and analogs by Dick *et al*.[23]

The total synthesis of (+)-pumiliotoxin A is outlined in the following Scheme 3.



Scheme 3 Total synthesis of (+) pumiliotoxin A according to Overman *et al*.[22]

The chiral alkyne **B-1**[18] was treated successively with *n*-BuLi, Et_2AlCl and epoxide **A-3** providing the coupling product in a 95% yield. The benzyloxycarbonyl group was cleaved with $Ba(OH)_2$ in refluxing H_2O-diglyme to generate the amino alcohol **B-2**. Iodide-promoted cyclisation of the formaldiminium ion formed from **B-2** gave the isomerically pure alkylidene indolizidinone **B-3** with a yield of 60%. Deiodination of **B-2** followed by cleavage of the benzyl protecting group finally provided (+)-(15*S*)-pumiliotoxin A with a 75% yield.

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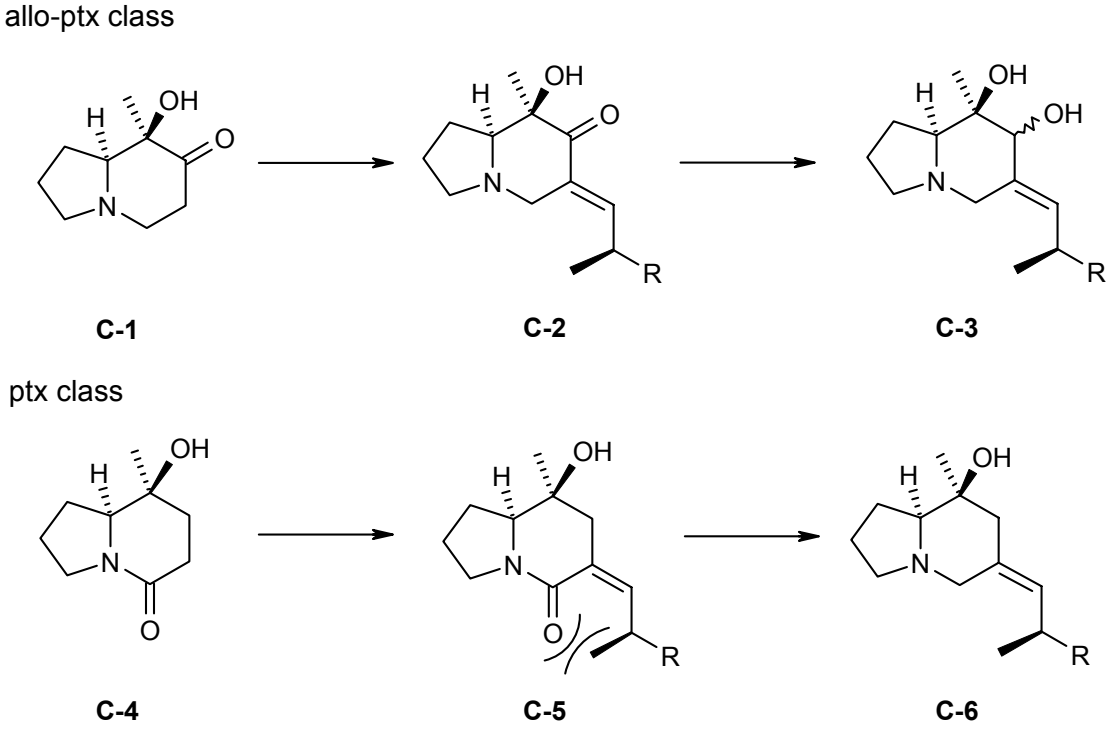
[21] (a) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, 110, 612. (b) Arnold, H.; Overman, L. E.; Sharp, M. J.; Witschel, M. C. Org. Syn. **1991**, 70, 111. (c) Overman, L. E.; Sarkar, A. K. *Tetrahedron Lett.* **1992**, 33, 4103. (d) Overman, L. E.; Rodriguez-Campos, I. M. *Synlett* **1992**, 995.

[22] (a) synthesis of ptx A and B : Overman, L. E.; Sharp, M. J. *Tetrahedron Lett.* **1988**, 29, 901. (b) synthesis of allo-ptx 339A : Overman, L. E.; Robinson, L. A.; Zablocki, J. *J. Am. Chem. Soc.* **1992**, 114, 368. (c) synthesis of ptx-267A, 323 B' and 339A : Caderas, C.; Lett, R; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, 118, 9073-9082.

[23] Bargar, T. M.; Lett, R. M.; Johnson, P. L.; Hunter, J. E.; Chang, C. P.; Pernich, D. J.; Sabol, M. R.; Dick, M. R. *J. Agric. Food Chem.* **1995**, 43, 1044.

A third approach that has been employed for the introduction of the alkylidene side chain is the *aldol - dehydration sequence* (c) illustrated in Scheme 4.



Scheme 4 Application of the aldol approach for the alkylidene chain introduction

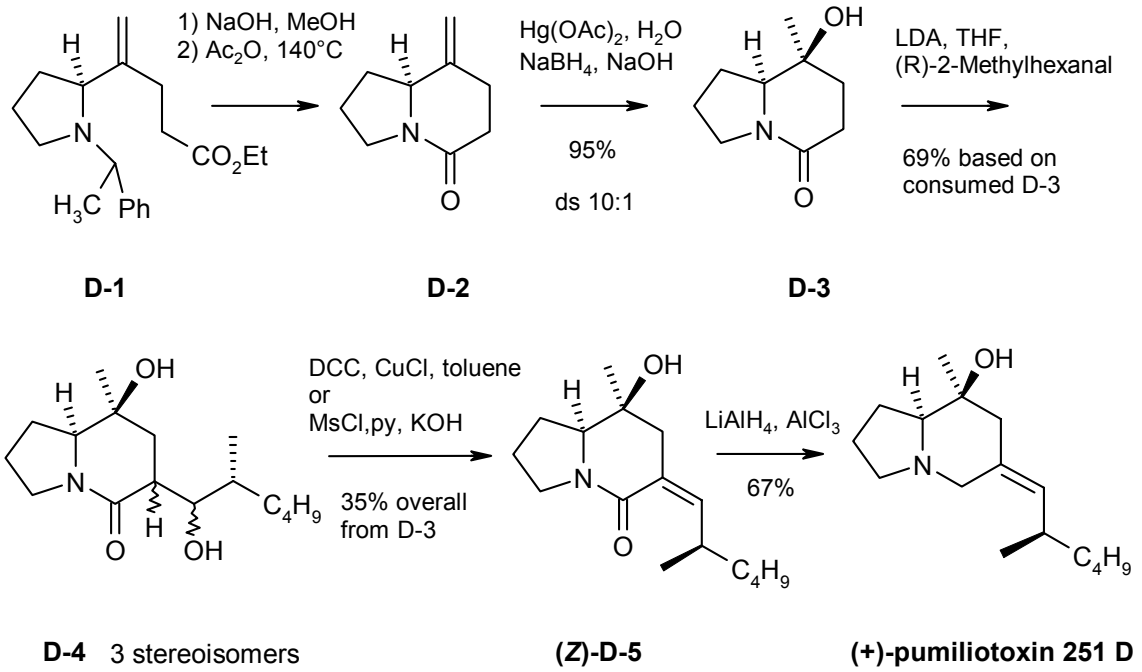
The allo-pumiliotoxin series **C-3** can be obtained by the reduction of the indolizidine ketone **C-2** prepared by the two step aldol addition-dehydration sequence starting from the ketone **C-1**. The prospects for the successful application of this transformation are good due to the thermodynamic preference of trisubstituted exocyclic enones to exist in an (*E*)-configuration. Indeed some examples for total syntheses of allo-pumiliotoxins have been reported in the past that based on this strategy.[24]

The applicability of the aldol addition-dehydration sequence for the synthesis of the pumiliotoxin series C-4 is limited, since in the elimination step the thermodynamically disfavoured exocyclic (*Z*)-enone is formed. This excludes nonselective dehydration protocols and requires reactions proceeding exclusively via an E1 or an E2 mechanism. Additionally, the aldol addition should generate either the *syn* or the *anti* aldols that have to be eliminated stereospecifically by the E1 or E2 protocols.

These problems become evident as seen in the total synthesis of (+)-pumiliotoxin 251D reported by Gallagher and co-workers (Scheme 5).[25]

[24] For allo-ptx 267A and 339B see : (a) Overman, L. E.; Goldstein, S. W. *J. Am. Chem. Soc.* **1984**, 106, 5360. (b) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, 57, 1179. for allo-ptx 323B' see : Tan, C.-H.; Holmes, B. A. *Chem. Eur. J.* **2001**, 7, 1845-1854.

[25] Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, 113, 2652.



Scheme 5 Total synthesis of (+)-pumiliotoxin 251D according to Gallagher *et al.* [25]

As part of their approach vinyl pyrrolidine **D-1** was transformed into the bicyclic indolizidinone **D-2**. Stereoselective introduction of the axial tertiary alcohol was achieved using a hydroxymercuration-reduction sequence (95% yield, ds = 10:1). Since the tertiary alcohol **D-3** represents an important intermediate for the synthesis of pumiliotoxins, many other synthetic methods for the preparation of this compound have been developed in addition to the strategy, introduced by Gallagher.[26]

Addition of (*R*)-2-methylhexanal to the lithium enolate of lactam **D-3** gave a mixture of three aldol isomers **D-4** together with 23% of recovered **D-3**. Stereospecific *syn*-elimination of one isomer, isolated with a 27% yield, using DCC-CuCl[27] yielded exclusively the desired (*Z*)-ene lactam **(D-5)**, while *anti*-elimination (CH_3SO_2Cl, KOH)[28] of the remaining inseparable mixture of isomers gave only a 2.6:1 mixture of **(*E*)-** and **(*Z*)- D-5**. Deoxygenation of **(*Z*)-D-5** with $LiAlH_4$-$AlCl_3$ completed the synthesis of (+)-pumiliotoxin 251D.[29]

Recently, an additional synthetic application of the aldol strategy was described by Santos and Pili in the total synthesis of the (±)-Homopumiliotoxin 223G (Scheme 6).[30] They reported the stereoselective

[26] (a) Barrett, A. G. M.; Damiani, F. *J. Org. Chem.* **1999**, 64, 1410-1411. (b) Cossy, J.; Cases, M.; Pardo, D. G. *Synlett* **1996**, 909-910. (c) Ni, Y.; Zhao, G; Ding, Y. *J. Chem. Soc., Perkin Trans.* 1, **2000**, 3264–3266. (d) Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, 55, 8905.

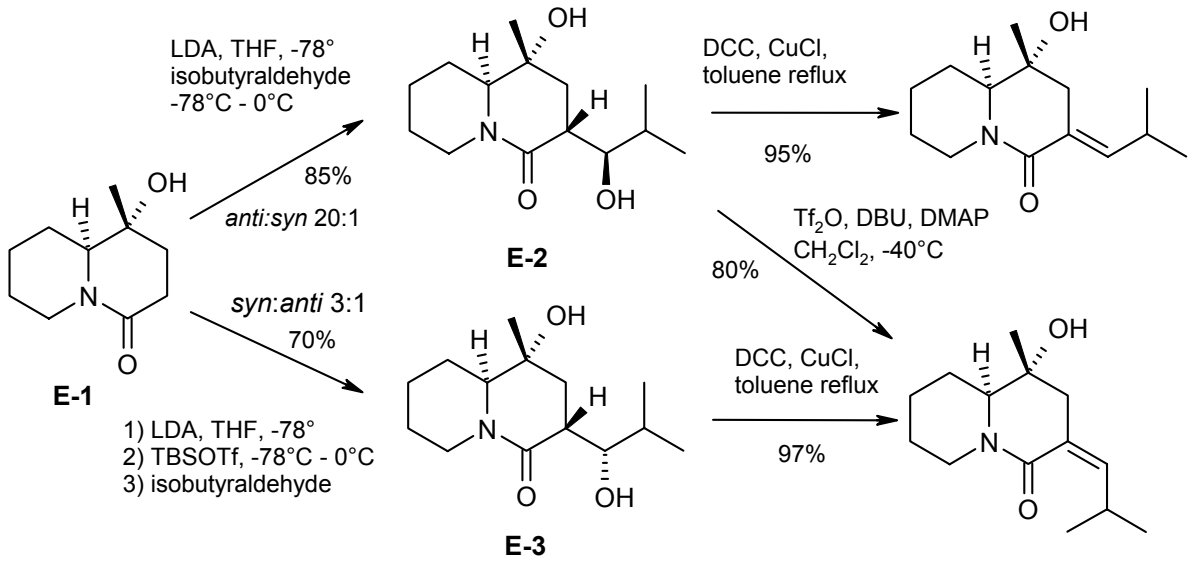
[27] Corey, E. J.; Andersen, N. H.; Carlson, R. M.; Paust, J.; Vedejs, E.; Vlattas, I.; Winter, R. E. K. *J. Am. Chem. Soc.* **1968**, 90, 3245.

[28] Bouffard, F. A.; Johnston, D. B. R.; Christensen, B. G. *J. Org. Chem.* **1980**, 45, 1130.

[29] Large differences between the reported optical rotation for compound D-5 by Gallagher *et al.* and own measurements suggest that the compound D-5 was a partial racemate at the stereogenic centre of the side chain For further discussions see 2.9.4.

[30] Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, 42, 6999-7001.

aldol addition of isobutyraldehyde to the bicyclic amide **E-1**. Under aldol conditions analogous to those reported by Gallagher *et al*., the *anti* aldol isomers were formed preferentially (*anti*/*syn* 20:1) with a 85% yield. In contrast, under Mukaiyama aldol conditions the *syn* aldol isomers predominated. Both isomers could be stereospecifically dehydrated by an *anti* elimination using Stork protocol[31] or a *syn* elimination using DCC/CuCl resulting in respectable yields.



Scheme 6 Part of the total synthesis of (±)-homopumiliotoxin 223G by Santos and Pili [30]

Finally, two other strategies for the construction of the pumiliotoxin alkaloids should be mentioned. The stereospecific hydrostannylation or hydrosilylation of an alkyne is the key transformation for the construction of the double geometry in these strategies. Kibayashi *et al*. utilised an intramolecular *Nozaki-Kishi cyclisation* (path d in the retrosynthesis Scheme 1) as the central step in their efficient approach to the allopumiliotoxins.[32] This pivotal step generates the indolizidine framework, installs the (*E*)-alkylidene side chain and establishes the C-7 hydroxyl configuration in a single operation. A similar approach was used by Wang and Montgomery with the development of a nickel-catalysed hydrosilylation of an alkyne and application for the total synthesis of allo-pumiliotoxin 267 A.[33]

The radical hydrostannylation of an alkyne and subsequent palladium catalysed substitution of the resulting vinylstannane by carbon monoxide is another reported strategy applied to the total synthesis of pumiliotoxins[34] and allo-pumiliotoxins. However, the stereoselectivity of the radical initiated hydrostannylation was low (~ 3:1).

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[31] Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, 104, 310.
[32] (a) Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, 115, 11393-11409. (b) Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1992**, 114, 10653-10654. (c) Kibayashi, C. *Pure Appl. Chem.* **1994**, 66, 2079.
[33] Wang, T.-C.; Montgomery J. *J. Am. Chem. Soc.* **1999**, 121, 6098-6099.
[34] Total synthesis of ptx A and allo-ptx 225F : Hirashima, S.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **1999**, 121, 9873–9874;

In conclusion it is clear that the pumiliotoxin alkaloids have proven to be valuable research tools in pharmacology and may serve as models for the development of new myotonic or cardiotonic agents as well as insecticides. A number of innovative syntheses of the pumiliotoxin A and allopumiliotoxin alkaloids have been developed in the last 15 years. The significance of these synthetic accomplishments is heightened by the absence of alkaloids in captive-raised dendrobatid frogs[35] and the scarcity and threatened existence of these frogs in nature. Besides the access to substantial quantities of the natural alkaloids, chemical total synthesis has provided numerous analogs of the pumiliotoxin A and allopumiliotoxin alkaloids which have contributed substantially to define structure-activity relationships. For example, it is now clear that cardiotonic and myotonic activities in the pumiliotoxin A series are markedly dependent on the structure of the alkylidene side chain.[36] Thus, the development of new, high convergent synthetic ways to the pumiliotoxin alkaloids remains a challenge in organic synthesis.

1.1.2 Polyhydroxylated Indolizidines

A variety of alkaloids possessing a polyhydroxylated indolizidine structure have been isolated from natural sources, including plants and microorganisms. Some of them are excellent inhibitors of biologically important pathways, including the binding and processing of glycoproteins and show potent glycosidase inhibitory activities.[37] Among naturally occurring polyhydroxylated indolizidines, castanospermine[38] (a potent *R*-glycosidase inhibitor), swainsonine[39] (a potent *R*-mannosidase inhibitor)

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[35] Daly, J. W.; Secunda, S. I.; Gorraffo, H. M.; Spande, T. F.; Wisnieski, A.; Nishihira, C.; Cover, J. F.; *Jr. Toxicon* **1992**, 30, 887.

[36] (a) Daly, J. W.; McNeal, E. T.; Overman, L. E.; Ellison, D. H. *J. Med. Chem.* **1985**, 28, 482. (b) Daly, J. W.; McNeal, E. T.; Gusovsky, F.; Ito, F.; Overman, L. E. *J. Med. Chem.* **1988**, 31, 477. (c) Daly, J. W.; Gusovsky, F.; McNeal, E. T.; Secunda, S.; Bell, M.; Creveling, C. R.; Nishizawa, Y.; Overman, L. E.; Sharp, M. J.; Rossignol, D. P. *Biochem. Pharmacol.* **1990**, 40, 315. (d) Siegl, P. K. S.; Overman, L. E. *Abstracts International Union of Physiological Science*s, Vancouver, Canada, July 1986.

[37] For leading reviews, see: (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron*: *Asymmetry* **2000**, 11, 1645-1680. (b) Elbein, A. D.; Molyneux, R. J. Alkaloid Glycosidase Inhibitors. In *Comprehensive Natural Products Chemistry*; Barton, D.; Nakanishi, K.; Meth-Cohn, O.; Eds.; Elsevier: Oxford, **1999**; Vol. 3, p 129. (c) Sears, P.; Wong, C.-H. *Chem. Commun.* **1998**, 1161-1170. (d) Ganem, B. *Acc. Chem. Res.* **1996**, 29, 340-347. (e) Dwek, R. A. *Chem. Rev.* **1996**, 96, 683-720. (f) Kaushal, G. P.; Elbein, A. D. *Methods Enzymol.* **1994**, 230, 316. (g) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, 26, 182-190. (h) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, 48, 319-384. (i) Sinnot, M. L *Chem. Rev.* **1990**, 90, 1171-1202.

[38] (a) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworth, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, 20, 811-814. (b) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Stirton, C. H.; Carter, D.; Hegarty, M. P.; Bell, E. A. *Phytochemistry* **1988**, 27, 1403-1406.

[39] (a) Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, 95, 2055-2056. (b) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, 32, 2257-2264. (c) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, 39,29-32. (d) Molyneux, R. J.; McKenzie, R. A.; O'Sullivan, B. M.; Elbein, A. D. *J. Nat. Prod.* **1995**, 58, 878-886.

and lentiginosine[40] (an amyloglycosidase inhibitor) have attracted the greatest attention from both synthetic and biological points of view and represent good examples of tetrahydroxylated, trihydroxylated and dihydroxylated indolizidines, respectively (Fig. 3).

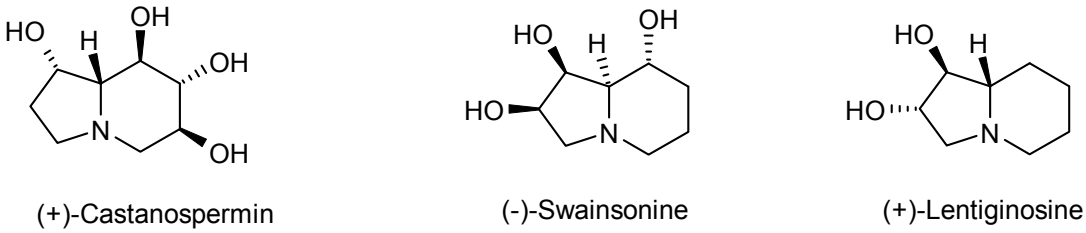


Fig. 3 Representative examples of glycosidase inhibitors with the structure of polyhydroxylated indolizidines.

To find structure-activity relationships, this interest has been extended to the synthesis of stereoisomers and analogues.[41,42,43,44] Although in some cases there is a close structural resemblance between the biologically active indolizidine and the natural sugar substrate, in many cases this resemblance does not exist. For instance, swainsonine, which is one of the strongest *R*-mannosidase inhibitors, lacks any significant resemblance with mannose. Since the structure-activity relationships in indolizidines are not straightforward, many stereoisomers and analogues have been synthesised and their biological activities tested. These analogues have been used as biochemical tools and have been examined as chemotherapeutic agents against diabetes,[45] cancer,[46] and HIV.[47] Their activity is believed to be a result of their ability to mimic the transition state involved in substrate hydrolysis.[37] For

[40] For recent references on the synthesis of lentiginosine and analogues, see: (a) Goti, A.; Cardona, F.; Brandi, A. *Synlett* **1996**, 761. (b) Goti, A.; Cardona, F.; Brandi, A.; Picasso, S.; Vogel, P. *Tetrahedron*: *Asymmetry* **1996**, 7, 1659. (c) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, 60, 398. (d) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, 60, 6806. (e) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, 60, 398. (f) Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, 35, 949. (g) Gurjar, M. K.; Ghost, L.; Syamala, M.; Jayasree, V. *Tetrahedron Lett.* **1994**, 35, 8871.

[41] For a recent review on the synthesis of polyhydroxy indolizidines, see: Burgess, K.; Henderson, I. *Tetrahedron* **1992**, 48, 4045-4066 and ref 3d,g.

[42] For a recent synthesis of castanospermine and a comprehensive listing of syntheses since **1992**, see: Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, 121, 3046-3056.

[43] Recent syntheses of swainsonine: (a) de Vicente, J.; Gómez Arrayás, R.; Cañada, J.; Carretero, J. C. *Synlett* **2000**, 53-56. (b) Mukai, C.; Sugimoto, Y.; Miyazawa, K.; Yamaguchi, S.; Hanaoka, M. *J. Org. Chem.* **1998**, 63, 6281-6287. (c) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, 62, 1112-1124. (d) Ferreira, F.; Greck, C.; Genêt, J. P. *Bull. Soc. Chim. Fr.* **1997**, 134, 615-000. (e) For a comprehensive listing of syntheses before **1996**, see: Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, 61, 7217-7221. (f) Zhou, W.-S.; Xie, W.-G.; Lu, Z.-H.; Pan, X.-F. *Tetrahedron Lett.* **1995**, 36, 1291-1294. (g) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, 59, 1358-1364. (h) Nemr, A. E. *Tetrahedron* **2000**, 56, 8579-8629.

[44] For recent examples of related, designed polyhydroxylated aza-Heterocycles see: (a) Le, V. D.; Wong, C.-H. *J. Org. Chem.* **2000**, 65, 2399-2409. (b) Heightman, T. D.; Vasella, A. T. *Angew. Chem.; Int. Ed. Engl.* **1999**, 38, 750-770.

[45] (a) Platt, F. M.; Neises, G. R.; Reinkensmeier, G.; Townsend, M. J.; Perry, V. H.; Proia, R. L.; Winchester, B.; Dwek, R. A.; Butters, T. D. *Science* **1997**, 276, 428-431. (b) Witczak, Z. J. Carbohydrates as New and Old Targets for Future Drug Design. In *Carbohydrates in Drug Design*; Witczak, Z. J.; Ed.; Marcel Dekker Inc. : New York, **1997**; p 1. (c) Robinson, K. M.; Begovic, M. E.; Rhinehart, B. L.; Heinke, E. W.; Ducep, J.-B.; Kastner, P. R.; Marshall, F. N.; Danzin, C. *Diabetes* **1991**, 40, 825. (d) Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C.-H.; Liu, P. S. *J. Org. Chem.* **1989**, 54, 2539- 2542.

[46] For a review, see: Gross, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, 1, 935-944.

example, the activity of castanospermine against glycosidases has been tied to the similarity of the six-membered ring to the glycosyl cation.[48] In a less obvious way, the anti-mannosidase activity of swainsonine has been related to the resemblance of the five-membered ring to the mannosyl cation.[49] It has been suggested that their rigid, bicyclic structures are responsible for their potent activity.[50]

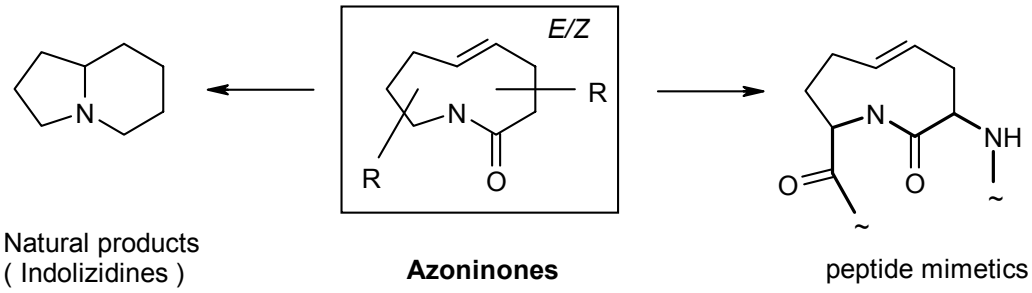
Due to their vicinal polyhydroxylated structure, most of the reported syntheses of castanospermine, swainsonine and analogues employ natural sugars as starting materials. However, this approach often has the drawback of lacking enough flexibility for the ready preparation of a wide range of stereoisomers from a common intermediate.

[47] (a) Ratner, L.; Heyden, N. V.; Dedera, D. *Virology* **1991**, 181, 180-192. (b) Wikler, D. A.; Holan, G. *J. Med. Chem.* **1989**, 32, 2084-2089. (c) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoog, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U. S. A.* **1988**, 85, 9229-9233.
[48] Szumilo, T.; Kaushal, G. P.; Elbein, A. D. *Arch. Biochem. Biophys.* **1986**, 247, 261-271.
[49] Tulsiani, R. P.; Harris, T. M.; Touster, O. *J. Biol. Chem.* **1982**, 257, 7936-7939.
[50] Hempel, A.; Camerman, N.; Mastropaolo, D.; Camerman, A. *J. Med. Chem.* **1993**, 36, 4082-4086.

1.2 Azoninones as Key Intermediates in Natural Product Synthesis

1.2.1 Synthesis of Azoninones

The synthesis of medium-sized ring lactams is both a challenge, as their formation from acyclic precursors is disfavoured by enthalpy and entropy and of practical importance, since they occur as the skeletons of a variety of biologically active compounds and natural products. The presence of a double bond within the cyclic structure enormously enhances their applicability, since this functionalisation enables the efficient synthesis of naturally occurring pyrrolizidines, indolizidines and quinolizidines as well as bicyclic amino acids, intensively used as dipeptide mimetics.



Many synthetic routes for the preparation of saturated and unsaturated medium-sized ring lactams have been developed and discussed in numerous reviews[51] due to their central role.

Unsaturated nine-membered ring lactams (azoninones), an important subclass of cyclic lactams, are key compounds for the synthesis of indolizidine derived compounds. Basically, there are two main approaches to the azoninones, either by a cyclisation of suitable functionalised long-chain precursors or by ring expansion of appropriately substituted smaller rings.

The easiest way to generate lactams via a cyclisation strategy appeared to be the intramolecular reaction of ω-amino esters but in many cases the direct conversion failed or was low yielding. The use of activating groups either at the carboxyl or amino function and high dilution conditions to prevent di- or polymerisation significantly increased the yields of unsaturated lactams as shown during the synthesis of manzamine alkaloids (Scheme 7).[52] The azacycloundecane ring fragment **F-3** was generated by a cyclisation of the ω-amino acid **F-1** via an intermediary formed pentafluorophenylether **F-2** in a 93% yield under high dilution conditions. In this case the *Z*-configured 5,6-double bond supported the smooth lactamisation by a pre-orientation of the carbon chains.

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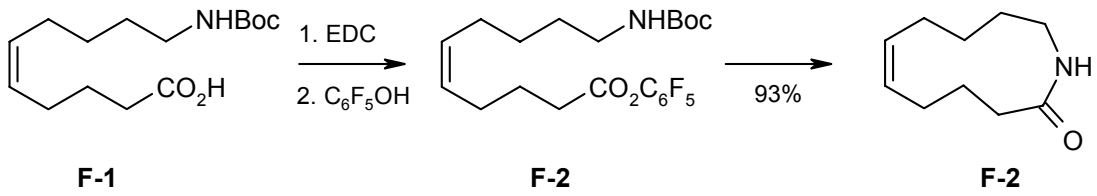
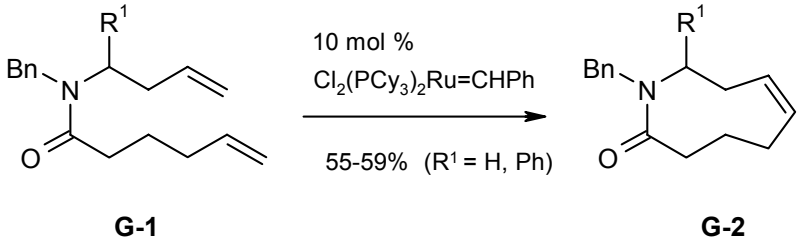
[51] See (a) Nubbemeyer U. *Top. Curr. Chem.* **2001**, 216, 125-196. (b) Yet, L.; *Chem. Rev.* **2000**, 100, 2963-3007 and literature cited therein.

[52] (a) Winkler, J. D.; Stelmach, J.; Siegel, M. G.; Haddad, N.; Axten, J. M.; Dailey, W. P.; III. *Isr. J. Chem.* **1997**, 37, 47. (b) T. Vidal *et al*. *Tetrahedron* **1998**, 54, 5959-5966.



Scheme 7 Formation of an unsaturated cyclic amide by lactamisation

A more intensively explored approach for the generation of unsaturated cyclic lactams via a cyclisation is the ring-closing metathesis (RCM). The applicability of the RCM is based on the ease of generating suitable reactants, the reliability in running the cyclisations with high yield, the toleration of many functional groups and the stereoselective formation of *E*- or *Z*-olefins. A large number of 6 to 12-membered lactams have been prepared using this methodology.[53] Eight- to ten-membered unsaturated ring lactams have been intensively studied for their potential use as mimetics of cyclic peptides.[54] As a typical example the diethylenic amides **G-1** were cyclised with the Grubbs Catalyst in good yields to the azoninones **G-2** (Scheme 8).[54b] The authors pointed out that seven and eight-membered unsaturated lactams can easily be obtained by RCM reactions whereas in the case of N-*unprotected* reactants no cyclisation was observed. Since the preferred conformation of secondary amides is the *trans*-conformation, the cyclisation is entropically disfavoured due to the wrong orientation of both reactive chain ends. When tertiary amides like **G-1** were used, the yields were substantially better, presumably caused by the presence of a suitable pre-orientated *cis*-rotamer.



Scheme 8 Synthesis of nine-membered lactams using ring closing metathesis

N-Substitution of a secondary amide to induce a conformational change of the amide has also been applied for the synthesis of other medium-sized ring lactams.[55]

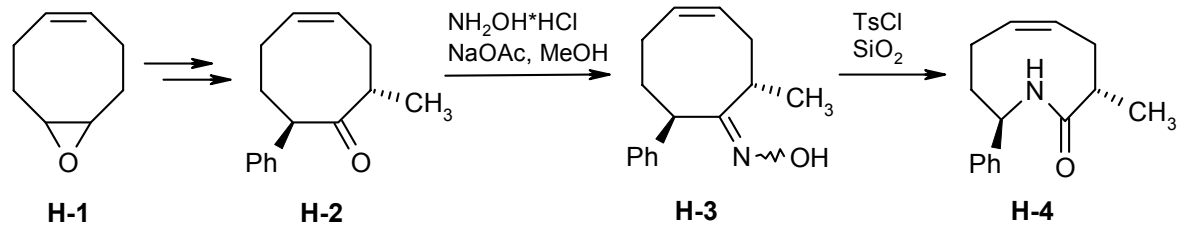
Another strategy for the synthesis of unsaturated azoninones is the ring enlargement of a smaller ring by the insertion of N or C atoms. This can be achieved by numerous rearrangement reactions such as

[53] For reviews of the RCM see (a) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, 3, 32. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, 54, 4413. (c) Armstrong, S. K. *J. Chem. Soc. Perkin Trans.* 1 **1998**, 371. (d) Schuster, M.; Blechert, S. *Angew. Chem.; Int. Ed. Engl.* **1997**, 36, 2036. (e) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, 28, 446. (f) Schmalz, H.-G. *Angew. Chem.; Int. Ed. Engl.* **1995**, 34, 1833. (g) Fürstner, A.; Langemann, *Synthesis* **1997**, 793. (i) Fürstner, A. *Top. Catal.* **1997**, 4, 285. (k) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, 36, 2124. (l) Fürstner, A. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 3012.

[54] For recent examples see (a) Creighton, C. J.; Reitz A. B. *Org. Lett.* **2001**, 6, 893-895. (b) Vo-Thanh, G.; Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Synlett* **2001**, 1, 37-40. (c) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. R. *J. Am. Chem. Soc.* **1998**, 120, 4334-4344.

[55] Chao, W.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, 41, 9199.

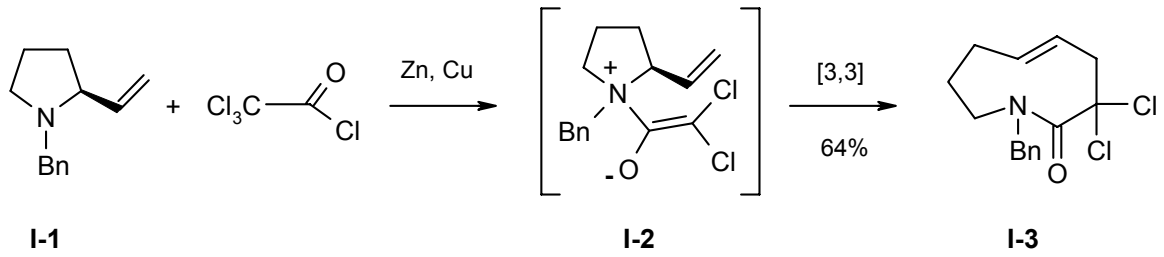
Beckmann-, Schmidt- and aza-Claisen rearrangements. An example for the construction of the unsaturated azoninone system by the Beckmann rearrangement is illustrated in Scheme 9 :



Scheme 9 Azoninone synthesis via Beckmann rearrangement[56]

The N-insertion reactions only allow expansions by a single additional ring atom to lactams, whereas C-insertions are characterised by a higher flexibility. Furthermore the highly ordered transition state during a sigmatropic process enables the construction of stereogenic centres by asymmetric induction and a transfer of chirality. For the generation of unsaturated heterocycles the Claisen rearrangement is the method of choice. An energetically preferred conformation of the reactants combined with a high stereocontrol during the rearrangement allows the synthesis of strained *E*-azoninones that cannot be achieved by other methods.

The first example for the formation of an *E*-azoninone by an ketene Claisen rearrangement was described in 1991 by Edstrom *et al.*(Scheme 10).[57]



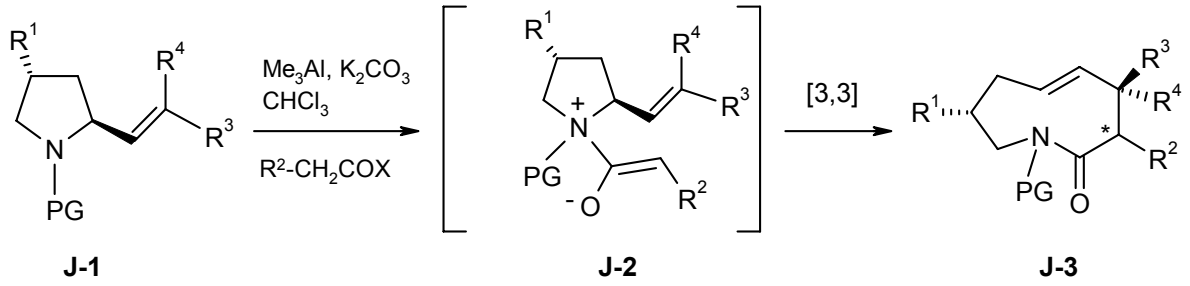
Scheme 10 Ketene Claisen rearrangement of vinyl pyrrolidine I-1

The ketene Claisen rearrangement of N-benzyl-2-vinyl pyrrolidine **I-1** with an *in-situ* generated dichloroketene led to the azoninone **I-3** in a yield of 64% via the presumed intermediate zwitterionic form **I-2**. Though the double bond included in the medium-sized ring was found to be exclusively *E* configured, the rearrangement suffered from the complete loss of chiral information. The high potential of this reaction was intensively examined. By variations of the reaction conditions and mechanistic studies the rearrangement could be improved to a highly stereoselective process.

[56] (a) Olson, G. E.; Voss, M. E.; Hill, D. E.; Kahn, M.; Madison, V. S.; Cook, C. M. *J. Am. Chem. Soc.* **1990**, 112, 323-333. (b) Wilson, S. R.; Sawicki, R. A.; *J. Heterocycl. Chem.* **1982**, 19, 81-83.

[57] (a) Edstrom, E. D. *J. Am. Chem. Soc.* **1991**, 113, 6690-6692. (b) Edstrom, E. D. *Tetrahedron Lett.* **1991**, 2, 5709.

An extension of this reaction and the application of a variety of α-substituted carboxylic acid halides as precursors of the ketenes is possible by the intermediate generation of the active zwitterionic species. This method was first introduced by Nubbemeyer and Diederich and used the activation of the acylic precursor by a lewis acid and the base induced deprotonation of an intermediate acylammonium salt (Scheme 11).[58]

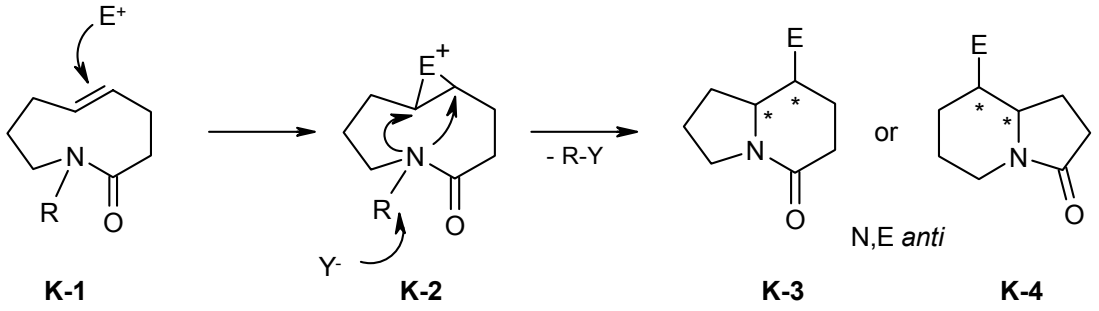


Scheme 11 The zwitterionic aza-Claisen rearrangement

These variations in reaction conditions now allowed to benefit from the advantage of a defined transition state during the aza-Claisen rearrangement. A high level of simple diastereoselectivity and high extent of 1,3- and 1,4-chirality transfer of the aza-Claisen rearrangement was reported.[58,63,64] The stereochemical details of the improved variants of the aza-Claisen rearrangement play a central role for the interpretation of the results of this work and will therefore be discussed more detailed (see chapter 2.1.2).

1.2.2 Construction of Indolizidinone Framework by Ring Contraction of Azoninones

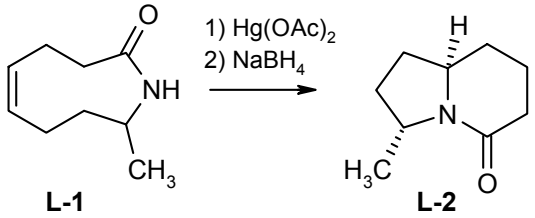
The key step for the application of azoninones in natural product synthesis is the transannular ring contraction, as depicted in Scheme 12.



Scheme 12 Construction of the indolizidine core via transannular ring contraction.

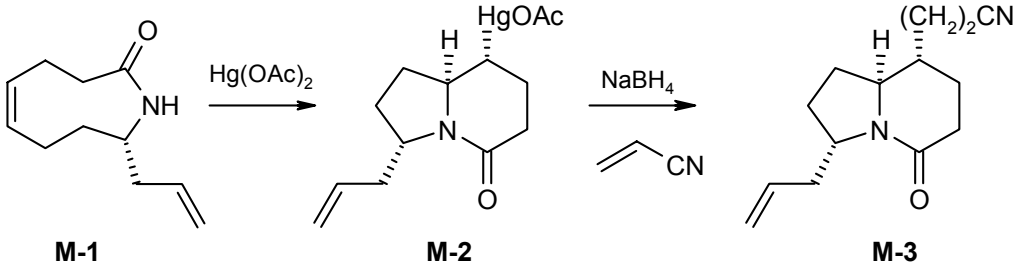
[58] (a) Nubbemeyer, U. *J. Org. Chem.* **1995**, 60, 3773-3780. (b) Nubbemeyer, U. *J. Org. Chem.* **1996**, 61, 677-3686. (c) Diederich, M.; Nubbemeyer, U. *Chem. Eur. J.* **1996**, 2, 894-900. (c) Diederich, M.; Nubbemeyer, U. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 1026.

After the attack of the electrophile E^+ on the azoninone **K-1** an intermediate cyclic onium ion **K-2** is formed that is subjected to an intramolecular attack by the nitrogen atom. The N,E-*anti* configured products **K-3** or the regioisomer **K-4** are generated after the removal of the nitrogen protecting group R^1 by a nucleophile Y^-. At the beginning of this work only a little about the factors that control the regio- and stereoselectivities were known. Some earlier examples have shown that the transannular ring contraction could proceed stereoselectively. The first example of a regio- and stereoselective transannular ring contraction was reported in 1979 by Wilson and Sawicki (Scheme 13).[59] The *Z*-configured azoninone **L-1** underwent, upon treatment with mercuric acetate in aqueous tetrahydrofuran, a transannular cyclisation. Reduction with sodium borohydride resulted in the product **L-2**. IR evidence (C=O absorption at 1640 cm^{-1}) verified the formation of a six-membered lactam and the NMR spectrum indicated the presence of a single isomer.



Scheme 13 First transannular cyclisation of a *Z*-azoninone

Some years later Kahn and Devens[60] studied the cyclisation of 9-allylhexahydro-azonin-2-one **M-1** with mercuric diacetate during their synthesis of a non-peptide mimic of an immunosuppressant tripeptide (Scheme 14). In this case also one diastereomer **M-2** was isolated, which reacted further with acrylonitrile.

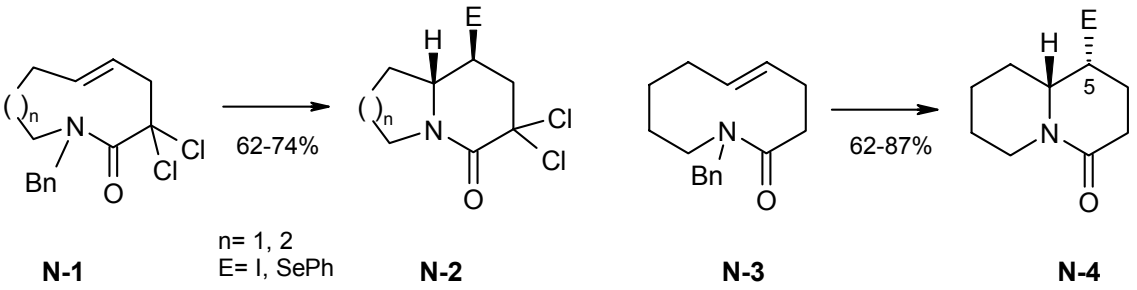


Scheme 14 Transannular cyclisation during the synthesis of an immunosuppressant

The first cyclisation of an *E*-configured azoninone was reported by Edstrom[57] in 1991 who studied the cyclisation of similar macrocycles (Scheme 15). A single bicyclic product **N-2** was obtained in all cases with complete regio- and stereocontrol. If the reaction was performed on the 10-membered lactam **N-3** without chlorosubstituents a total reversion of the C-5 centre was obtained. This result was

[59] (a) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, 44, 330. (b) Wilson, S. R.; Sawicki, R. A.; *J. Heterocycl. Chem.* **1982**, 19, 81-83. (c) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, 44, 287.
[60] Kahn, M.; Devens, B. *Tetrahedron Lett.* **1986**, 27, 4841.

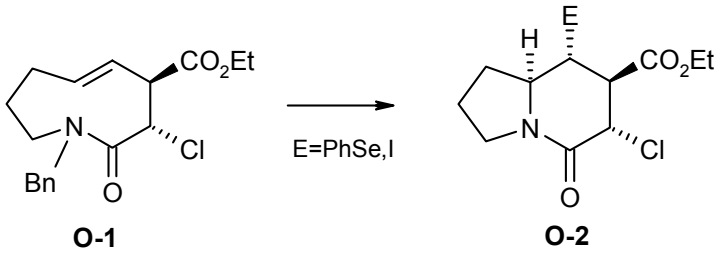
explained by a competitive attack on the bridged ion of the external halide and subsequent substitution by the nitrogen thus forming **N-4**.



Scheme 15 Diastereoselectivity in the transannular cyclisation reactions of Edstrom and Hegedus

The cyclisation of a differently substituted azoninone[61] was examined by Hegedus[62] in 1996. This cyclisation led to indolizidines with the same relative configuration as in indolizidine **N-2**.

The formation of an inverse absolute configuration at C-5/C-6 was reported by Diederich and Nubbemeyer[63] who applied this cyclisation to α,β-substituted 9-membered ring lactams **O-1**, prepared via a diastereoselective aza-Claisen rearrangement (Scheme 16). The transannular ring closure reactions with iodine or phenylselenium chloride provided bicyclic lactams **O-2** with complete regio- and stereoselectivity.

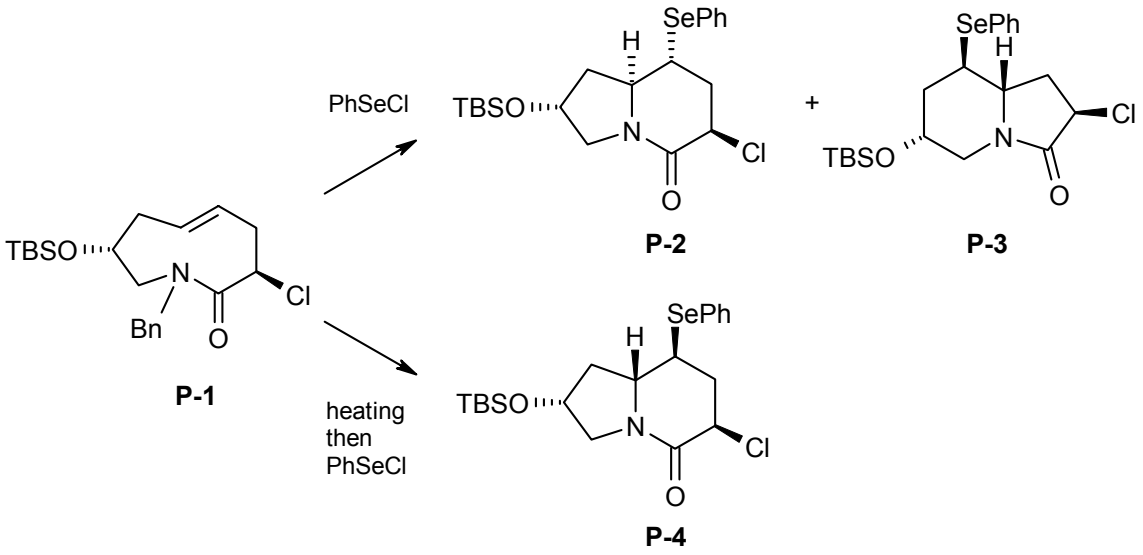


Scheme 16 Inverted stereoselectivity in transannular ring contraction reactions

The presence of multiple influences of the structure of the azoninones on the stereochemical course of the transannular ring contraction was recently confirmed by a mechanistic study in 1998.[64]

Depending on the reaction and workup conditions during the preparation of azoninones, three different types of indolizidines could be synthesised with the transannular ring contraction (Scheme 17).

[61] Instead of 2x Cl at C-3, this position was substituted by OMe and CH_3
[62] Deur, C. J.; Miller, M. W.; Hegedus, L. S. *J. Org. Chem.* **1996**, 61, 2871-2876.
[63] Diederich, M.; Nubbemeyer, U. *Chem. Eur. J.* **1996**, 2, 894-900.
[64] Sudau, A.; Nubbemeyer, U. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 1140-1143.



Scheme 17 Change of regio- and stereoselectivity in the transannular ring contraction

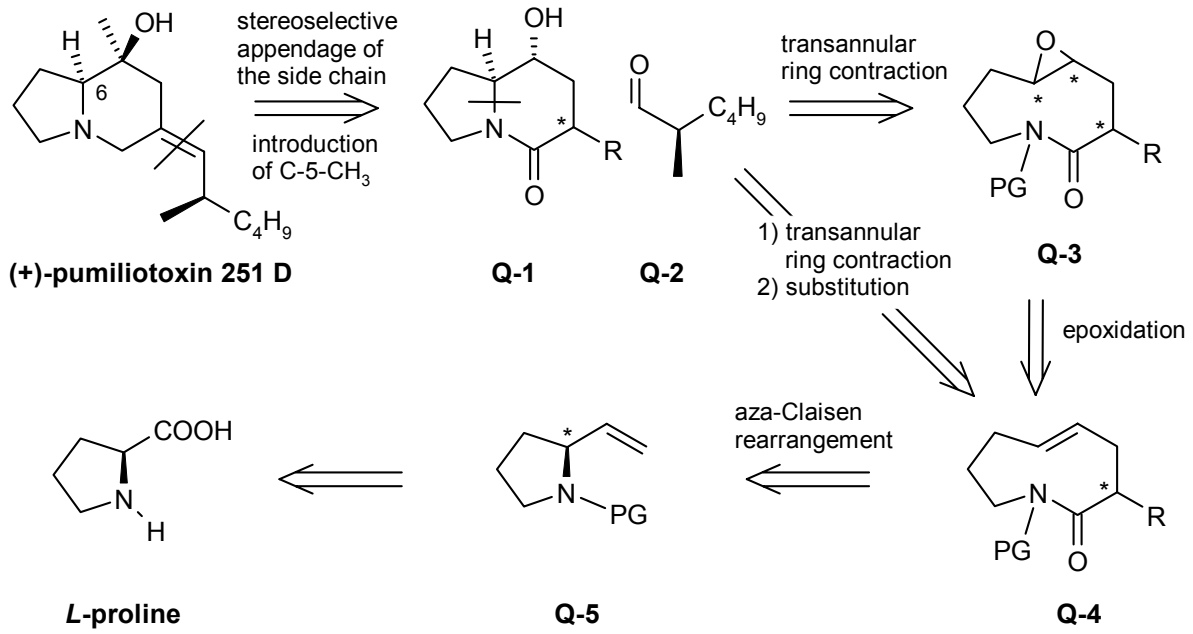
Apart from the indolizidinones **P-2** and **P-4** for the first time the formation of a five-membered amide **P-3** was observed. However, the initial yields of these cyclisations were low and the factors leading to the different structures were not fully understood.

1.3 Objectives

Unsaturated azoninones represent important key substrates for the synthesis of indolizidine alkaloids and other biologically active substances. Their conversion into the indolizidine core using transannular reaction sequences is promising, since both *D*- and *L*-proline derived indolizidine alkaloids are potentially accessible. However, limited information is available regarding the control of stereo- and regioselectivity during this process. The directed stereoselective synthesis of either *D*- or *L*-proline indolizidines and the regioselective formation of five or six-membered cyclic lactams is a synthetic problem that remains to be solved for the successful application of this reaction in natural product synthesis.

With the zwitterionic aza-Claisen rearrangement, a short and stereoselective access to *E*-azoninones became possible. The examination of transannular cyclisation reactions of these azoninones was therefore a major part of this work. Since many natural indolizidines contain carbon and oxygen substituents at the indolizidine core, additional this work looked at new synthetic methods for their introduction during a transannular cyclisation resulting in a functional bicyclic precursors of natural products.

The application of this method in the synthesis of a naturally occurring indolizidine alkaloids was examined as another part of this work. (+)-Pumiliotoxin 251D is a naturally occurring compound with intriguing biological properties and is only synthetically available in sufficient amounts. Scheme 18 summarises our strategy for the construction of this compound.



Scheme 18 Retrosynthesis of (+)-pumiliotoxin 251D

Focussing on a convergent synthesis the inspection of pumiliotoxin 251D revealed two main retrosynthetic disconnections, namely the side chain linkage and the N-C-6 bond. We planned the introduction of the side chain via a stereoselective aldol addition of the precursor **Q-1** and the chiral aldehyde **Q-2**. The C-3 substituent R in this compound may be used for a stereospecific elimination and the formation of the *Z*-alkylidene side chain, for instance via an Boord-elimination process (in case R = Cl). The tertiary alcohol at C-5 can be introduced by a two step Swern oxidation/Grignard addition sequence. Overall the target has been subdivided into the major fragments of the bicyclic core and the side chain of the aldehyde.

The second retrosynthetic disconnection represents the transannular cyclisation sequence of the epoxide **Q-3**. Since nucleophilic epoxide opening reactions proceed stereospecifically under *anti*-attack of the nucleophile, the configuration at C-6 is inverted by the intramolecular attack of the amide nitrogen atom. Therefore, a stereoselective epoxidation of **Q-4** is necessary for the successful application of this sequence. Since mild reaction conditions are usually required for epoxidation reactions, the prospects for a stereoselective epoxidation are good.[65]

Alternatively, the hydroxy indolizidinone core could be constructed via a transannular ring contraction (PhSeBr, I_2 or Br_2 as electrophile) of azoninone **Q-4** followed by a substitution at C-5 by an oxygen nucleophile.

The azoninone **Q-4** can be prepared by the aza-Claisen rearrangement of vinyl pyrrolidines **Q-5**. The observed high transfer of chirality during this rearrangement enables the stereoselective introduction of the substituent at C-3 that could be advantageous in a subsequent stereospecific elimination sequence. Finally, the vinyl pyrrolidine **Q-5** is synthetically accessible from *L*-proline as ex-chiral pool compound in five steps according to known synthetic methods.

[65] For the discussion of reaction conditions and chiral stability of azoninones see chapter 2.2.2, page 43.