Planar Chirality − Synthesis and Transformations of 8- to 10-Membered Heterocycles Bearing (*E*)-Olefins

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Medium-sized heterocycles (8-membered to 10-membered) are prevalently found in organic chemistry as key intermediates in the synthesis of more complex structures or as core structures in natural products or pharmaceutically important compounds. At present, the production of such rings remains a challenge in organic synthesis. During the past decade, an increasing amount of interest has focused on the generation of cyclic lactones and peptides, as well as on hairpins and β-turn mimics, and such medium-sized rings were thought to represent suitable fragments. Furthermore, heterocyclic structures of this type are a characteristic of a range of complex natural products, and total synthesis of these is a broad field for organic chemists to test new strategies and to develop new methods. The aim of this review is to discus some modern strategies for synthesizing unsaturated 8- to 10-membered heterocycles, with the scope restricted to the production of ring systems incorporating a N, O, and S function in combination with (*E*)-olefins. The planar-chiral properties thus induced have been exploited for further stereoselective and regioselective reactions. Although a number of conversions has described only the generation of simple structures without complicated stereogenic properties, most of them seem to offer undiscovered potential in terms of stereoselective syntheses. However, the emphasis of the methods is focused on stereoselective processes. The review is subdivided into two major chapters: ring-closure and ring-enlargement reactions, and additional information is given on cycloadditions and fragmentations.

Introduction

"Planar chirality" is a controversial term. On one hand, stereogenic information of such a type can be described as a form of chirality originating from a helix. A sequence of three nonplanar vectors is characterized by a defined torsion angle with a topographic descriptor *P* (plus) or *M* (minus) depending on its sign.[1] On the other hand, the terms "stereogenic center", "axis", "plane", and helix are accepted.[2] Thus, a stereogenic plane can be described as a planar arrangement of at least four centers (atoms), with a fifth center placed outside of this original plane.

The term "planar-chiral" is popularly used for appropriate η^n-arenemetal[3] and η^n-olefinmetal complexes,[4] cyclophanes, and ansa compounds.[5] The smallest type of planar arrangement of atoms is an olefin subunit; a ring incorporating an (*E*) double bond corresponds to the requirements of a planar-chiral compound. Using Schlögl nomenclature,[6] the descriptors *pS* (*M*) and *pR* (*P*) can be used to describe the topographic properties of the ring arrangement.

Investigation of the planar-chiral properties of medium-sized 8-membered to 10-membered rings bearing (*E*)-olefins requires durable conformations with measurable half-life

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Udo Nubbemeyer was born in Lengerich/Westfalen in 1960. He studied chemistry at the University of Hannover and received his diploma degree in 1986. Diploma and PhD theses were undertaken in the group of Prof. Dr. E. Winterfeldt (University of Hannover), research interests focusing on stereoselective spiropiperidine syntheses. After receiving his PhD in 1989, he spent a postdoctoral spell at the Ciba-Geigy Laboratory at the University of Fribourg (Switzerland) with Prof. D. Bellus and Dr. B. Ernst (1989−1990), investigating reactions of ketenes and allyl sulfides, and also the generation of functionalized cyclobutanones. In 1991 he moved to the Freie Universität Berlin to begin his "Habilitation" in the group of Prof. Dr. J. Mulzer, this was completed in 1996. Since then he has been working as assistant lecturer and Privatdozent at the FU Berlin. Since 1999 he has held a temporary professorship of Organic Chemistry at the Technische Universität in Dresden. His major topics of interest are olefin synthesis, aza Claisen rearrangements, radical cyclizations, medium-sized rings, total synthesis of natural and pharmaceutically important products, alkaloids, eicosanoids, steroids, and amino acids.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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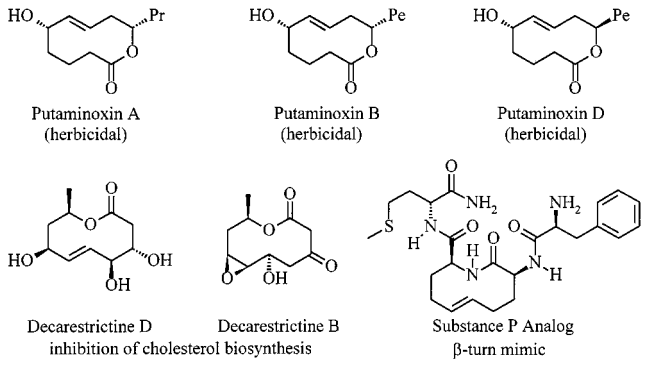
times. While optically active planar-chiral, 8-membered rings are known to be stable, 9- and 10-membered rings suffer from fast racemization, because of the facile flipping of the double bond with respect to the ring.[7] In contrast, a range of unsaturated 9-membered and 10-membered rings bearing defined additional stereogenic centers have been found to maintain the planar-chiral information of the (*E*)-olefin at room temperature. Most information has originated from investigations of carbocyclic ring systems.[8] Many natural products (predominantly terpenes) are included in this field[9] and most synthetic efforts have been concentrated here.[10]

During the past decade, interest in synthesizing heterocyclic, medium-sized rings has increased continuously. On one hand, several important natural and pharmaceutically important compounds have been isolated and their biological properties determined. The synthesis of these targets, or the variation of lead structures, is a versatile tool for organic chemists. The putaminoxins (herbicides),[11] the decarestricines B and D (agents for lowering cholesterol levels),[12] and a conformationally constrained β-turn mimic[13] serve as representative examples (Scheme 1).



Scheme 1

On the other hand, the unsaturated medium-sized heterocycles might serve as useful key intermediates in the synthesis of more complex structures. It should be pointed out that the conformation of the ring (planar diastereomer) influences the outcome of a reaction (*anti* Curtin−Hammett, cf. below: C_4 insertion). The defined arrangement of stereogenic centers and the planar-chiral properties of the olefin practically promise highly selective consecutive processes depending on the conformation of the system. Again, most information concerning this topic originates from carbocyclic systems.[14] In the reaction of heterocycles, the short transannular distance from reaction center to the potentially nucleophilic heteroatom influences all chemical transformations.[15]

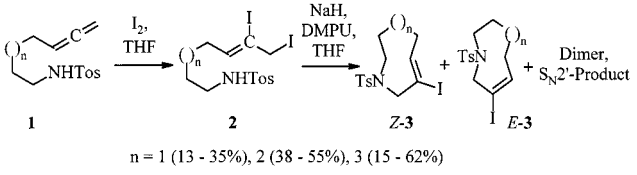
However, efficient syntheses of such heterocyclic core fragments appear extremely useful. This review discusses some modern strategies for synthesizing and using unsaturated, medium-sized heterocycles with potential planar-chiral properties.

Ring-Closure Reactions

Ring-closure reactions represent by far the greatest proportion of reactions aimed at the synthesis of medium-sized heterocycles reported over the past decade. All cyclizations have needed conditions of a greater or lesser degree of high dilution to avoid any intermolecular reactions. The ease of the cyclization increases from 8-membered ring formation to ten-membered ring formation, while the major challenge to smooth generation of the desired rings has been posed by the inclusion of the (*E*)-olefin subunit.

The ring-closure methodology can be classified into C−X (primarily carboxylic group conversion) and C−C bond formation. Ring closures by C−C bond formation can be subdivided into two strategic pathways: The first involves generation of a C=C double bond in the cyclization step, the second a new C−C single bond. Over the last decade, the first strategy in particular has gained more in importance, because of extensive investigations in the field of ring-closing olefin metathesis. Methodology based on the second strategy has focused on metal-mediated allylations and on radical cyclizations.

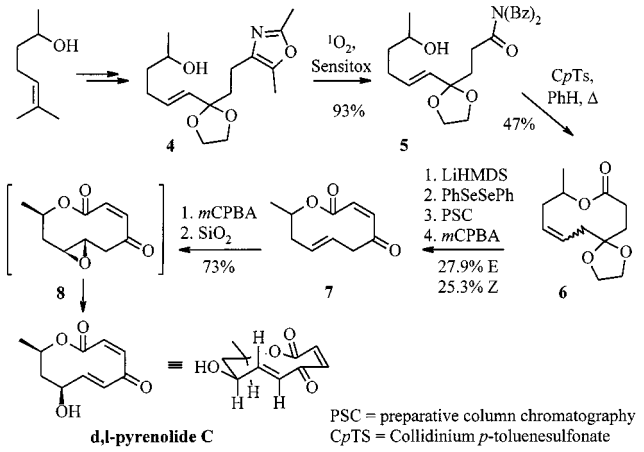
Eight- to ten-membered cyclic amines may be generated according to Gallagher's procedure.[16] *N*-(ω-Allenyl-1-alkyl)toluenesulfonamide **1** added iodine to yield the allyl iodide **2**. A subsequent base-induced S_N2 reaction produced the medium-sized azacycle **3**, along with some S_N2' product and some dimer (0−40 %). On generating the azocine (n = 1), the less constrained (*E*)-olefin (*E*)-**3** was formed exclusively, albeit in moderate yield (13−35 %). Formation of the azonines (n = 2) resulted in a 1:1 mixture of (*E*)-**3** and (*Z*)-**3** (38−55 %). Finally, on synthesizing the ten-membered (n = 3) ring, the (*Z*)-azecine (*Z*)-**3** was isolated as the major isomer (15−62 %). The yield always depended strongly on the reaction conditions used, and it was possible to suppress formation of side products on generating the 9- and 10-membered rings (Scheme 2).



Scheme 2

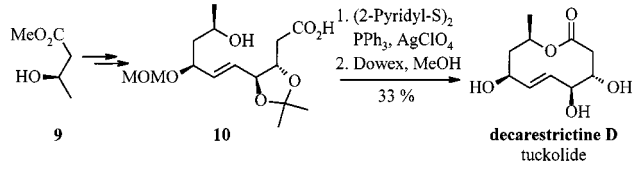
Ten-membered ring lactones have been formed by cyclization of activated 9-hydroxy carboxylic acids. Wasserman employed an oxidative cleavage of the oxazole **4** in a step prior to the lactonization:[17] $^1O_2$ was added to the oxazole **4** to give the intermediate triamide **5**, which cyclized in the presence of a base to give the corresponding lactone **6** in 47% yield. Although the (*E*)-olefin had been introduced stereoselectively, by means of a Wittig reaction, while synthesizing the *seco* material **4**, some isomerized olefin (*Z*)-**6** was evident after the cyclization step; it could be separated by column chromatography of an appropriate derivative. After several subsequent transformations, the (*E*)-olefin

(*E*)-**7** was epoxidized diastereoselectively with *m*CPBA to give **8** as an intermediate. A final regioselective oxirane opening of (*E*)-**8** produced the antifungal (±)-pyrenolide C. The favored conformation was proven by NOE analysis (*rel*-8*S*-10*R*-*p*S). The corresponding epoxide originating from (*Z*)-**7** was found to be destroyed during the course of the β-elimination (Scheme 3).



Scheme 3

The synthesis of optically active tuckolide (decarestricine D), a new cholesterol biosynthesis inhibitor, began from the *seco*-acid **10**, synthesized in several steps from (−)-[methyl β-hydroxybutanoate] (**9**).[18] The activation−cyclization sequence followed the Corey−Nicolaou method, to yield the lactone in 33% yield. A range of other, well-established cyclization pathways failed. The acidic removal of the protective group gave the desired lactone without any isomerization of the (*E*)-olefin. The parent compound 9-hydroxynonanoic acid did not lactonize under the conditions reported, indicating that, in the case of the *seco*-acid **10**, the combination of stereogenic centers and an appropriate diol protecting group produced efficient preorientation to support the ring closure (Scheme 4).

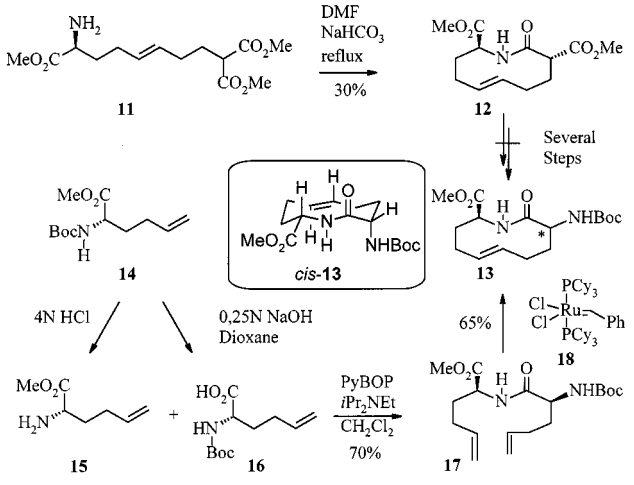


Scheme 4

The synthesis of β-turn mimetics includes the stereoselective generation of a rigid, ten-membered ring lactam **13**, bearing an (*E*) double bond.[13] A classical approach, constructing the azecinone **12** by means of a nucleophilic attack of the amino group onto one ester function of the malonate **11** in refluxing DMF, succeeded in only 30% yield. The optical purity of the reactant was maintained under the harsh cyclization conditions, however. After ring closure, the *trans*-lactam **12** was formed. The intention was to convert this into the desired product *trans*-**13** in several steps. This sequence was abandoned, however, because of severe problems in differentiating between the C-3 and C-10 ester functions. Otherwise, the creation of an ideal type-I β-turn mimetic required the generation of the *cis*-**13** lactam diastereomer, but the related synthesis according to the condensation route failed.

The formation of medium-sized ring lactams by means of ring-closing olefin metathesis is still one of the most intriguing strategies. Reaction conditions and catalysts tolerating a wide range of different functional groups and ring sizes have been developed during the last decade. The ease of generating suitable reactants, the reliability and high yields of the cyclizations, and the increasing stereoselectivities in constructing the (*E*)- or (*Z*)-olefins have characterized metathesis as one of the most powerful methods in macrocycles synthesis.[19]

The *cis* substance P analog was synthesized by means of a convergent sequence, twice using the reactant amino acid **14**: After peptide coupling of the subunits **15** and **16** to **17**, a ring-closing metathesis with Grubbs' catalyst **18** under carefully optimized high-dilution conditions gave the desired *cis*-azecinone *cis*-**13** in 65% yield, along with about 10% of the dimer. Compared with the lactamization route described before, this latter sequence indicated that the metathesis path constituted an exceptionally more straightforward route by which to generate the medium-sized ring (Scheme 5).

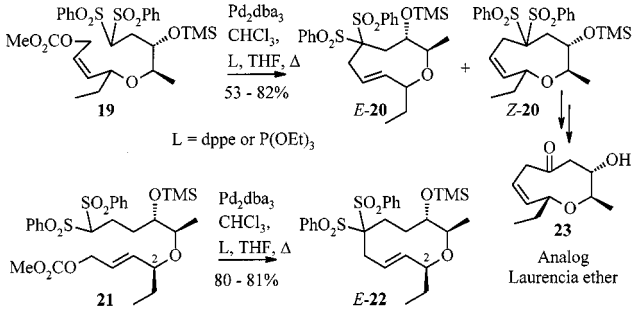


Scheme 5

The structural properties of *cis*-**13** were investigated carefully. The double bond was found to be of (*E*) configuration. X-ray analysis of the lactam showed two different conformations in a unit cell, found to be nicely in accord with the minimum energy arrangements determined by molecular modeling calculations: Both structures bore (3*S*), (10*S*), and (*pS*) configurations, the variation was found in the lactam area and could be described as a corner flipping (chair-chair versus chair-boat). Additionally, the conformational mobility was investigated by NMR techniques.

Palladium-catalyzed allylations of stabilized carbanions (Tsuji−Trost reaction) served as ring-closing steps in the syntheses of nine-membered and ten-membered cyclic ethers.[20] The generation of oxonenes likewise started from

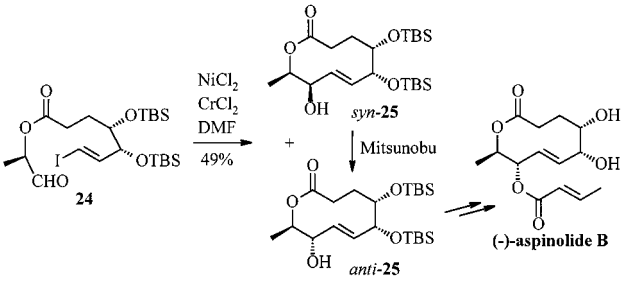
(*E*)- or (*Z*)-allyl carbonates **19**: Treatment of **19** with catalytic amounts of Pd^0 and dppe or $P(OEt)_3$ as ligands resulted in mixtures of the product ethers **20**. Dppe-mediated reactions resulted predominantly in oxonenes bearing (*Z*)-olefins (*Z*)-**20**. In contrast, the presence of $P(OEt)_3$ preferentially caused the formation of the corresponding (*E*)-olefins (*E*)-**20** in 50−80% yield. The best ratio was obtained when starting from (*Z*)-**19**. The (*E*)-configured oxonenes were found to be unstable: It was possible to observe an (*E*)-to-(*Z*) isomerization when the pure products were subjected to the reaction conditions for protracted periods. The phenomenon was explained by a consecutive sequence of a Pd-catalyzed opening of the constrained ether (*E*)-**20**, isomerization, and a final ring closure to generate the thermodynamically more stable (*Z*) analogue (*Z*)-**20**. The synthesis of the larger ten-membered rings was found to be diastereoselective: (*E*)-Olefins (*E*)-**22** were exclusively built up in high yields on cyclizing the (*E*)-allyl carbonates (*E*)-**21**. The (*E*)-oxacyclodecenes (*E*)-**22** were found to be stable; no further double-bond isomerization could be observed, implying a less constrained ring framework. The geminal bis(phenylsulfonyl) group of (*Z*)-**20** was converted into a ketone, which should represent the useful intermediate **23** in natural product syntheses (laurencia ether analogue) (Scheme 6).



Scheme 6

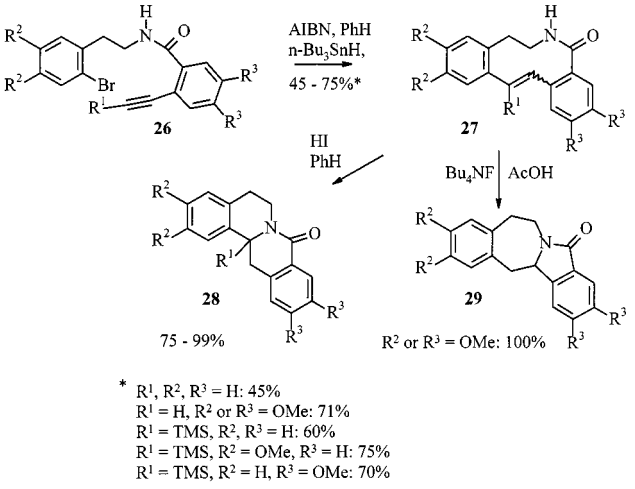
The first total synthesis of (−)-aspinolide B was carried out by a strategy involving a Hiyama−Kishi coupling as the key step:[21] The (*E*)-vinyl iodide **24** was generated in an chiral-pool synthesis starting from the corresponding alkyne, by radical addition of Bu_3SnH and a subsequent metal iodine exchange. The $CrCl_2/NiCl_2$-mediated cyclization gave the lactones **25** in about 50% yield, the *syn* and *anti* products **25** being formed in a 1.5:1 ratio (low facial selectivity). Focussing on the natural-product synthesis, the *syn* material *syn*-**25** was converted into the desired diastereomer *anti*-**25** by a Mitsunobu inversion (56% yield of *anti*-**25** over two steps from **24**). Esterification with crotonic acid/DCC and final desilylation gave (−)-aspinolide B, with all spectral data found to be identical with those of an authentic sample (Scheme 7).

The synthesis of isoquinoline alkaloids through an azecinone **27** and a consecutive transannular cyclization was found to be an intriguing strategy for preparing the basic ring system of protoberberine.[22] Initially, the ten-membered ring **27** should have been formed with the aid of a Pd^0-catalyzed reaction, but all attempts failed. In contrast,



Scheme 7

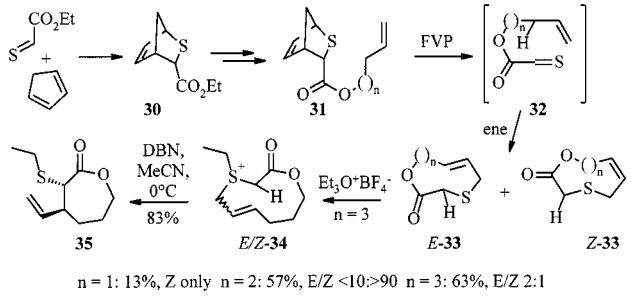
a radical cyclization generated the desired lactam; the almost rigid bromoacetylene **26** (R^1 = H) could be activated by means of the addition of AIBN and Bu_3SnH to induce a subsequent *endo*-selective attack of the aryl radical at the triple bond. Azecinones **27** could be isolated in about 45% (R^2, R^3 = H) or 71% yield (R^2 or R^3 = OMe) as mixtures of (*E*)- and (*Z*)-olefins. With the corresponding silyl acetylene **26** (R^1 = TMS), the yield of **27** (R^1 = TMS) increased to 60−75%, with a single double-bond isomer formed. The most electron-rich aromatic reactants (R^2, R^3 = OMe) gave the best results. Final transannular ring contractions allowed the regioselective formation of the tetracycles **28** and **29**, respectively. Apparently, the electron-rich character of the aromatic rings did not influence the transannular reactions, indicating that the double bond was not in plane with the aryl systems, as found by some semi-empirical calculations (planar diastereomeric properties!) (Scheme 8).



Scheme 8

A rather unusual method of generating medium-sized ring thiaalkenolides involved an intramolecular ene reaction of thioaldehydes.[23] The α-mercapto esters **31** (derived from a hetero Diels−Alder cycloaddition of cyclopentadiene and ethyl thioformylformate to **30** and transesterification to **31**) underwent a retro Diels−Alder reaction under FVP conditions to form an intermediate thioaldehyde **32**. An immediate intramolecular ene reaction generated the 3-thialactones **33**. While 8-membered and 9-membered rings (n = 1, 2) produced olefins (*Z*)-**33** exclusively, the corresponding 10-membered rings (n = 3) occurred as mixtures of (*E*)-**33** and

(*Z*)-**33**, which was found to be inseparable either by column chromatography or by crystallization [co-crystallization of (*E*)-**33** and (*Z*)-**33**]. A stereoconvergent process was found, demonstrating the synthetic potential of (*E*)/(*Z*)-**33**: After *S*-alkylation to **34**, a Wittig rearrangement resulted in the ε-caprolactone **35** as a single diastereomer (Scheme 9).



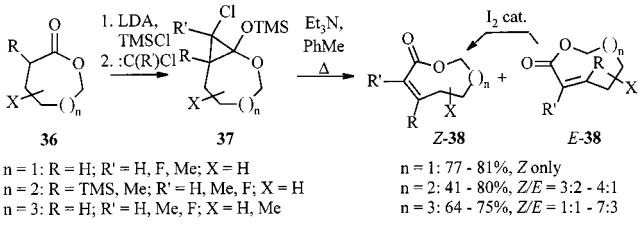
Scheme 9

Fragmentations

Though well known for synthesizing medium-sized rings, fragmentation reactions have only occasionally been used to generate heterocyclic structures. In principle, a fragmentation should be a useful process with which to investigate the generation of such core structures: Bicyclic reactants incorporating a framework of annulated 5-membered and 6-membered rings with a range of defined stereogenic centers are easily achievable, and the final breaking of the central bond promises smooth and versatile formation of substituted heterocycles. On the other hand, the formation of a medium-sized ring generates a species suffering from severe transannular repulsive and/or attractive interactions, particularly as far as 8- to 10-membered constrained systems are concerned. The backbone heteroatom has to be considered as a potential nucleophile interacting with acceptor-substituted positions at the opposite face of the ring, thus inducing transannular reactions.

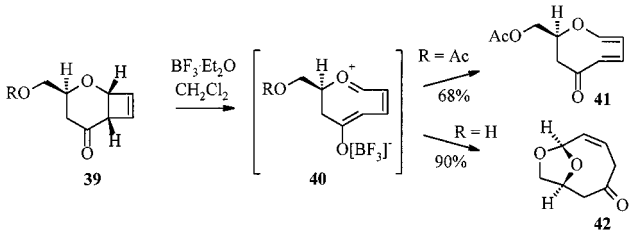
Fragmentations of bicyclo[*n*.1.0] or -[*n*.2.0] systems appeared to be a useful strategy for generating medium-sized heterocycles. The bond breaking should be driven because of the additional loss of ring constraint. Admittedly, expansion by only one or two additional atoms would require a relatively large ring as starting material in synthesizing 8- to 10-membered systems. Several difficulties in building up these heterocycles were only surmounted on generating the appropriate reactants.

Fragmentations of bicyclo[*n*.1.0] systems to achieve 8- to 10-membered lactones **38** started from ketene acetals **37**, generated in situ:[24] After [2+1] cycloaddition of a chlorocarbene with **36**, the ring expansion could be induced by heating **37** to > 100°C in the presence of a base. The double bond of **38** formed in the fragmentation step was found to be exclusively (*Z*) in oxacyclooctenes ($n = 1$), while up to 50% (*E*) stereochemistry was observed in the synthesis of oxonenes **38** ($n = 2$). The synthesis of 10-membered lactones **38** ($n = 3$) predominantly gave (*E*)-olefins. Finally, (*E*)-to-(*Z*) isomerization was easily accomplished by addition of catalytic amounts of I_2 in refluxing benzene (Scheme 10).[25]



Scheme 10

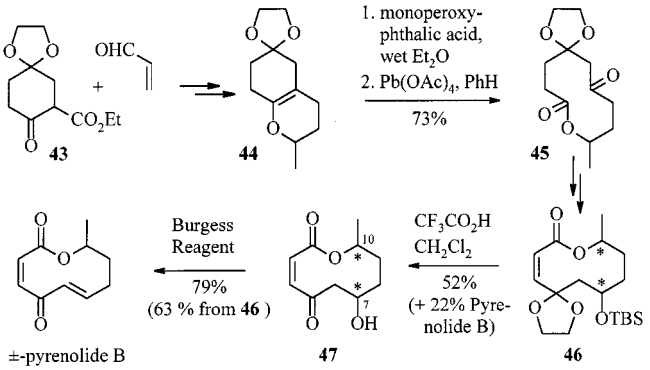
The Lewis acid mediated fragmentation of a bicyclo[4.2.0] system **39** has been described by Do Khac.[26] A suitably protected glucal underwent a [2+2] photocycloaddition with acetylene to give bicycle **39**. Treatment of **39** (R = Ac) with $BF_3{\cdot}Et_2O$ resulted in the monocyclic system **41** (R = Ac); the configuration of the olefins was determined by means of ^1H NMR spectra.[27] The reaction was thought to pass through an intermediate, unsaturated, cyclic oxonium ion **40** (R = Ac), which lost the Lewis acid (BF_3) on formation of **41**. Alternatively, the unprotected oxonium ion **40** (R = H) was found to be converted into the bicyclic acetal **42**, indicating the trapping of the hard cation in **40** by the hydroxy group of the side chain (Scheme 11).



Scheme 11

On synthesizing the 10-membered lactone (±)-pyrenolide B, with phytotoxic properties, Hesse reported an oxidative cleavage of the central double bond of the bicyclo[4.4.0] system **44**.[28] Oxo ester **43** was transformed into the bicycle **44** in four steps, the double bond having been introduced by an acid-catalyzed dehydration of the corresponding semiketal to give the enol ether **44**. A sequence of epoxidation and a subsequent Criegée oxidation gave the oxo lactone **45**. After reduction of the ketone and the introduction of the (*Z*)-3,4-double bond to generate **46** as a mixture of diastereomers (7−10 *syn* and *anti*), the deprotection of the masked ketone function to give **47** also simultaneously afforded some pyrenolide B. The stereoselective formation of the (*E*) double bond was achieved by dehydration of ketone **47** with Burgess reagent in 79% yield (63% overall from **46**). Both

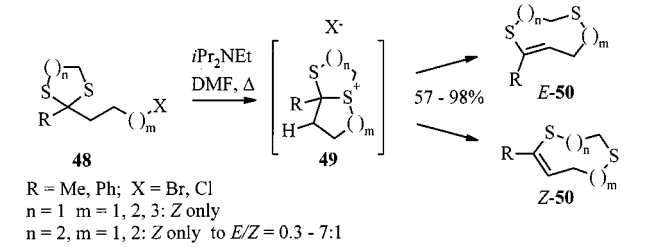
diastereomers of **47** delivered the same diastereomeric pyrenolide B [(*E*)-6,7-olefin] (Scheme 12).



Scheme 12

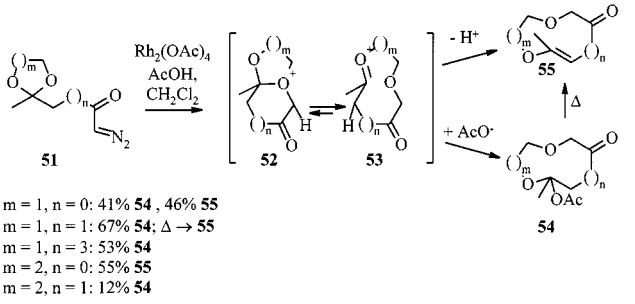
An intriguing strategy for generating medium-sized heterocycles was a cascade of initial annulation and subsequent fragmentation. The nucleophilicity of the heteroatom was used to generate an intermediate bicyclic onium ion, which should undergo an efficient fragmentation. Charge neutralization was thought to be the driving force of the second step.

Investigating syntheses of haloperidol analogs (potential nonpeptidic HIV-1 protease inhibitors), De Voss found that the soft nucleophile S of a thioketal **48** underwent an annulation through an intramolecular S_N2 reaction to give **49**, rather than a competing intermolecular amine alkylation.[29] The sulfonium ion **49** thus formed underwent a base-mediated elimination to give dithiacycloalkenes **50**. The reaction was dramatically faster in DMF than in xylene, supporting the hypothesis that a charged intermediate had been involved. On generating medium-sized rings from dithioxolanes **48** (n = 1, m = 2−4), the (*Z*)-olefins (*Z*)-**50** were found as exclusive products. The formation of (*E*)-configured systems (*E*)-**50** could be achieved by using 1,3-dithiolane reactants **48** (n = 2): The best result was obtained on synthesizing the 10-membered heterocycle (*E*)-**50** (n = 2, m = 3) in 98% yield and with an (*E*)/(*Z*) ratio of 6.7:1 (Scheme 13).



Scheme 13

When the same strategy was applied to oxygen-containing systems **51**, the ring closures were initiated by carbenoid addition.[30] Diazo ketones **51** cyclized in the presence of $Rh_2(OAc)_4$ to give an intermediate oxonium enolate, which was immediately protonated to **52/53** to prevent Stevens rearrangements. The oxonium ions **52/53** tended to suffer from a final attack of a nucleophile to yield a saturated compound **54**, or from proton elimination (H in **53**) resulting in the unsaturated medium-sized cyclic oxo ether **55**. In most experiments, the formation of saturated products **54** predominated. On treatment of the dioxolanes **51** (m = 1), **54** and **55** were formed in equal amounts when the 8-membered ring was produced (n = 0, activated proton H in **53**), while the larger rings (n = 1, 2; nonactivated proton in **53**) delivered the saturated products **54** exclusively. Heating of **54** (n = 2) caused β-elimination to the corresponding **55** and some exomethylene analogue. The dioxane series **51** (m = 2) was characterized by similar behavior: The unsaturated 9-membered ring **55** (n = 0, activated proton H in **53**) was generated smoothly as a mixture of (*E*)- and (*Z*)-olefins. Proton elimination produced an enol ether, which might have undergone an efficient (*E*)/(*Z*) epimerization. Consequentially, the *cis* products were reported to be the major isomers. As expected, adaptation of the reaction to synthesize larger rings (n = 1, 2; nonactivated proton in **53**) gave only poor results: The yield of **54** (n = 1) was < 15% (Scheme 14).



Scheme 14

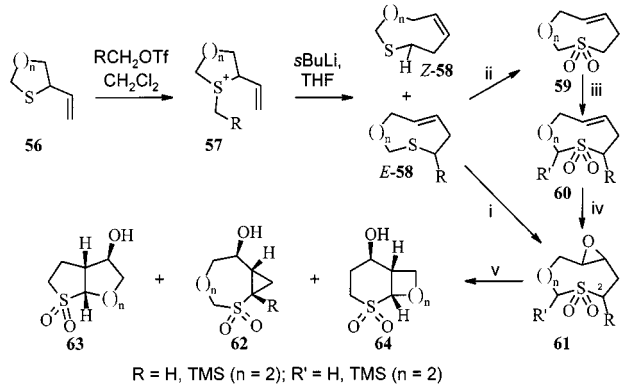
Ring-Expansion Reactions by C Insertion

In contrast to the heteroatom insertion reactions (Baeyer−Villiger, Beckmann, Schmidt), which allow expansion of the nascent heterocycle by only a single additional ring atom, C insertions have been found to be characterized by higher flexibility. Sigmatropic rearrangements employed normal N, O, and S heterocycles as precursors to generate the medium-sized rings. Because of the fact that the ring systems involved expansions by two, three, or four additional atoms, starting from reasonably easily accessible 3- to 7-membered heterocyclic reactants offered the prospect of an efficient synthesis of medium-sized rings with up to eleven ring atoms. Furthermore, the well-known stereochemical characteristics of the sigmatropic processes, thanks to their highly ordered transition states, promised the transfer of chiral information to the nascent ring-expanded heterocycles. Until now, by far the greatest proportion of reported ring enlargements have used a Claisen rearrangement[31] as the key step, the related (hetero) Cope reactions[32] − extensively used in synthesizing carbocycles − and Wittig rearrangements[33] have only seldomly been found to generate medium-sized heterocyclic rings.

En gros, the C insertion reactions can be classified as C_3-type and as C_4-type rearrangements. A two-step C_4-type process involving carbenechromium addition and a CO insertion has also been reported.

C_3 Insertion

The synthesis of 8- and 9-membered unsaturated thioethers **58** (n = 1, 2) has been carried out by means of a ring expansion by three additional C atoms.[34] The 2-vinyltetrahydrothiophene **56** (n = 1) and the homologous tetrahydrothiopyran (n = 2) were easily *S*-methylated with methyl and TMSmethyl triflate, respectively, to give the corresponding sulfonium salts **57** as starting materials. After deprotonation with *s*BuLi, a 2,3-Wittig rearrangement resulted in the ring-expanded systems **58**. The nascent 8-membered ring **58** (n = 1, R = H) was formed with a (*Z*)/(*E*) ratio of about 85:15; the isomers could not be separated by column chromatography because of a concomitant, rapid (*E*)-to-(*Z*) conversion. In contrast, the 9-membered rings (*E*)-**58** (n = 2, R = H, TMS) were stereoselectively generated with stable (*E*)-olefins, while the corresponding (*Z*) system (*Z*)-**58** (n = 2) could be attained by means of a subsequent photochemical isomerization (Scheme 15).



Scheme 15

Stereospecific transannular reactions have been investigated. The olefin moiety of **58** was epoxidized, using an excess of *m*CPBA, and the thioether was converted into the corresponding sulfone. Suitable precursors **61** for anionic ring contractions were obtained in a single step. Treatment of **61** with *n*BuLi resulted in transannular opening of the epoxide to yield varying ratios of the bicyclic systems **62**−**64**. The ring junctions in all bicycles **62**−**64** was found to be exclusively *cis*, independently of the reactant oxiranes, indicating a stereoconvergent process. Although the 9-membered ring sulfone **61** (n = 2) should adopt different conformations with varying planar-chiral properties, only a single arrangement seemed to be reactive, causing a Curtin−Hammett-type selective transannular ring closure.

The regioselectivity of the transannular ring contractions strongly depended on the reaction conditions used for proton abstraction at C-2 or C-8/9. The ratios obtained upon treatment of the sulfones **61** (R = R′ = H) varied from 1:0 to 1:4. Deprotonation at C-2 resulted in the bicyclo[5.1.0] (n = 1) and -[6.1.0] (n = 2) systems **62**. Deprotonation of **61** at C-8/9 took variable regiochemical courses: While the 8-membered **61** sulfone (n = 1) generated bicycle **63**, the 9-membered **61** (n = 2) gave the system **64**.

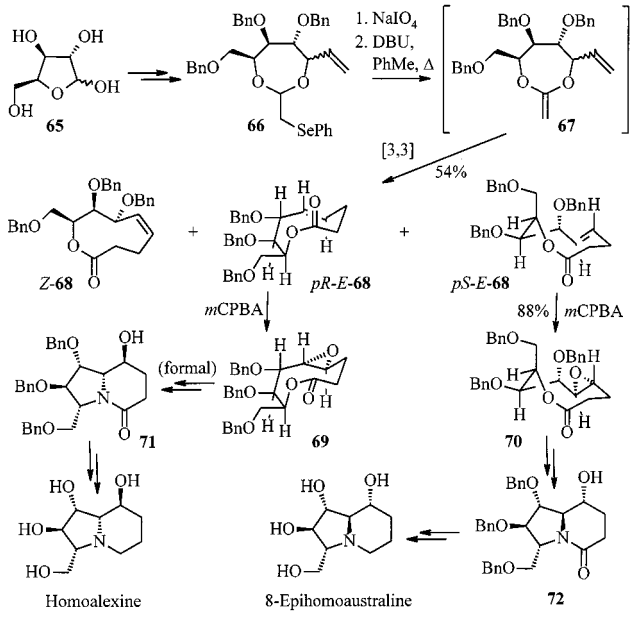
Regioselective metallation of the cyclic sulfones has been achieved by desilylation of **61** (n = 2, R or R′ = TMS). The introduction of the TMS group at C-2 was the result of the appropriate synthesis of thiuronium salt **57** (n = 2, R = TMS). Alternatively, (*E*)-**58** (n = 2) was carefully oxidized to give sulfone **59**. A subsequent deprotonation/silylation gave a mixture of regioisomers **60** (n = 2, R = H or TMS, R′ = TMS or H). A final oxidation yielded the epoxides **61** (n = 2, R = H or TMS, R′ = TMS or H) as mixtures of partially separable diastereomers.

The anionic desilylation of the 2-TMS material **61** (R = TMS) predominantly gave bicycle **62** (along with some *trans* isomer), if any, **64** occurred as the minor compound (*cis*/*trans* mixture). The ratios **62**/**64** varied from > 10:1 to 2:1. The desilylation of the 9-TMS reactant produced **64** (*cis*/*trans* mixture) as the major product; in most attempts, less than 20% of the regioisomer **63** was isolated, and **64**/**63** varied from > 10:1 to 4:1. Summing up the results, overall the anionic desilylation of **61** produced higher regioselectivities on generating the bicyclic products **62** to **64**, but all reactions suffered from lower stereoselectivities because of the higher reaction temperatures.

Some preliminary transannular ring contractions have been accomplished by treating the unsaturated cyclic sulfides with strong acids: Only *cis*-fused bicyclic sulfonium salts were obtained, independently of the double bond geometry in the reactant thioether. The rate of the process varied linearly with acidity.[34c]

A further C_3 insertion had been described by Pearson, synthesizing ring-expanded analogues of the pyrrolizidine alkaloids alexine and australine as novel glycosidase inhibitors.[35] In this case, a ring expansion by two additional centers was achieved. Starting from L-(−)-xylose **65**, the acetal **66** was built up in several steps. The method developed by Holmes[36] was applied, with the intention of producing 9-membered lactones stereoselectively bearing a (*Z*)-olefin subunit. The selenoacetal was converted into the corresponding ketene acetal **67** by an oxidation-elimination sequence. A Claisen rearrangement then permitted the formation of the desired 9-membered ring **68**; in contrast to the literature precedent, a mixture of (*E*)-**68** and (*Z*)-**68** olefins [moderately (*E*)-selective] was obtained. The (*E*)-configured unsaturated lactone (*E*)-**68** was found to occur as a mixture of two planar diastereomers *pS* and *pR*, which could be separated by column chromatography.[37] The *pS*-lactone (*E*)-**68** underwent a slow conversion into the *pR* conformation on heating to about 110°C. Basic cleavage of the mixtures of all lactones resulted in the ring-opened products [(*Z*) in 39% yield, and (*E*) in 37%] (Scheme 16).

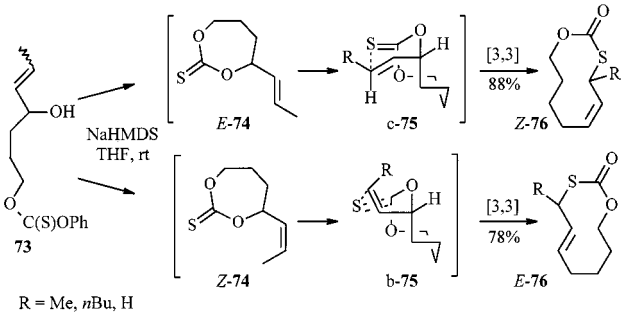
It proved possible to use the planar diastereomeric properties of the (*E*)-olefins to produce new stereogenic centers. Epoxidation of the double bonds led stereospecifically to



Scheme 16

the epoxy lactones **69** and **70**, respectively. The oxidizing reagent always attacked the unshielded face of the double bond, permitting the complete conversion of the planar-chiral information into new stereogenic centers. After introduction of the nitrogen atom, the indolizidinones **71** and **72** were generated; these could be employed as key intermediates in the total syntheses of the glycosidase inhibitor analogs homoalexine (formal) and 8-epihomoaustraline.

A related hetero analogue of a Claisen rearrangement, generating cyclic 10-membered thiocarbonates **76**, had been described by Kurihara.[38] Suitable reactants were generated in situ by cyclization of the *seco*-phenyl thiocarbonates **73**. The 8-membered cyclic thiocarbonates **74** thus formed bore side chains with double bonds of defined configuration. In contrast to open-chain Claisen rearrangements, passing through chair-like transition states to form (*E*)-olefins in the nascent product,[31] the synthesis of the unsaturated 10-membered heterocycles **76** is thought to involve boat or chair transition states b-**75** or c-**75** on constructing the thiolactones **76**. Obviously, the substitution pattern of the reactant olefin influences the nascent transition state **75**, directing the formation of the olefin: the reactants bearing (*E*) double bonds (*E*)-**74** preferentially adopted a chair-like transition state c-**75** with R^1 in a quasiequatorial position, resulting in an unsaturated, (*Z*)-configured, 10-membered ring (*Z*)-**76**. In contrast, the reactant (*Z*) isomer, (*Z*)-**74**, presumably passed through a boat-like transition state b-**75**, avoiding any 1,3-diaxial repulsive interactions of R^1. The newly formed olefin of the 10-membered thiocarbonate (*E*)-**76** was found to be of (*E*) configuration (Scheme 17).

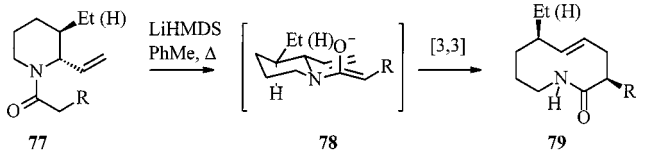


Scheme 17

C_4 Insertion

3,3-Sigmatropic rearrangements have been widely used to achieve a ring expansion by four additional atoms. For generating heterocycles, the Claisen methodology has been the method of choice: A highly ordered transition state permits the conversion of an optically active reactant into a medium-sized heterocycle bearing defined stereogenic centers and − in most cases stereoselectively − an (*E*) double bond, producing planar-chiral properties.[31]

The synthesis of azecinones **79** started from 2-vinylpiperidines **77**.[39] After *N*-acylation with an appropriate carboxy function, an amide enolate aza Claisen rearrangement resulted in the corresponding 10-membered ring lactam **79**. In the case of terminally unsubstituted olefins, a complete 1,4-chirality transfer has been observed. The stereochemical outcome of the process was rationalized with the aid of a chair-like transition state **78**, minimizing repulsive interactions. Furthermore, the amide enolate in **78** should have been (*Z*)-configured. In contrast to the related Ireland ester enolate rearrangements, the aza variant required higher temperatures (refluxing in PhMe) to give the products. One optically active azecinone **79** served as key intermediate in an asymmetric total synthesis of fluvirucin A_1 (Scheme 18).



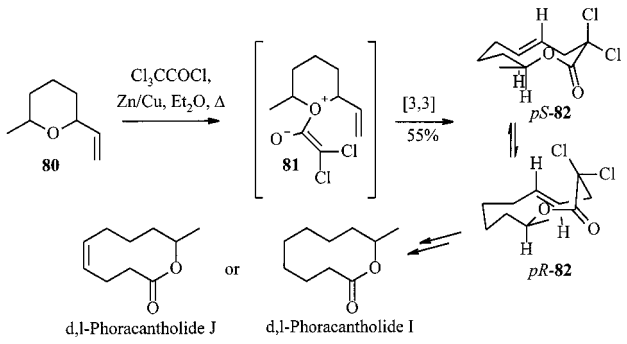
R = H (H): 40%, R = Me (H): 75%, R = OMe (H): 84%, R = Me (Et): 74%

Scheme 18

With the aim of enhancing the driving force behind the generation of constrained medium-sized rings, zwitterionic processes in Claisen-type rearrangements have been investigated. Two-step reactions have been developed as suitable methodologies, as so-called ketene Claisen rearrangements. Initially, the nucleophilic heteroatom of the 2-vinyl heterocycle reactant added at an acceptor system to generate the vinyl double bond of the Claisen framework, achieving the charge separation. The sigmatropic rearrangement then resulted in the ring-expanded product, with charge neutralization involved as a promoting effect.

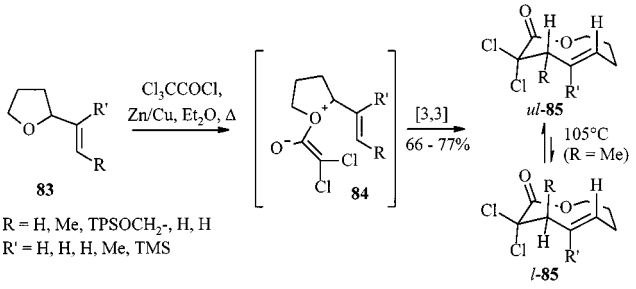
Initial investigations were carried out by Malherbe and Bellus, studying rearrangements of 2-vinyltetrahydropyran **80** or the sulfur analog with dichloroketene generated in situ.[40] The ring expansions to **82** were achieved − hypothetically through the zwitterion **81** − in > 70% yield. The

10-membered lactones **82** were used as key intermediates in the racemic total syntheses of phoracantholides I and J. The unsaturated lactones **82**, bearing (*E*)-olefins, were described as flexible compounds adopting two major conformations: Flipping of the double bond with respect to the ring resulted in a mixture of (racemic) planar diastereomers *pR*-**82** and *pS*-**82**, characterized by a double set of peaks in the NMR spectra (Scheme 19).



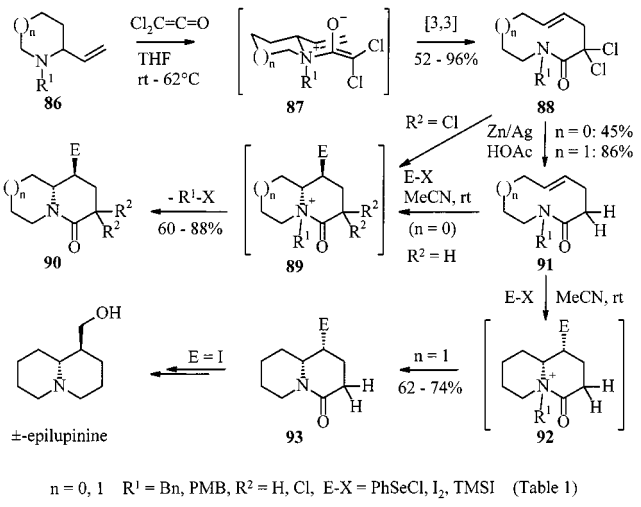
Scheme 19

A similar reaction starting from 2-vinyltetrahydrofuran **83** was used to synthesize unsaturated, 9-membered ring lactones **85** as core fragments of bioactive marine lactone metabolites.[41] Because the reactant olefin **83** was used as a mixture of (*E*)- and (*Z*)-olefins, two product lactones **85** were obtained. The mixture of diastereomers **85** [(4*R*/*S*) and *pR*/*S*] reflected the ratio of the reactant passing through the hypothetical zwitterion **84**. The conformational interconversion was found to be negligible at temperatures below 50°C; the *unlike* conformer *ul*-**85** was found to be somewhat more stable − heating of (*like*) *l*-**85** to 105 °C produced a mixture of *ul*-**85** and *l*-**85** in 85:15 ratio. The planar diastereomer *ul*-**85** underwent a subsequent [2+2] cycloaddition in the course of the rearrangement to give a single adduct. The reaction was found to be stereoselective, the regiochemical outcome has yet to be established (Scheme 20).



Scheme 20

The aza ketene Claisen rearrangement has been described by Edstrom.[42] An initial addition of an electron-deficient ketene to the nitrogen atom of an allylamine **86** hypothetically produced a zwitterion **87**, which immediately underwent a [3,3] sigmatropic rearrangement to form the γ,δ-unsaturated amide function of **88**. Because charge neutralization is the major driving force of the process, the reaction required comparatively low temperatures of room temp. to 62°C (Scheme 21).



Scheme 21

Starting from *N*-benzyl-2-vinylpyrrolidine (*n* = 0) and -piperidine (*n* = 1) **86**, ketene Claisen rearrangements using dichloroketene generated in situ produced the corresponding azoninone and azecinone **88** (R^1 = Bn) in 64 and 96% yields, respectively. Replacement of the *N*-protecting group of **86** by the more electron-rich PMB (*p*-methoxybenzyl) substituent (R^1 = PMB), resulted in an observed decrease in yields of **88** to 52 and 54%, respectively. Although the double bond in the medium-sized ring **88** was found to be exclusively of (*E*) configuration, both rearrangements suffered from a complete loss of chiral information because of the use of symmetrically terminally substituted olefins (= CH_2) and ketenes (=CCl_2) as reactants. The NMR spectra of the azecinone **88** (*n* = 1) were characterized by the coexistence of two conformers. In contrast, the 9-membered ring **88** (*n* = 0) was found to be a single species. Both medium-sized lactams have been used in transannular ring contractions to yield the corresponding quinolizidinones **90** (*n* = 1) and indolizidinones **90** (*n* = 0), respectively. The (*E*) double bonds of **88** suffered from an external attack of an electrophile (I^+, $PhSe^+$, Me_3Si^+), the resultant onium ion underwent a regioselective and stereoselective addition by the N center of the lactam to give an acylammonium salt **89**. The benzyl group was then removed by a von Braun type degradation, to form the corresponding benzyl halide. Surprisingly, the relative configuration of bridgehead hydrogen atom and the adjacent substituent were found to be *trans* when quinolizidinones **93** were synthesized. After dechlorination with Zn/Ag/HOAc to give the lactams **91**, the transannular ring contraction of the azoninone (*n* = 0) took the expected path, generating indolizidinone **90** (R^2 = H). In contrast, the analogous reactions involving the azecinone **91** (*n* = 1) resulted in bicyclic compounds **93**, hypothesized as through the acylammonium ion **92** as a quasi *syn* adduct of E and N at the double bond. Finally, one quinolizidinone **93** (*n* = 1, E = I) has been employed as a key intermediate

in a total synthesis of (±)-epilupinine (for detailed information see Table 1).

Table 1. Ring enlargement by means of ketene Claisen rearrangement of 2-vinyl-substituted azacycles, transannular ring contraction (ref.[42])

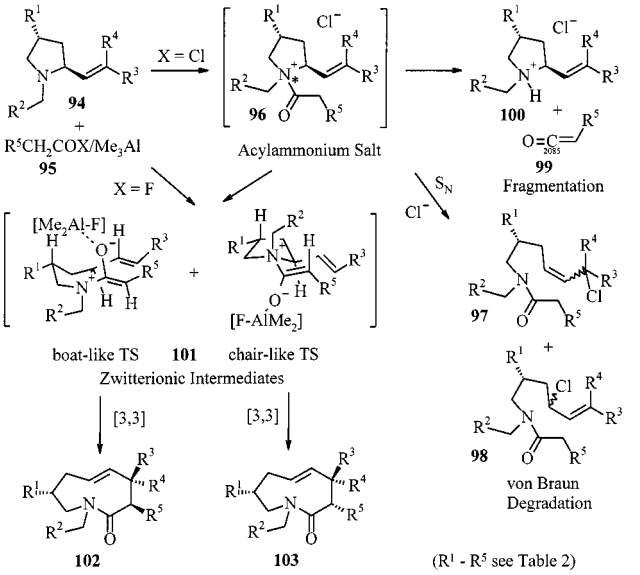
Entry	R^1	N	Yield [%] **88** (**91**)	Yield [%] **90**, [**90**], (**93**)[a] E = I	E = PhSe	E = TMS
1	Bn	0	64 (45)	88 [87]	79 [64]	72
2	PMB	0	52	–	–	–
3	Bn	1	96 (86)	85 (62)	84 (74)	–
4	PMB	1	54	–	–	–

[a] Yield **90**: R^2 = Cl; [**90**]: R^2 = H; (**93**): R^2 = H.

The mild reaction conditions and the obviously high potential driving force of the ketene Claisen rearrangement recommended the use of the process with more complex systems.[43,44] The first series of this type of reaction suffered from severe limitations, restricting the method to a limited range of ketenes and allylamines. On one hand, only electron-deficient ketenes would add to the allylamines, and useful yields of the lactams had been achieved only on treatment with dichloroketene. On the other hand, either the rearrangement had to be restricted to monosubstituted olefins in the amino fragment, or the driving force had to be increased by a loss of ring strain during the process. Furthermore, two competing processes should be mentioned. Firstly, the tertiary amines **94** and the acid chlorides **95** (X = Cl) initially formed acylammonium salts **96**, which underwent a von Braun type degradation through an attack of the nucleophilic chloride ion at the allyl system to give allyl chlorides **97/98** and carboxamide functions. Secondly, the use of acyl chlorides as reactants produced the corresponding ketenes **99**, while the allylamines were deactivated as ammonium salts **100** (Schotten–Baumann conditions). Three changes to the reaction conditions resulted in a pioneering overcoming of these limitations, converting 2-vinylpyrrolidines **94** into the corresponding azoninones **102/103** (Scheme 22).

The first of these was the addition of stoichiometric amounts of a Lewis acid, especially trimethylaluminum, to the reaction mixture: A range of α-substituted carboxylic acid halides **95** (X = Cl, F) as precursors of the ketenes may be used to overcome the restriction concerning the ketene component but, previously, the rearrangement had failed when using α,α-difunctionalized carboxylic acid halides. The Lewis acid might have increased the acidity of the α-protons by interacting with the carbonyl group of the acid, facilitating the formation of the intermediate zwitterions **101**, and/or it might have stabilized the zwitterionic intermediate **101**, suppressing the elimination of ketene **99**. Furthermore, allylamines **94** bearing 1,2-disubstituted double bonds could be successfully rearranged, overcoming a restriction concerning the carbon framework.

The second was the replacement of the acyl chlorides **95** (X = Cl) by the corresponding acyl fluorides **95** (X = F) as the substituents on the ketene precursors: the von Braun type degradation, as the major competing reaction ob-

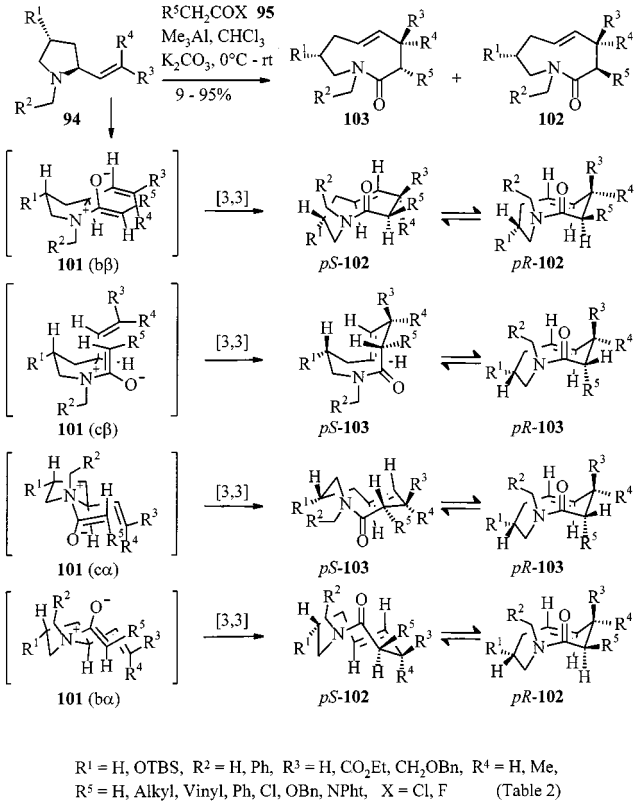


Scheme 22

served, was efficiently suppressed. The fluoride counter-ion was known to be less nucleophilic but more basic. Furthermore, the potential formation of a stable Al–F bond should rule out the fluoride as a latent nucleophile. The acyl fluorides **95** were found to be less reactive than the corresponding acyl chlorides, causing some difficulties in the rearrangement with *n*-alkylcarboxylic acid derivatives. Such transformations needed longer reaction times, and the yields of the corresponding rearrangement products were moderate.[45]

The third measure was the use of a second base to trap all proton acids generated during the course of the rearrangement; in most cases a two-phase system of solid potassium carbonate as a suspension in dichloromethane or chloroform gave the best results.

When the optimized reaction conditions were employed, the stereochemical advantages of the Claisen rearrangements were combined with an efficient synthesis of the azoninones **102** and **103**, bearing defined (*E*)-configured double bonds in the medium-sized rings (Scheme 23). As is the case for all known Claisen rearrangements, complete 1,3-chirality transfer was observed on treating the (*E*)-allylamines **94** (R^1, R^4 = H) with acetyl chloride **95** (X = Cl, R^5 = H). Both enantiomers of the core framework were constructed starting from the same L-(–)-proline derivative reactant, choosing either an (*E*)- (R^4 = H) or a (*Z*)-allylamine (R^3 = H) **94**. Furthermore, a high degree of internal asymmetric induction could be observed when α-substituted acyl halides **95** ($R^5 \neq$ H) were involved in the synthesis of the lactams **102/103**. In most cases, the diastereomeric excess was > 5:1 in favor of the 3,4-*trans*-lactam **103** (Entries 3–14, Table 2). The phenylacetyl halide rearrangement (R^5 = Ph, Entry 7, Table 2) only gave a nearly equal mixture of *cis*- and *trans*-azoninones **103** and **102** (R^5 = Ph). The stereochemical outcome of the rearrangement of **94** (R^1 = H) was explained by its passing through a chair-like transition state **101** (cα) with minimized repulsive inter-



Scheme 23

actions and a defined (*Z*)-enolate geometry (as is known for all amide enolates). However, its passing through the chair-like transition state **101** (cβ) could not be ruled out: Both **101** (cα) and (cβ) would result in the same diastereomer *pS*-**102**! Surprisingly, the rearrangement of the 4-*tert*-butyldimethylsilyloxy-2-vinylpyrrolidines **94** (R^1 = OTBS, R^3, R^4 = H) took another course. The stereochemical outcome had to be rationalized by passing through a boat-like transition state **101** (bβ) to give the 3,8-*trans*-lactams **102** (R^1 = OTBS, Entries 15−19, Table 2).[44,46] The corresponding *cis* product **103** (R^1 = OTBS) resulting from the expected chair-like intermediate **101** (cβ) has only once been isolated, as a minor compound (Entry 17, Table 2). The completeness of the 1,4-chirality transfer should be pointed out.

Prima facie, the configuration of the transiently produced stereogenic ammonium center in **101** should be negligible: In the rearrangement of the 2-vinylpyrrolidines **94**, passing through a chair-like transition state **101** (c) would result in a lactam **103**, passing through the boat-like **101** (b) counterpart should result in the corresponding product **102**, independently of α- and β-acylation, respectively.

Screening the results of the rearrangements of the allylamines **94** (R^1 = H), chair-like transition states should have been favored. The *N*-acylation should have been directed by the side chain adjacent to the opposite face of the 5-membered ring to give **101** (α) (1,2-*anti* induction, as found by analyzing appropriate acylammonium salts). Con-

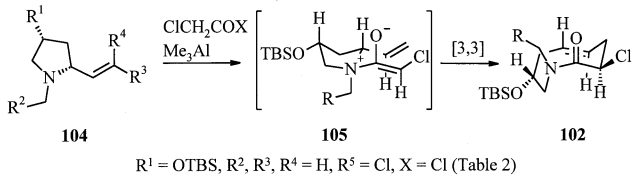
Table 2. Ring enlargement through zwitterionic aza Claisen rearrangement with 2-vinylpyrrolidines (refs.[43−46])

Entry	R^1	R^2	R^3	R^4	R^5	X	Yield [%]	Ratio **103/102**	Ref.
1	H	H	CO_2Et	H	H	Cl	70	–	[43a]
		Ph				Cl	60	–	[43b]
2	OTBS	H	CO_2Et	H	H	Cl	53	–	[43a]
3	OTBS	H	CO_2Et[a]	H	H	Cl	47	–	[43a]
4	H	H	CO_2Et	H	Me	Cl	77	> 95:< 5	[43b]
		Ph[b]				F	73	> 6:< 1	[45a]
5	H	Ph[b]	CO_2Et	H	CH_2CH_2Cl	F	51	> 6:< 1	[45a]
6	H	H	CO_2Et	H	$CH{=}CH_2$	Cl	80	> 95:< 5	[43b]
		Ph[b]				F	72	> 3:> 1	[45a]
7	H	H	CO_2Et	H	Ph	Cl	32[c]	45:55	[43b]
		Ph[b]				F	79	1:2	[45a]
8	H	H	CO_2Et	H	Cl	Cl	72	> 95:< 5	[43b]
		Ph				Cl	22	90:10	[43b]
		Ph				F	81	90:10	[45a]
9	H	H	CO_2Et	H	OBn	Cl	68	80:20	[43b]
		Ph				Cl	30	80:20	[43b]
10	H	H	CO_2Et	H	NPht	Cl	35[c]	> 94:< 6	[43b]
11	H	Ph	CH_2OBn	H	Cl	Cl	11	87:13	[43b]
12	H	Ph[b]	H	Me	CH_2CH_2Cl	F	51	> 6:1	[45a]
13	H	Ph[b]	H	Me	Ph	F	87	1:> 4	[45a]
14	H	Ph	H	Me	Cl	Cl	9	1:1	[45a]
						F	91	3:1	[45a]
15	OTBS	H	H	H	Ph	Cl	17[c]	1:> 10	[44]
		Ph				Cl	26[c]	1:> 10	[44]
		Ph				F	95	1:> 10	[46]
16	OTBS	H[a]	H	H	Cl	Cl	22	1:> 10	[44]
17	OTBS	H	H	H	Cl	Cl	29[c]	1:> 10	[44]
		Ph				Cl	20[c]	1:5	[44]
		Ph				F	92	1:> 10	[46]
18	OTBS	Ph[b]	H	H	OBn	F	73	1:> 10	[46]
19	OTBS	Ph	H	H	NPht	Cl	17	1:> 10	[44]

[a] Reaction with (2*R*)-vinylpyrrolidine. − [b] Rearrangement failed when acid chloride was used. − [c] Up to 50% of the reactant recovered.

sequentially, the rearrangement must have proceeded through **101** (cα), as is known for the acyclic 3,3-sigmatropic reaction, leading predominantly to lactams **103**. However, passing through **101** (cβ) would also serve as a satisfactory explanation for generating lactam **103**.

In contrast, the *N*-acylation of the 2,4-*trans*-disubstituted pyrrolidines **94** (R^1 = OTBS) was directed by the bulky silyl ether, producing a *syn* arrangement of vinyl and acyl group in an intermediate ammonium salt **101** (β) (1,3-*anti* induction, 1,2-*syn*). An appropriate conformation to undergo a Claisen rearrangement, then, was presumably the boat-like form **101** (bβ), with minimized 1,3-repulsive interactions resulting in the lactams **102**. However, the 2,4-*cis*-disubstituted pyrrolidine **104** (R^1 = OTBS, R^3, R^4 = H) gave the expected lactam diastereomer **102** via a chair-like transition-state conformation **105** (Table 2) (Scheme 24).[44,46]

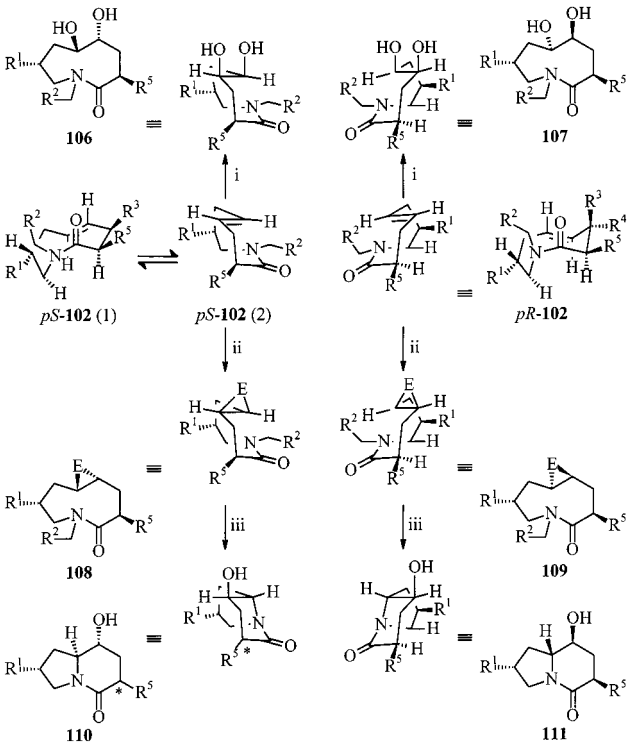


Scheme 24

The lactam and the olefinic unit characterized the heterocyclic cores **102** and **103** as constrained ring systems, the conformations of which were found to be strongly dependent on the substitution pattern and the relative configuration of the stereogenic centers. The planar-chiral properties of the medium-sized rings with internal (*E*) double bonds had to be taken into account when analyzing the 9-membered rings. The rearrangements of the (2*S*)-vinylpyrrolidines **94**, passing through a boat-like transition state **101** (b), initially effected the formation of the medium-sized ring with a *pS* arrangement of the (*E*) double bond *pS*-**102**. This planar diastereomer *pS*-**102** was obviously unstable: NMR and NOE analyses indicated the coexistence of one preferred *pS*-**102** (1) and at least one additional minor conformation, *pS*-**102** (2), as a highly flexible equilibrium of some arrangements of the lactam function. Finally, the epimerization [flipping of the (*E*) double bond] to give the *pR* arrangement *pR*-**102** of the olefin with respect to the ring generated the most stable and rigid conformation. Preliminary force field calculations on the azoninones **102** and molecular mechanics calculations on the related (*E*)/(*Z*)-1,5-nonadiene confirmed these observations.[47] In contrast, the lactams **103** (R^4 = H), generated via chair-like zwitterions **101** (c), were found to be generated directly in a stable *pS* arrangement of the (*E*) double bond (Schemes 23−25).

Nevertheless, a high activation barrier has to be surpassed in order to achieve the change in the planar chiral information (*pS*-**102** → *pR*-**102**).[48] This fact has permitted the isolation and the characterization (incl. several X-ray analyses) of the conformers of the 9-membered rings (Scheme 23).

The planar diastereomer azoninones *pS*-**102** and *pR*-**102** were subjected to cycloadditions in the syntheses of the



Scheme 25. i) $RuCl_3$ cat., $NaIO_4$, H_2O, MeCN, EtOAc, 0 °C; then Ac_2O, Py, DMAP cat., CH_2Cl_2, room temp. or $Me_2C(OMe)_2$, *p*TsOH cat., Me_2CO; ii) CH_2N_2, $Pd(OAc)_2$ cat., Et_2O, room temp. or $N_2C(CO_2Et)_2$, $Pd(OAc)_2$ cat., PhMe, 60 °C or *p*-TosN=I−Ph, $Cu(OTf)_2$ cat., MeCN, 10 °C or *m*CPBA, CH_2Cl_2, phosphate buffer (pH = 7), 0°C or room temp.; iii) TMSI, (LiI), $CHCl_3$, room temp., or TMSI, LiI, $CHCl_3$, −10 °C; for yields see Tables 3 and 5

azonanones **106**−**109** (Scheme 25, Table 3). Low-temperature reactions (≤ 25°C) allowed an almost complete conversion of the planar-chiral information of the reactants into new chiral centers in the products. Cyclopropane-, aziridine-, and oxirane-annulated azonanones **108** and **109** had been synthesized, as well as the dihydroxylated (protected) 9-membered ring lactams **106** and **107**. If the reaction required higher temperatures, the diastereoselectivity decreased severely because of the competing flipping of the double bond (*pS* → *pR*) with respect to the ring (Table 3 Entry 4/5, 2nd reaction).[49]

The oxirane functions of the epoxy azonanones **108** and **109** underwent regioselective openings and consecutive transannular ring-contraction sequences to generate the 8-hydroxyindolizidinones **110** and **111** with complete stereoselectivities and high regioselectivities (Table 5, Entries 13−16). Exclusive formation of δ-valerolactams was always found when the reactions were performed at room temp., although the reactant azonanones were characterized by high conformational mobility of the amide function with diastereomeric properties. As expected, the conversions of the (5*S*,6*S*)-azonanones **109** exclusively yielded bicyclic **111** because of their short N−C6 distances, as determined by X-ray analyses and some optimized force field calculations

Table 3. Cycloadditions of planar chiral azoninone **102** (ref.[49])

Entry	Lactam **102**	R^5	Yield azonanones [%] **108/109**				**106/107**	
			E = CH_2	E = $C(CO_2Et)_2$	E = N-*p*Ts	E = O	E = 2 × OH[a]	E = 2 × OH[b]
1	*p*S	Ph	–	–	58/–	100/–	95/–	–
2	*p*R	Ph	–	–	–	13/82	–	–
3	*p*R	OBn	–	–	–	–/91	–	–
4	*p*S	Cl	92/–	12/18	56/–	92/–	71/–	70/–
5	*p*R	Cl	9/91	–/52	–/86	17/55	10/88	

[a] Diol protected as acetonide. – [b] Diol protected as bis(acetate).

(Table 5, Entries 14/15). In contrast, the (5*R*,6*R*)-azonanones **108** followed different reaction paths, to generate the bicycles **110** (Table 5, Entries 13, 16). The conformation of **108**, determined by X-ray and NOE analyses, bore a slightly shorter N–C5 distance, implying the formation of (some) γ-butyrolactam product. Obviously, the lactam function of the azonanones **108** was characterized by some flexibility, to generate at least one additional, significantly more reactive conformer resulting from *pS*-**102** (2) with a shorter N–C6 distance to induce efficient δ-valerolactam **110** formation. The defined hydroxylated indolizidinones **110** and **111** thus formed should serve as useful key intermediates in the synthesis of leguminose type alkaloids and pumiliotoxins. Some *intra*annular distances are given in Table 4 (N–C5 and N–C6).[46,49]

Initial investigations showed that the planar diastereomer azoninones *pS*-**102**, *pR*-**102**, and *pS*-**103** underwent regioselective and diastereoselective ring contraction to form indolizidinones **114**–**117** (Scheme 26, Table 5).[46] The rigid conformations of the lactams involved gave rise to defined *anti* attack of an external electrophile at the unshielded face of the double bond (*pS* → *re* attack, *pR* → *si* attack) and intramolecular trapping of the resultant cation **112** and **113** by the lactam nitrogen atom (*pS* → *si* attack, *pR* → *re* attack). The intermediate (acyl)(benzyl)ammonium ions thus formed underwent an immediate von Braun degradation to give the indolizidinones **114**–**117**. In breach of the Curtin–Hammett principle, the lactams allowed defined additions to the double bond with respect to the predominant conformation. The planar-chiral information of the 9-membered ring **102** and **103** (*pS* or *pR*) could be transformed into defined stereogenic centers of **114**–**117** by means of the ring contraction. While the reactions of the rigid azoninones *pS*-**103** (R^3 = CO_2Et, Table 5, Entries 1–3) and *pR*-**102** (R^3, R^4 = H, Table 5, Entries 6, 9, 12) exclusively yielded bicycles **115** and **117**, respectively, with δ-valerolactam functions, the *pS*-**102** rings (R^3, R^4 = H, Table 5, Entries 4/5, 7/8, 10/11) followed different reaction paths, generating two further products, **114** and **116**. Obviously, the lactam function of the kinetically formed azoninones *pS*-**102** had shown some flexibility under the reaction conditions, generating at least two reactive conformations, *pS*-**102** (1, as found in the NMR spectra) and *pS*-**102** (2, hypothetical, Scheme 26), with diastereomeric properties. Variation of the transannular reaction conditions (method A or B, Table 5) made it possible to pick out for predominance of either one of these conformations, yielding either the **114** series or the **116** series, respectively (Scheme 26).[46] Some intraannular distances in **102** are listed in Table 5. One indolizidinone, **115** (R^1, R^4, R^5 = H, R^3 = CO_2Et), had been employed as a key intermediate in a total synthesis of a dendroprimine (indolizidine alkaloid).[50]

An alternative pathway, using a zwitterionic aza Claisen rearrangement to generate azoninones, had been described by Hegedus.[51] 2-Vinylpyrrolidines **118** and carbenechromium complexes **119** underwent photochemical reactions in the presence of Lewis acids to give the corresponding 9-membered ring lactams **120**, with (*E*) double bonds, in up to 71% yield (Scheme 27). Though reactants and products suffered from some degree of instability towards Lewis acids, the presence of zinc chloride or dimethylaluminum chloride was essential for initiating the rearrangement. In

Table 4. Transannular distances in azoninones and azonanones (R^1 = OTBS, R^2 = Ph, R^3, R^4 = H) (refs.[46,49])

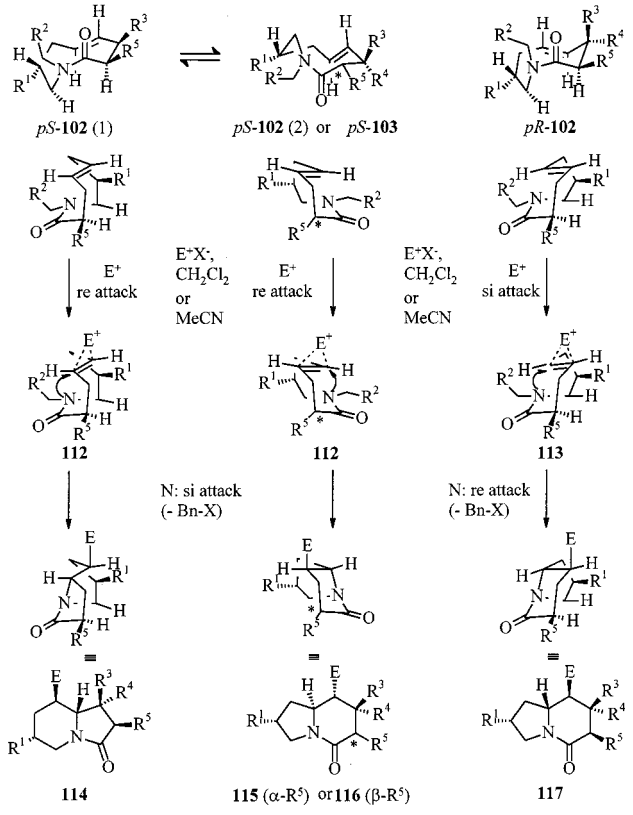
Compound	R^5 (X)	Transannular distance [Å] N–C5 (calcd.)	N–C5 (found)	N–C6 (calcd.)	N–C6 (found)	ΔE_{rel} [kJ/mol]	Ref.
pS-**102** (1)	Cl	3.13	3.09	3.22	3.21	8.8	[46]
pS-**102** (2)	Cl	3.34		3.04		19.6	[46]
pR-**102**	Cl	3.33	3.31	2.97	2.98	0	[46]
108 (1)	Cl (O)	3.18	3.13	3.23	3.24	0	[49]
108 (2)[a]	Cl (O)	3.30		2.82		17.5[a]	[49]
109	Cl (O)	3.36	3.39	2.91	3.00	–	[49]
109	OBn (O)	3.35	3.38	2.92	3.05	–	[49]

[a] A third conformation **108** [(*E*) arrangement of lactam –O and N–Bn] was calculated: distance N to C5: 3.3 Å; N to C6: 2.89 Å; ΔE_{rel}: 11.5 kJ/mol. ΔE_{rel} calcd. for the minimum conformation of the compound: ΔE_{rel} = 0 [*pR*-**102**, **108** (1)].

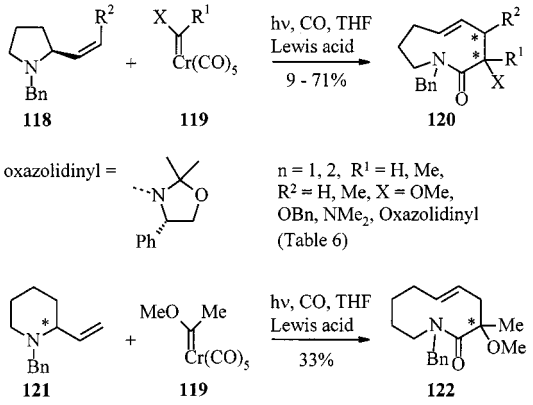
Table 5. Transannular ring contractions of planar-chiral azoninones and epoxides (R^2 = Ph, R^4 = H) (refs.[43,44,46,49])

Entry	Lactam	R^1	R^3	R^5	Method[a]	Yield indolizidinones [%] **114/115/116/117** E = I	E = Br	E = PhSe	**110/111** (E = OH)	Ref.
1	*pS*-**103**[b]	H	CO_2Et	H	B	–	–	–/22/–/–	–	[43b]
2	*pS*-**103**	H	CO_2Et	H	B	–	–	–/70/–/–	–	[43b]
3	*pS*-**103**	H	CO_2Et	Cl	B	–	–	–/70/–/–	–	[43b]
4	*pS*-**102**	OTBS	H	Ph	A	47/–/16/–	40/–/–/–	44/–/–/–	–	[46]
5	*pS*-**102**	OTBS	H	Ph	B	–/–/99/–	11/–/44/–	–/–/95/–	–	[46]
6	*pR*-**102**	OTBS	H	Ph	A or B	–/–/–/49	–/–/–/72	–/–/–/69	–	[46]
7	*pS*-**102**	OTBS	H	OBn	A	12/–/24/–	16/–/–/–	38/–/8/–	–	[46]
8	*pS*-**102**	OTBS	H	OBn	B	–/–/70/–	–	–/–/74/–	–	[46]
9	*pR*-**102**	OTBS	H	OBn	A or B	–/–/–/40	–	–/–/–/20	–	[46]
10	*pS*-**102**	OTBS	H	Cl	A	–	25/–/–/–	19/–/1.5/–	–	[46]
11	*pS*-**102**	OTBS	H	Cl	B	–/–/15/–	–/–/82/–	–/–/81/–	–	[46]
12	*pR*-**102**	OTBS	H	Cl	A or B	–/–/–/64	–	–/–/–/64	–	[44][46]
13	**108** (E = O)	OTBS	H	Ph	B	–	–	–	60/–	[49]
14	**109** (E = O)	OTBS	H	Ph	B	–	–	–	–/32	[49]
15	**109** (E = O)	OTBS	H	OBn	B	–	–	–	–/57	[49]
16	**108** (E = O)	OTBS	H	Cl	B	–	–	–	47/–	[49]

[a] Method A: addition of the lactam to the reagent at −20°C; method B: addition of the reagent to the lactam at room temp. – [b] R^2 = H (two-step ring contraction).



Scheme 26



Scheme 27

contrast to the classical ketene Claisen process, it was possible to use electron-rich ketene equivalents such as alkoxy or amino ketenes, since the donor substituents stabilized the carbenechromium complex **119**. Furthermore, α,α-disubstituted lactams have been synthesized but the stereoselectivity observed was low. Determination of the stereochemical outcome of the reaction proved that the 1,4 chirality transfer was not complete: A Mosher analysis of an appropriate azoninone **120** gave a loss of about 10% of the chiral information. The presence of a chiral carbene complex **119** (R^1 = oxazolidinyl) was found to have a negligible influence on the stereoselectivity of the rearrangement. Generally, this variant of the rearrangement was found to be very sensitive to any steric hindrance. Additional substituents in any position (eg. $R^2 \neq$ H) resulted in severe decreases in yield and stereoselectivity. Additionally, one example of a 2-vinylpiperidine (**121**) rearrangement was given, the corresponding azecinone **122** was formed in about 33% yield. Some details are outlined in Table 3. In analogy to Edstrom's experiments,[42] the 9- and 10-membered ring lactams **120** and **122** underwent regioselective and stereoselective transannular ring contractions to give the corresponding indolizidinones and quinolizidinones, respectively (vide supra Scheme 21) (Table 6).

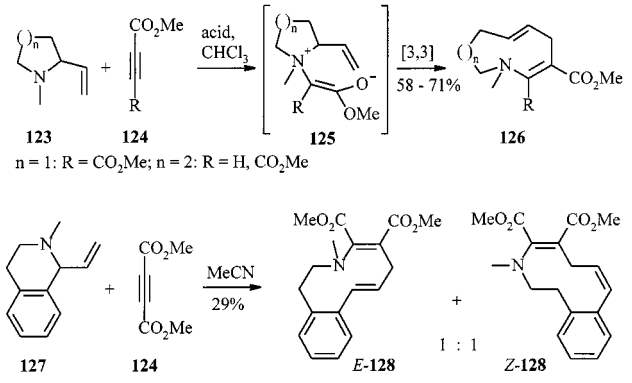
If the carboxylic acid halides were replaced by propargyl esters **124**, the initial reactions of allylamines **123** could be described as Michael additions (**123** to **124**) to form the zwitterions **125**. The subsequent rearrangement step con-

Table 6. Ring enlargement by means of carbenechromium Claisen rearrangement (ref.[51])

Entry	*n*	R^1	X	R^2	Lewis acid	Yield [%]	*de* **120/122**
1	1	Me	OMe	H	$ZnCl_2$	71	–
2	1	Me	OBn	H	$ZnCl_2$	66	62% *de*[a]
3	1		$-(CH_2)_3-O-$	H	$ZnCl_2$	15	–
					Me_2AlCl	22	
4	1	H	NMe_2	H	Me_2AlCl	9	–
5	1	H	oxazolidine[b]	H	$ZnCl_2$	19	74% *de*[a]
6	1	Me	OMe	Me	$ZnCl_2$	20	60% *de*
7	1	Me	OBn	Me	$ZnCl_2$	40	33% *de*[c]
8	2	Me	OMe	H	Me_2AlCl	33	–

[a] Determined by Mosher analysis of a derivative. – [b] Chiral oxazolidine. – [c] Mixture of 3,4-diastereomers.

sequently resulted, stereoselectively, in a vinylogous carbamate **126** bearing (*E*) double bonds. Rearrangements of 2-vinylpyrrolidines or 2-vinylpiperidines **123** resulted in the generation of the corresponding 9- and 10-membered azacycles **126**, respectively, in moderate to high yields.[52] While the 9-membered ring **126** ($n = 1$) was found to be unstable, the azecine **126** ($n = 2$) could be stored and fully characterized without any decomposition. The chiral information of the reactant stereogenic center in **123** was lost during the course of the reaction. The method was used to generate a 3-benzazecine **128**, on treating the vinyl isoquinoline **127** with diethyl acetylenedicarboxylate. In contrast to the experiments of Vedejs, the nascent styrene double bond was obtained as a mixture of (*E*)- and (*Z*)-olefins [(*E*)-**128**/(*Z*)-**128** = 1:1] (Scheme 28).



Scheme 28

Conclusion

Eight- to ten-membered unsaturated heterocycles in general, and 9-membered rings in particular, have been proven to be versatile reagents in total syntheses of natural and pharmaceutically important products. During the past decade, flexible reaction sequences to generate appropriate 8- to 10-membered rings have been developed, with high diastereoselectivities and high yields being obtained. In summary of the strategies, ring-closure reactions such as metathesis and some lactonizations/lactamizations on one hand and ring enlargements through Claisen/(Cope) rearrangements on the other hand, have been found to serve as the most powerful methodologies. A range of examples has demonstrated that the planar chiral information of the medium-sized rings represents a useful tool in attempting the formation of new stereogenic centers through transannular reactions or cycloadditions. The still unresolved potential of medium-sized heterocycles should presumably find widespread use in future.

Acknowledgments

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