Modular Asymmetric Synthesis of Functionalized Azaspirocycles Based on the Sulfoximine Auxiliary

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften der Rheinisch-Westfälischen Technischen Hochschule Aachen zur Erlangung des akademischen Grades einer Doktorin der Naturwissenschaften genehmigte Dissertation

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A. Theoretical Part

1. Introduction to azaspirocycles and aims of the project

Natural products are built up with structural patterns that inspire synthetic organic chemists.[1] The development of new methods and strategies for the construction of these patterns is a continuing focus of interest. The strengths and weaknesses of a synthetic approach can be evaluated by different criteria including conciseness, efficiency, flexibility, cost as well as other factors. Although in practice each method has its own pros and cons, the instructive value for each is substantial.

Most of the natural products are chiral and their biological activities depend essentially on receptors, which are themselves chiral. The drama caused by the administration of racemic thalidomide (Figure 1) to pregnant women shows the need for methods to prepare enantiomerically pure compounds.[2]

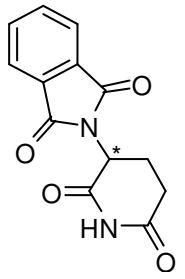


Figure 1. (±)-Thalidomide

1.1 Naturally occurring azaspirocycles

Azaspirocycles of type **1** (Figure 2) are found as building blocks in a number of highly interesting natural products.[1]

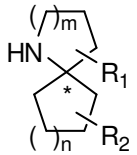
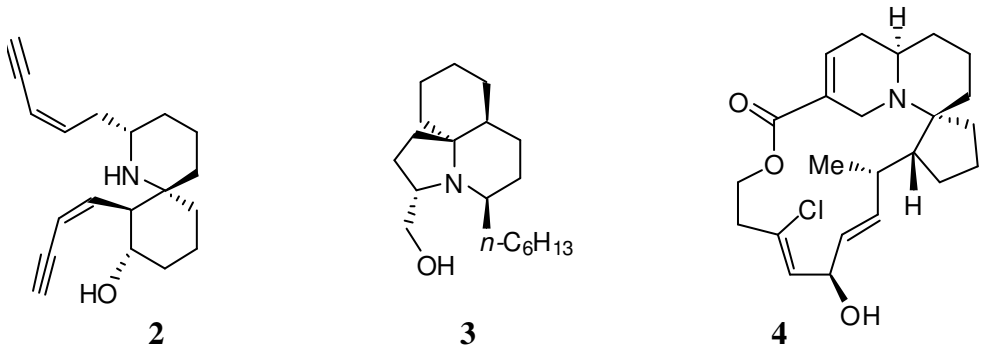


Figure 2. Azaspirocycles of type **1**

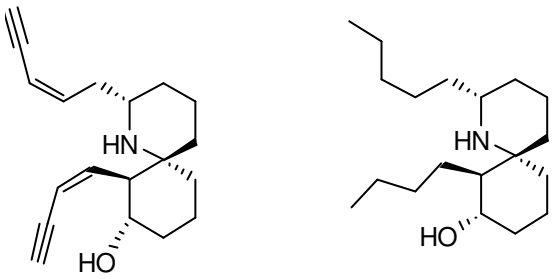
Inspection of the molecular architecture of the naturally occurring alkaloids histrionicotoxin **2**, lepadiformine **3** and halichlorine **4** (Figure 3), as well as others, reveals a common azaspirocyclic 6,6- or 6,5- or 5,6-fused ring system, respectively. Some of these alkaloids have important biological activity.



2 **3** **4**

Figure 3. Natural products having a common azaspirocyclic ring system

In 1971, WITKOP and co-workers reported the isolation and structure of a unique azaspirocyclic alkaloid named (–)-histrionicotoxin **2** (Figure 4).[3] Since its isolation, further 15 alkaloids of this family have been identified, varying only in the length and degree of saturation present in the two side chains. Histrionicotoxin **2** was isolated from the brightly colored "poison arrow" frog of the family *Dendrobates histrionicus* found in South America. Alkaloid **2** and its hydrogenation product, the unnatural perhydrohistrionicotoxin **5**, are both useful biochemical tools for probing the mechanism of transsynaptic transmission of neuromuscular impulses.



2 **5**

Figure 4. Histrionicotoxin **2** and perhydrohistrionicotoxin **5**

Cylindricine A **6** and lepadiformine **3** (Figure 5) are marine alkaloids with a common novel pyrroloquinoline skeleton.[4,5]

The cylindricines were isolated from the marine ascidian *Clavelina cylindrica* by BLACKMAN and co-workers between 1993 and 1995. Cylindricine A **6**, for example, showed some biological activity in the brine shrimp assay.

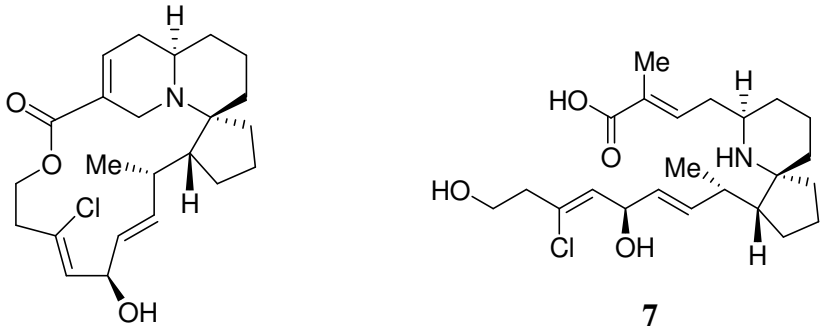
Lepadiformine **3** was isolated in 1994 by BRIARD and co-workers from *Clavelina lepadiformis* and exhibits moderate cytotoxic activity against various tumor cell lines in vitro, as well as high in vitro and in vivo cardiovascular effects.

6 **3**

Figure 5. Cylindricine A **6** and lepadiformine **3**

In 1996, UEMURA and co-workers isolated a novel marine alkaloid from the sponge *Halichondria okadai* in Japanese waters.[6] Halichlorine **4** (Figure 6) was shown to inhibit the induced expression of VCAM-1 (vascular cell adhesion molecule-1) at IC_{50} 7 $\mu g.mL^{-1}$. VCAM-1 regulates the transport of leucocytes, which makes it a potential target for the treatment of arteriosclerosis, inflammatory diseases and cancer. Interestingly, closely related pinnaic acid **7** displays inhibitory activity against $cPLA_2$ (cytosolic phospholipase A_2).

The unique structure and biological activity of these compounds have promoted a variety of synthetic approaches.[7] ITOH and co-workers analyzed the biological effects on human cultured cells of several compounds having the spirocyclic core subunit, which were prepared in the course of total synthetic studies of halichlorine **4**. Some of these compounds were unexpectedly found to exhibit apoptosis-inducing activity (cellular suicide) as a novel biological function.



4 **7**

Figure 6. Halichlorine **4** and pinnaic acid **7**

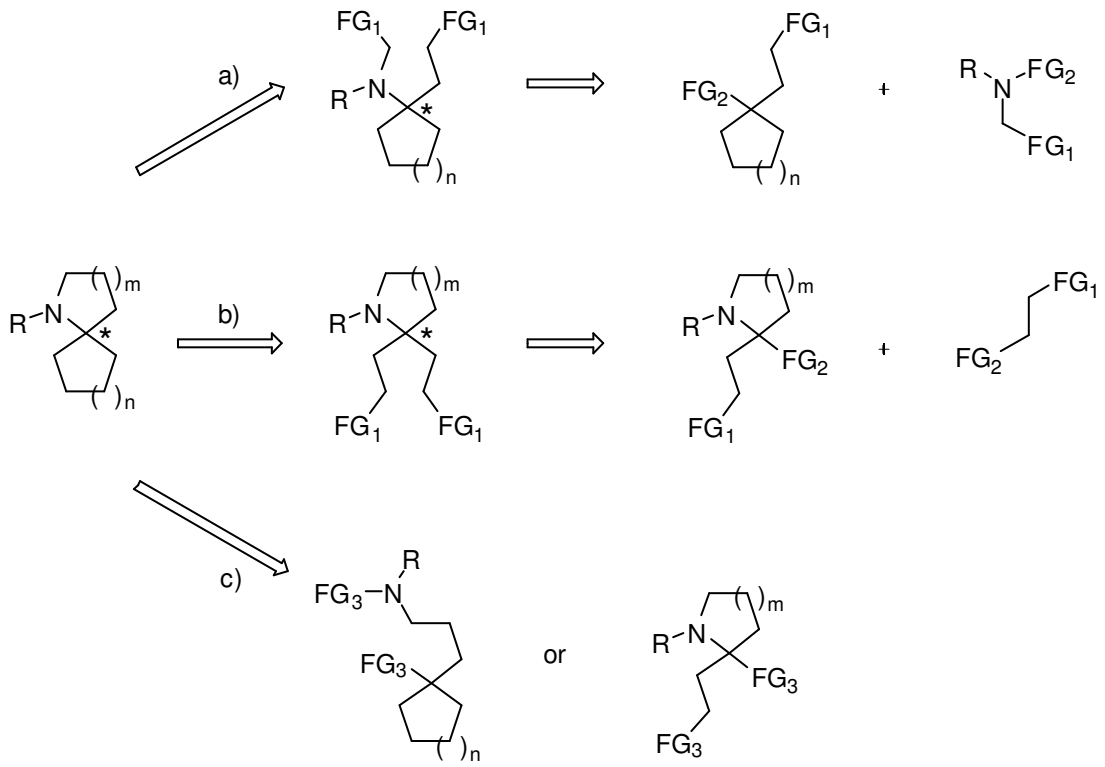
1.2 Retrosynthetic analysis of azaspirocyclic core structures

The focus of this chapter is the construction of azaspirocyclic alkaloids of type **1** (Figure 2). This system incorporates two rings connected by a spiro ring fusion containing a nitrogen atom adjacent to the ring junction.

The synthesis of such azaspirocycles involves two main synthetic challenges. The first problem is the construction of the tertiary carbon atom bearing the nitrogen atom that will ultimately become the spirocycle ring junction. This carbon atom is often a stereogenic center, which requires a stereochemical control in its formation. The second issue is the installation of the rings of the spirocyclic system: the carbocycle and the heterocycle.

According to DAKE the approaches to azaspirocycles of type **1** can be divided into three general groups (Scheme 1).[1] The first two strategies require a two-step process in which the tertiary carbon atom and the cycles are built up in separate events. The third approach combines both, generation of the tertiary carbon atom and one of the ring-closures.

- a) The carbocycle is already present. Then the tertiary carbon atom is built up and in a final step the heterocycle is closed.
- b) The heterocycle is already present. Then the tertiary carbon atom is built up and in a final step the carbocycle is closed.
- c) One of the cycles is already present, and in one step the tertiary carbon atom is built up and the other ring is closed.



Scheme 1. Retrosynthetic analysis of azaspirocycles according to DAKE

FG_1 = hypothetical functional groups that enable ring closure

FG_2 = hypothetical functional groups that enable formation of the spiro carbon atom

FG_3 = hypothetical functional groups that enable both: ring closure and construction of the tertiary carbon atom

1.3 Total syntheses of halichlorine and pinnaic acid

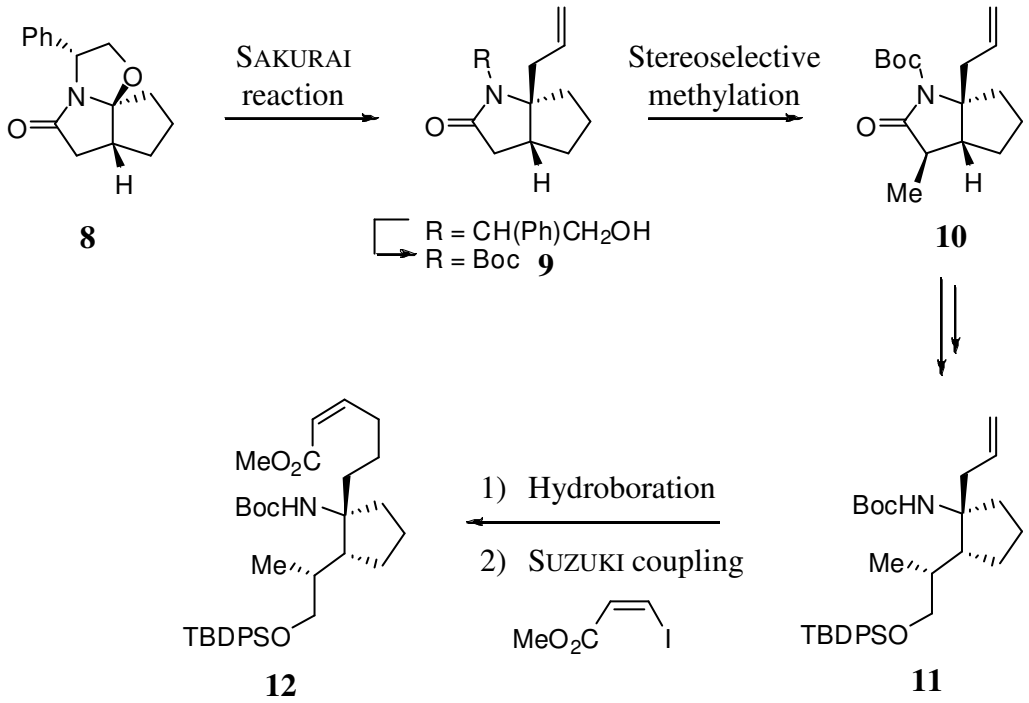
The 6-azaspiro[4,5]decane structures of halichlorine **4** and pinnaic acid **7** are even more impressive than their bioactivities. They have attracted considerable attention in the synthetic chemistry community and have recently been the topic of a specific review and a large number of reports describing efforts to synthesize them.[6]

In 1999, DANISHEFSKY and co-workers published the first asymmetric total synthesis of halichlorine and pinnaic acid.[8,9] It is so far the only one for halichlorine. In 2007 ZHAO et al. and ARIMOTO et al. published independently two new enantioselective total syntheses of pinnaic acid **7**.[10,11]

In 2004, HEATHCOCK and co-workers reported the total synthesis of the racemates of **4** and **7**.[12] Later some other groups published formal total syntheses of these marine alkaloids.[13,14,15]

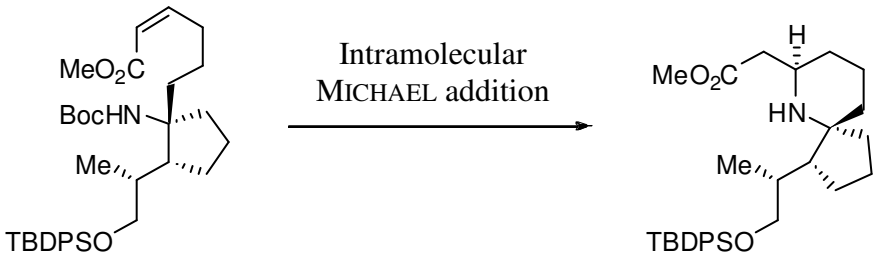
To illustrate route a) (Scheme 1) for the construction of azaspirocycles, the key steps of the first asymmetric total synthesis reported by DANISHEFSKY and co-workers, focusing on the construction of the azaspirocyclic structure, will be described.[8,9]

The synthesis starts with the known MEYERS lactam **8** (Scheme 2). The crucial tertiary stereocenter was introduced using a SAKURAI reaction. After replacement of the phenylglycinol moiety with a Boc-protecting group, a selective methylation of **9** from the convex face of the bicyclic lactam led to **10**. This compound was converted into **11**, which after hydroboration was submitted to an alkyl-SUZUKI coupling.



Scheme 2. Construction of the tertiary carbon atom by DANISHEFSKY et al.

At this stage two functional groups which enable the closure of the heterocycle are present: the nucleophilic nitrogen and the MICHAEL acceptor. The unsaturated ester **12** underwent intramolecular MICHAEL addition upon deprotection of the amino function with TFA and subsequent basification (Scheme 3).



12 **13**

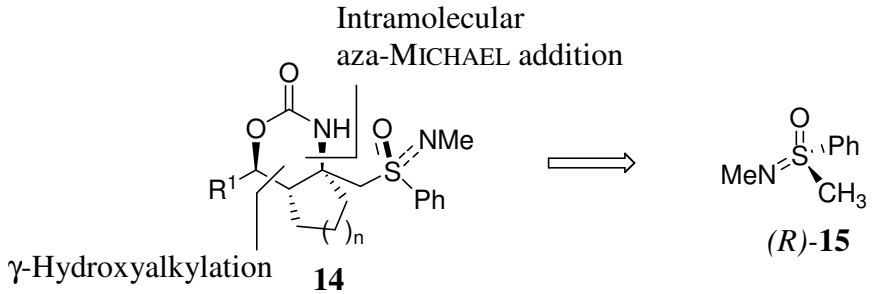
Scheme 3. Closure of the heterocycle by DANISHEFSKY et al.

1.4 Our approach to azaspirocycles

A number of methods have been developed for the construction of azaspirocycles of type **1**.[1] Although most of these target-molecule orientated methods are imaginative and high yielding, there is still an interest in the design of a more general method for the enantioselective construction of **1**.

The focus of this thesis was to develop a modular asymmetric synthesis of functionalized azaspirocycles of type **1** based on the sulfoximine auxiliary **15**.[16]

The synthetic approach to azaspirocycles described here is based on a two-step strategy in which the carbocycle with the tertiary *C* atom bearing the amino group is constructed (Scheme 4). This first part should take advantage of the methods developed in our group for the synthesis of β- and γ-amino acids from allylic sulfoximines.[17,18]



14 *(R)*-**15**

Scheme 4. Oxazinone **14**: A key intermediate in the synthesis of functionalized azaspirocycles

Using oxazinones of type **14**, containing the carbocycle, three contiguous stereogenic centers and the tertiary carbon atom bearing the nitrogen atom, we developed a modular method for the synthesis of azaspirocycle **16** (Figure 7).[19]

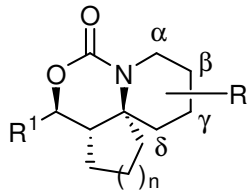


Figure 7. Azaspirocycle **16**

The challenging azaspirocyclic core and its promising biological profile make halichlorine **4** an ideal candidate for a synthetic venture.

2. Construction of the carbocycle having an amino-substituted tertiary *C* atom

2.1 The chiral auxiliary

2.1.1 Properties of the chiral auxiliary

Sulfoximines are used as highly versatile starting materials and auxiliaries in stereoselective synthesis. They are constitutionally and configurationally stable compounds which can be manipulated without special care. They show a unique combination of features, including chirality, carbanion stabilization, nucleofugacity, basicity, nucleophilicity, and a low redox potential (Figure 8).[16,20,21]

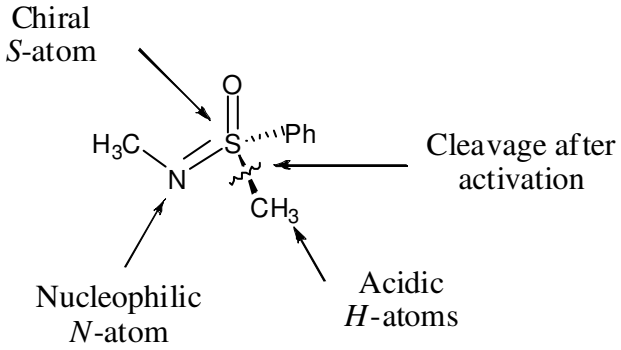


Figure 8. Chiral auxiliary *(R)*-**15**

Recent examples where several of these characteristics have been exploited in the GAIS group are the asymmetric synthesis of homopropargylic alcohols **17**,[22] dihydrofurans **18**,[23] proline derivatives **19**,[24] aziridines **20**,[25] medium-sized carbocycles **21**,[26] β-amino acids **22** and γ-amino acids **23**,[18,27] as well as others not depicted here (Figure 9).[28,29]

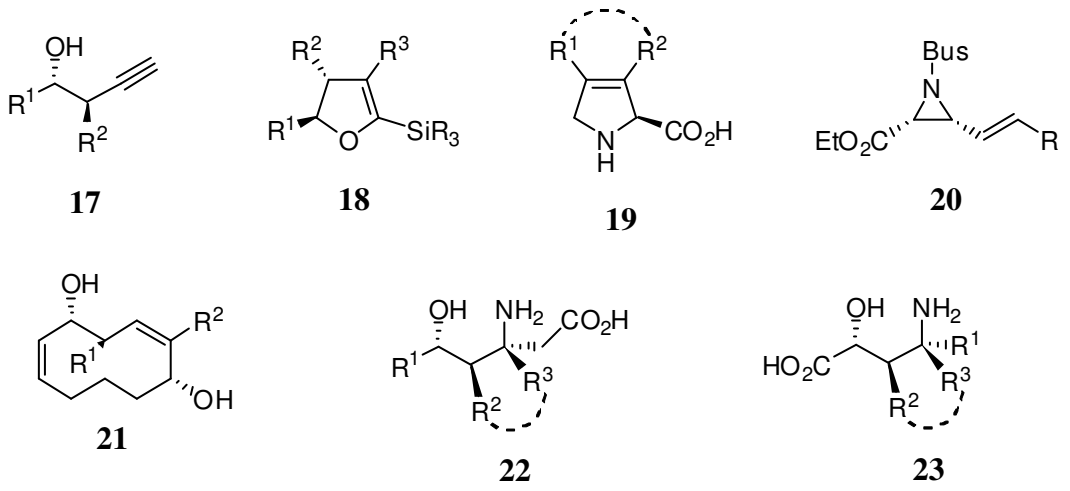
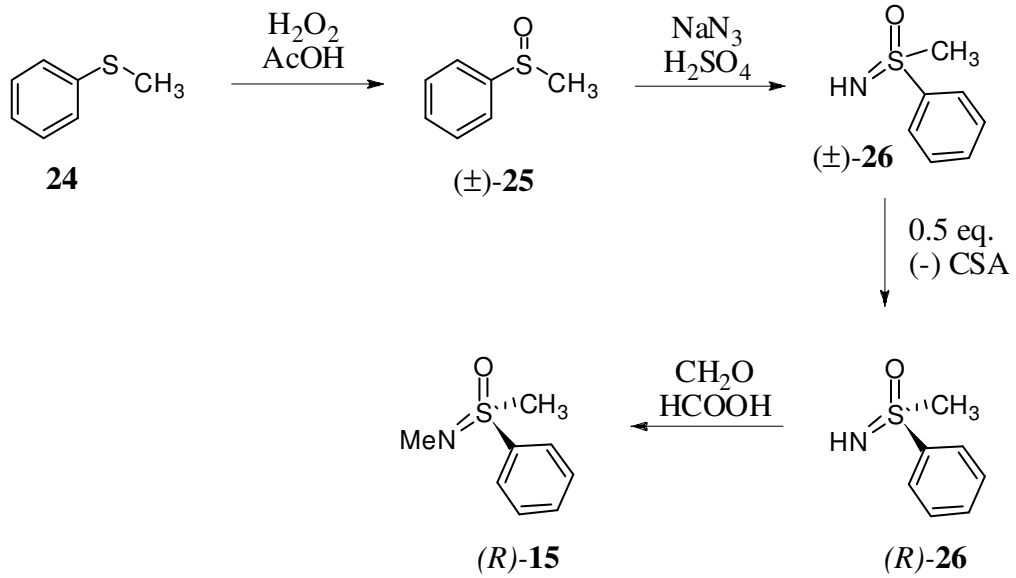


Figure 9. Application of **15** in asymmetric syntheses by GAIS and co-workers

2.1.2 Preparation of chiral auxiliary 15

Both enantiomers of the N,S-dimethyl-S-phenylsulfoximine **15** are available in enantiomerically pure form on preparative scale (Scheme 5).[30,31]



Scheme 5. Preparation of chiral auxiliary *(R)*-**15**

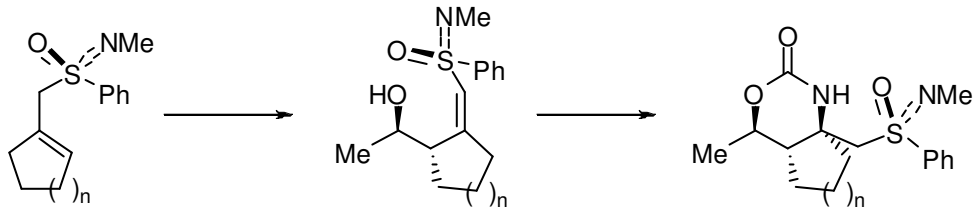
First thioanisole **24** is oxidized to the corresponding sulfoxide (±)-**25** using hydrogen peroxide and acetic acid. Then the imination with sodium azide in presence of sulphuric acid leads to racemic S-methyl-S-phenylsulfoximine (±)-**26**. At this stage the enantiomers are separated. An efficient resolution is carried out by the method of half-quantities developed by GAIS and

co-workers.[32] In order to obtain *(R)*-**26**, 0.5 eq. of the (–)-enantiomer of CSA must be employed. Sulfoximine *(R)*-**26** can be cleanly *N*-methylated under ESCHWEILER-CLARK conditions to give enantiomerically pure *(R)*-**15** (Scheme 5).

2.2 Synthesis of oxazinones 29a and 29b

Allylic sulfoximines **27a** and **27b** were transformed in three steps into oxazinones **29a** and **29b** in 62% and 58% overall yield, respectively (Table 1). This process creates three new stereogenic centers within **29a** and **29b** in a highly diastereoselective fashion. **29a** and **29b** contain the carbocycle of the target azaspirocycle as well as the tertiary *C* atom bearing the amino group. Thus **29a** and **29b** are key intermediates for the modular synthesis of the heterocyclic portion.

Table 1. Synthesis of carbocycles having an amino-substituted tertiary *C* atom and three contiguous stereogenic centers

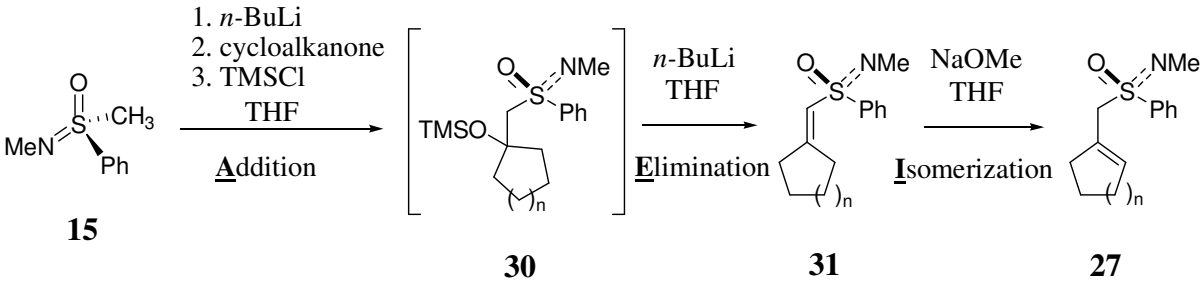


n=1	**27a**	**28a**: 78%, ≥98% de	**29a**: 79%, ≥98% de
n=2	**27b**	**28b**: 75%, ≥98% de	**29b**: 77%, ≥98% de

In the following chapters the steps leading to oxazinone **29** will be detailed.

2.3 Synthesis of cyclic allylic sulfoximines

Allylic sulfoximines play a special role in the chemistry of the sulfoximine family. They can be synthesized from **15** using the addition-elimination-isomerization (AEI) route developed by GAIS et al. (Scheme 6).[33,34]



Scheme 6. Synthesis of cyclic allylic sulfoximines via the AEI route

Lithiation of **15** with *n*-BuLi followed by addition of the cycloalkanone, gave the corresponding lithium alkoxide, which was directly converted into silylether **30** using TMSCl. Elimination with *n*-BuLi gave vinyl sulfoximine **31** in high yield. The crude mixture was used directly for the isomerization into the corresponding allylic sulfoximine **27** using sodium methoxide. This two pot procedure did not require the purification of any intermediate and lead to cyclic allylic sulfoximine **27** in high yield.

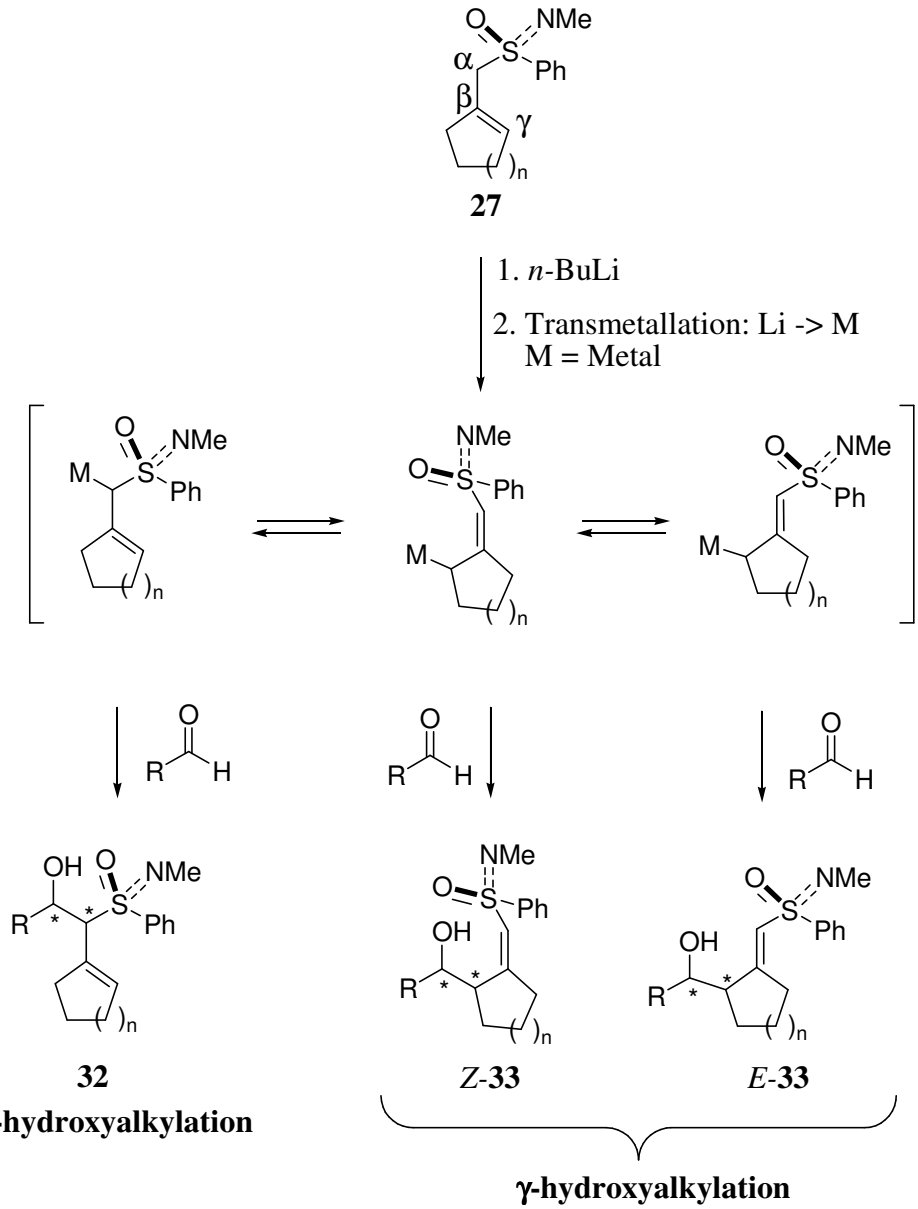
Here the five-membered (n=1) and six-membered (n=2) rings were synthesized. Using the same procedure seven-membered (n=3) and eight-membered (n=4) rings have also been successfully prepared (Scheme 6).[34]

2.4 Hydroxyalkylation of allylic sulfoximines

2.4.1 Introduction to hydroxyalkylation of cyclic allylic sulfoximines

Allylic sulfoximine **27** can be deprotonated at the α-position of the sulfoximine group to give α-sulfonimidoyl carbanion **27**-*Li*, the negative charge of which is also stabilized by the double bond (Scheme 7). Lithiated allylic sulfoximines can react either at the α- or γ-position leading to α- or γ-hydroxyalkylation products **32** or **33**, respectively. In the case of γ-hydroxy-alkylation both *Z*-**33** and *E*-**33** can result.

Therefore, both regioselectivity and diastereoselectivity have to be effectively controlled.

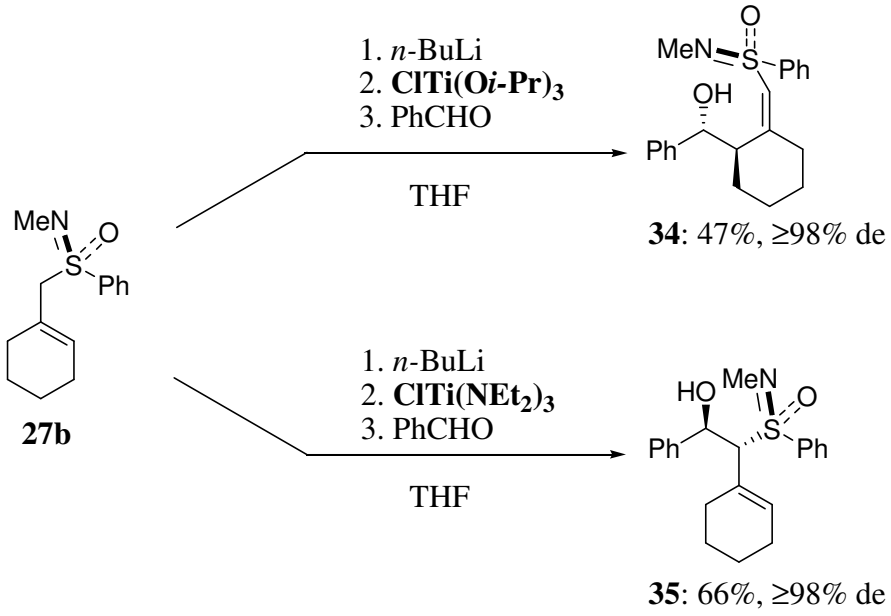


Scheme 7. Possible regioisomers and diastereoisomers in the hydroxyalkylation of allylic sulfoximines

The feasibility of a synthesis of *Z*-**33** from **27** was indicated by the results of REGGELIN and co-workers (Scheme 7).[35,36] They showed that lithium-titanium exchange using ClTi(O*i*-Pr)$_3$ of similar lithiated allylic sulfoximines allowed γ-hydroxyalkylation to occur, furnishing homoallylic alcohols similar to *Z*-**33** in high regio- and diastereoselectivity.

Later, such reactions were studied extensively by GAIS and co-workers.[37] They developed a useful and broad methodology for the hydroxyalkylation of allylic sulfoximines (Scheme 8). For example, on one hand lithiation of **27b** followed by lithium-titanium exchange with ClTi(O*i*-Pr)$_3$ gives the corresponding bis(2-alkenyl)diisopropyloxytitanium(IV) complexes,

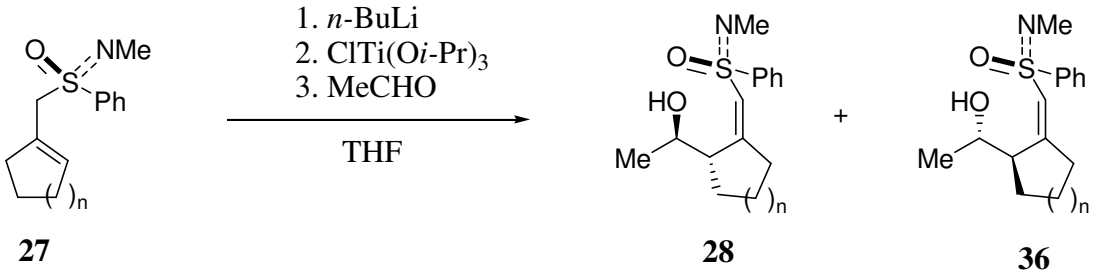
which react exclusively at the γ-position to furnish **34** in high diastereoselectivity. On the other hand the use of $ClTi(NEt_2)_3$ yields the corresponding mono(2-alkenyl)tris(diethylamino)-titanium(IV) complexes, which react with aldehydes exclusively at the α-position to give alcohol **35** in high diastereoselectivity. Direct reaction of **27b**-*Li* with aldehydes results in a α-hydroxyalkylation with low diastereoselectivities.



Scheme 8. Illustration of the hydroxyalkylation methodology developed by GAIS et al.

2.4.2 Application of the hydroxyalkylation reaction to the synthesis of azaspirocycles

The hydroxyalkylation methodology developed in the GAIS group was used to perform the titanium mediated γ-hydroxyalkylation of cyclic allylic sulfoximines (Scheme 9).



Scheme 9. Titanium-mediated γ-hydroxyalkylation of cyclic allylic sulfoximines with acetaldehyde

Lithiation of **27** followed by treatment of the lithiated allyl sulfoximines with 2.1 equivalents of ClTi(O*i*-Pr)$_3$ furnished the corresponding bis(allyl)titanium complexes admixed with ClTi(O*i*-Pr)$_3$ and Ti(O*i*-Pr)$_4$. This mixture was reacted with acetaldehyde in high regioselectivity (≥95%) and good diastereoselectivity (74–84% de) at the γ-position to afford homoallylic alcohols **28** and **36** (Table 2). **28a** had to be purified by preparative HPLC to obtain the diastereomerically pure major diastereomer, whereas **28b** could be obtained in pure form through crystallization from the mixture of diastereoisomers.

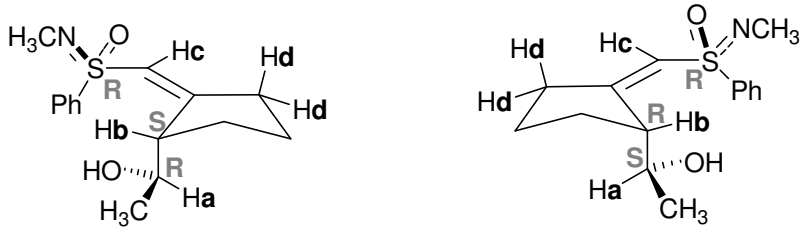
Table 2. Results of the hydroxyalkylation reactions

n	Starting material	Products	Total yield (**28** + **36**)	Yield **28**
1	**27a**	**28a** + **36a**	85%, 84% de	78%, ≥98% de
2	**27b**	**28b** + **36b**	86%, 74% de	75%, ≥98% de

2.4.3 Rationalization of the stereoselectivity outcome

In the case of the 5-membered ring (n=1), the minor diastereoisomer was isolated and its stereochemistry was determined using NOE experiments (Figure 10, Table 3).

In both cases H_c and H_d show a strong NOE effect whereas H_c and H_b do not. This clearly indicates that the double bond is *Z*-configurated. The value of the coupling constant between H_a and H_b (9.9 Hz for **28a** and 9.6 Hz for **36a**) accounts for *anti* orientation. Knowing the absolute configuration of the major product from an X-ray analysis of a later intermediate, it was possible to deduce the absolute configuration of the minor isomer.



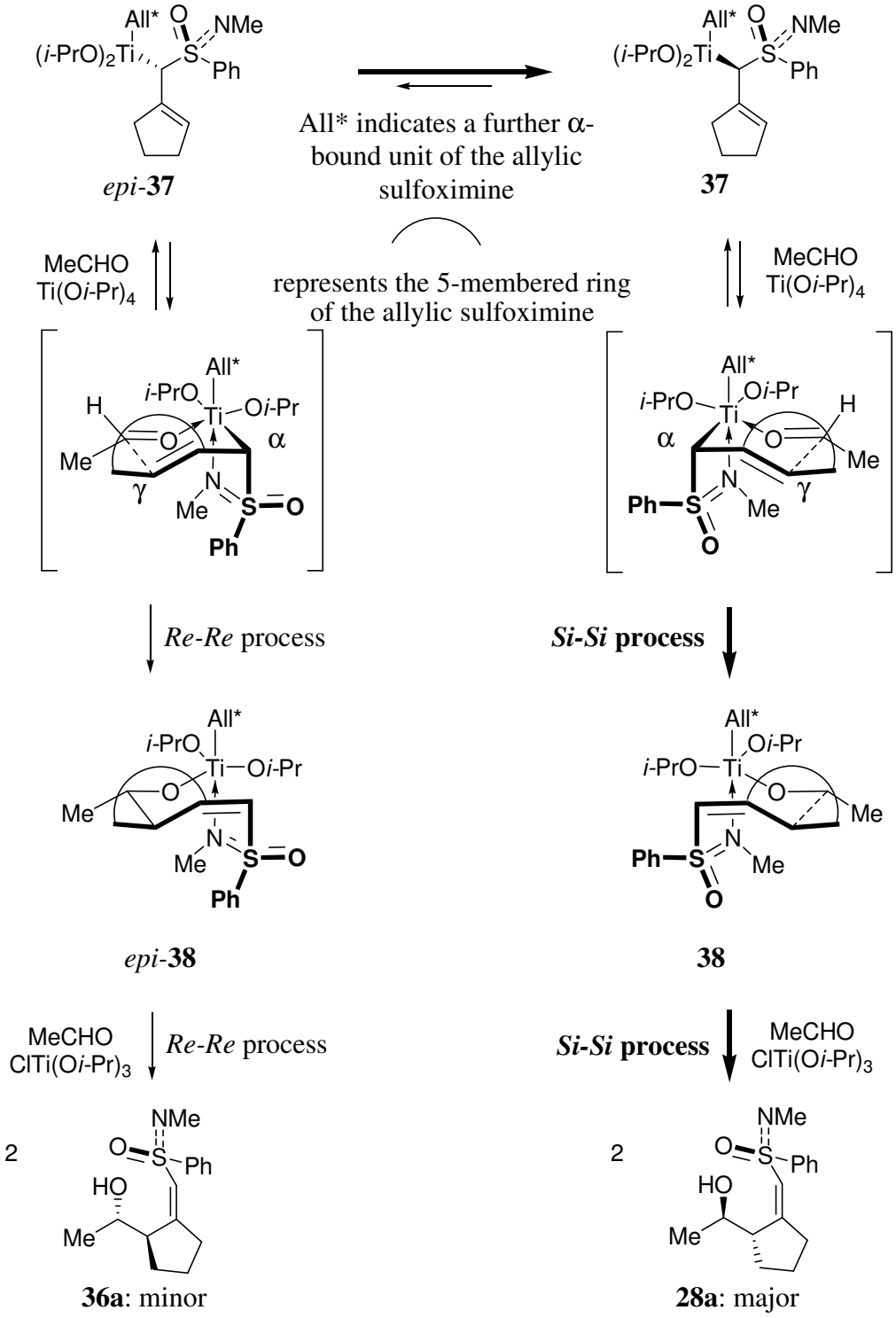
28a: major **36a**: minor

Figure 10. Structure of both diastereoisomers in the case of n=1

Table 3. Decisive criteria for the structure determination of the minor isomer **36a**

Information **28a**	Information **36a**	Interpretation
$J_{Ha\text{-}Hb}$ = 9.9 Hz	$J_{Ha\text{-}Hb}$ = 9.6 Hz	H_a and H_b are in *anti* orientation
NOE: $H_c \leftrightarrow H_d$ observed NOE: $H_c \leftrightarrow H_b$ not observed	NOE: $H_c \leftrightarrow H_d$ observed NOE: $H_c \leftrightarrow H_b$ not observed	*Z*-configurated double bond

Based on previous results[37] the existence of two equilibrating bis(alkenyl)titanium complexes **37** and *epi*-**37** can be postulated (Scheme 10). The equivalent of titaniumtetraisopropoxide which is formed during the titanation step probably coordinates to one of the sulfoximine N-atoms and thus generates a free coordination site at titanium. The aldehyde coordinates and via the depicted transition states the first allylic unit is delivered. In case of **37** the phenyl group of the sulfoximine moiety is in a favorable *exo*-position. That is why **37** is assumed to react faster with acetaldehyde than *epi*-**37**, leading to the major diastereoisomer **28a**. The (*R*)-configuration of the sulfonimidoyl group plays a key role and leads to a *Si*-*Si* process via a cyclic six-membered transition state. As intermediary product the mono(alkenyl)titanium complexes **38** and *epi*-**38** are formed. Similar to Ti(O*i*-Pr)$_4$ the excess amount of ClTi(O*i*-Pr)$_3$ probably generates a free coordination site in **38** or *epi*-**38**. Via similar transition states the complexes react a second time with acetaldehyde under formation of two molecules of homoallylic alcohol **28a** and **36a**.

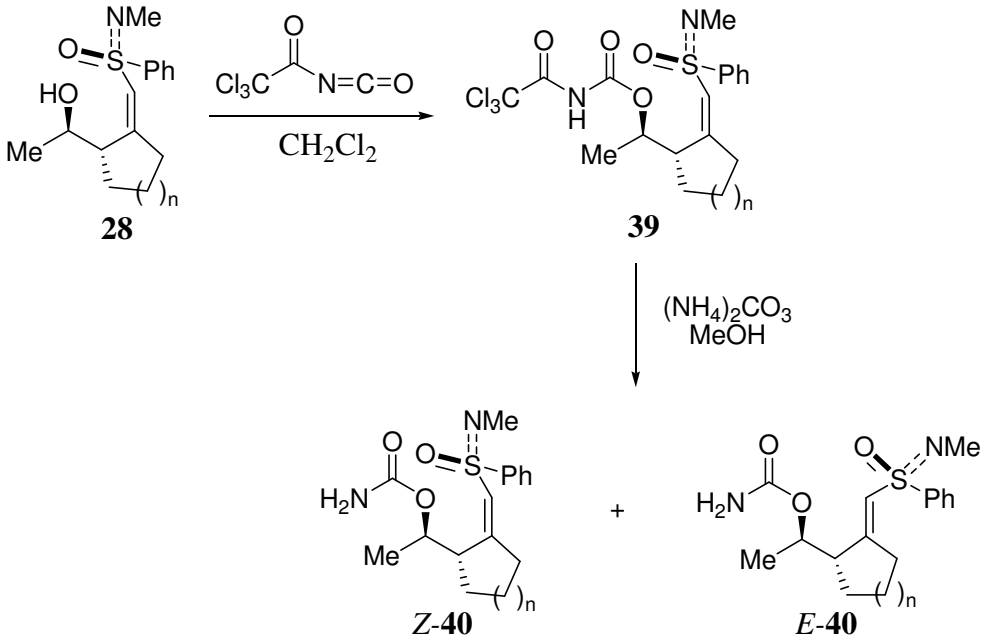


Scheme 10. Attempted rationalization of the diastereoselectivity

2.5 Formation of carbamates from homoallylic alcohols 28a and 28b

2.5.1 Results

Treatment of the enantio- and diastereopure homoallylic alcohol **28** with trichloroacetyl isocyanate followed by cleavage of the corresponding intermediate N-trichloroacetyl carbamate **39** with $(NH_4)_2CO_3$ in MeOH furnished carbamate **40** (Scheme 11).[17,18,27]



Scheme 11. Formation of carbamate **40** from alcohol **28**

In the case of n=1, only the *Z*-isomer of **40a** was detected, whereas in the case of n=2 an isomerization took place which gave a *Z*/*E*-mixture of **40b** (Table 4).

Table 4. Yield of carbamate **40** from alcohol **28**

n	Starting material	Yield (*Z*)-carbamate	Yield (*E*)-carbamate
1	**28a**	*Z*-**40a**: 84%	*E*-**40a**: -
2	**28b**	*Z*-**40b**: 73%	*E*-**40b**: 9%

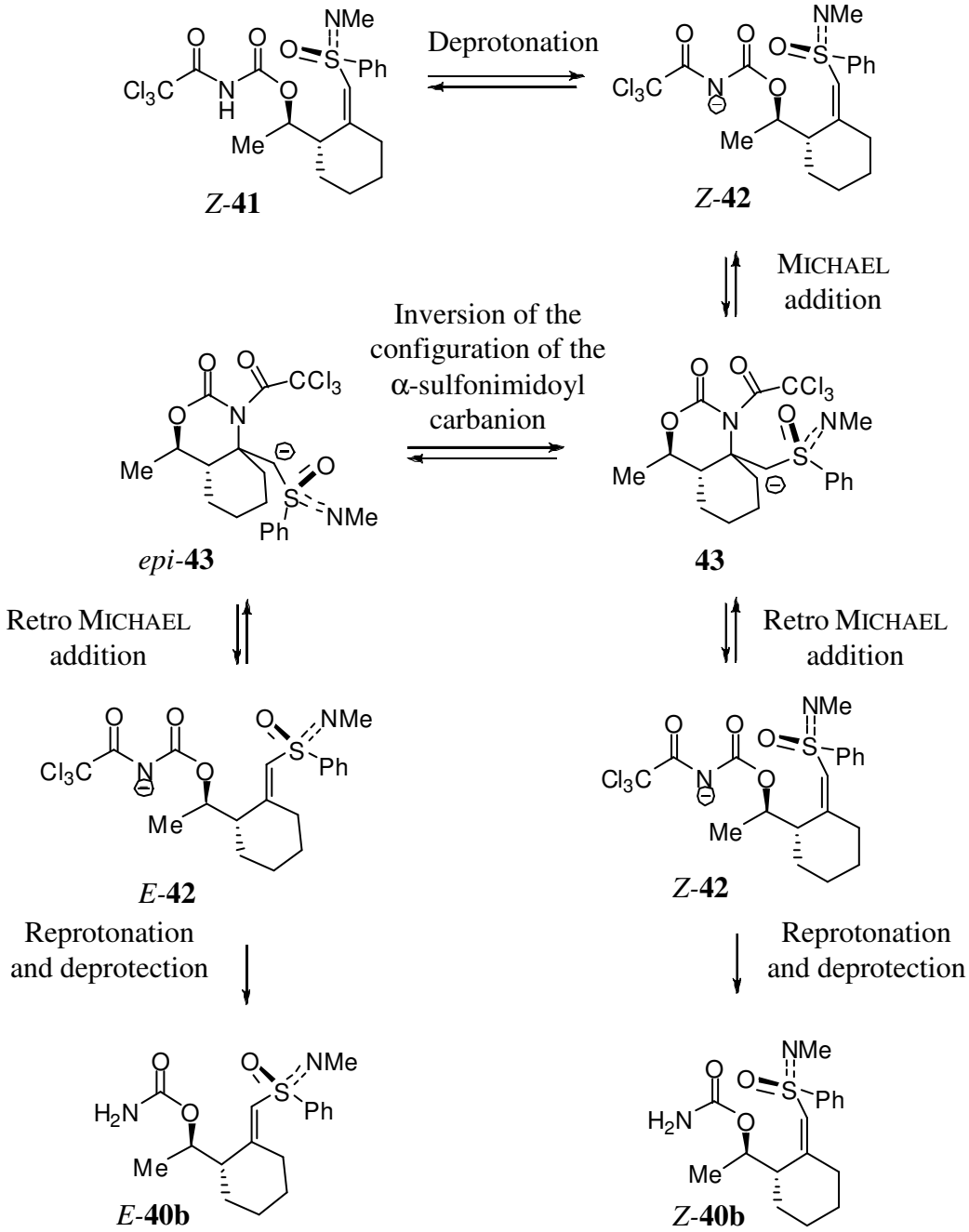
2.5.2 Mechanism for the *Z*/*E* isomerization

A *Z*/*E*-isomerization has been observed during the carbamate formation of similar alcohols.[18] In that study the corresponding N-trichloroacetyl carbamate was shown to be a mixture of *Z*- and *E*-isomers. The authors suggested that isomerization of the *Z*-isomer to the more stable *E*-isomer occurs through a reversible addition of the N-atom of the trichloroacetyl carbamate group to the activated double bond after proton transfer to the basic sulfonimidoyl group.

Although N-trichloroacetyl carbamate **39** was not isolated, an isomerization at this stage was excluded because of the following observation. In the case n=1 the use of concentrated aqueous ammonia for cleavage of the trichloroacetyl group led to a mixture of *Z*-**40a** and *E*-**40a**, whereas the use of $(NH_4)_2CO_3$ furnished diastereopure *Z*-**40a**. *E*-**40a** was not detected.

Another mechanism for the *Z*/*E*-isomerization can be envisaged. In this proposal, epimerization of the α-sulfonimidoyl carbanion occurs due to its configurational instability (Scheme 12).

First N-trichloroacetyl carbamate *Z*-**41** is deprotonated by ammonia or $(NH_4)_2CO_3$ at the N-atom, then an aza-MICHAEL addition takes place to give α-sulfonimidoyl carbanion **43**, which is not configurationally stable and isomerizes rapidly to *epi*-**43**. At this stage a retro-MICHAEL addition of carbanions **43** and *epi*-**43** can occur leading to deprotonated N-trichloroacetyl carbamates *Z*-**42** and *E*-**42**, respectively. After re-protonation and deprotection of the N-trichloroacetyl group, the double bond isomers *E*-**40b** and *Z*-**40b** are isolated.

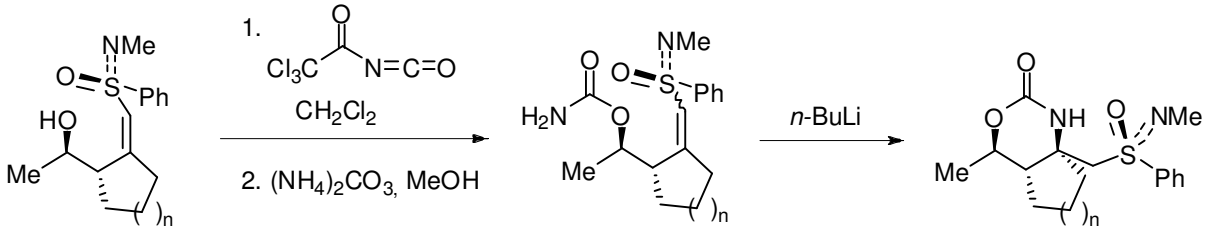


Scheme 12. Mechanism for the *Z/E*-isomerization of **40b**

2.6 Aza-MICHAEL addition

2.6.1 Results

A highly diastereoselective aza-MICHAEL addition of **40** with generation of the tertiary *C* atom and formation of the sulfonimidoyl-substituted protected 1,3-amino alcohol (oxazinone) was achieved by the carbamate method (Scheme 13).[17,18,27]



Scheme 13. Diastereoselective aza-MICHAEL addition

Treatment of alcohol **28** with trichloroacetyl isocyanate, followed by deprotection of the corresponding N-trichloroacetyl carbamate **39** with $(NH_4)_2CO_3$ in MeOH furnished carbamate **40**. The crude carbamate **40** was subjected to a treatment with *n*-BuLi and gave oxazinone **29** after a highly diastereoselective aza-MICHAEL addition (Table 5).

Table 5. Yields and diastereoselectivities of oxazinone **29** from alcohol **28**

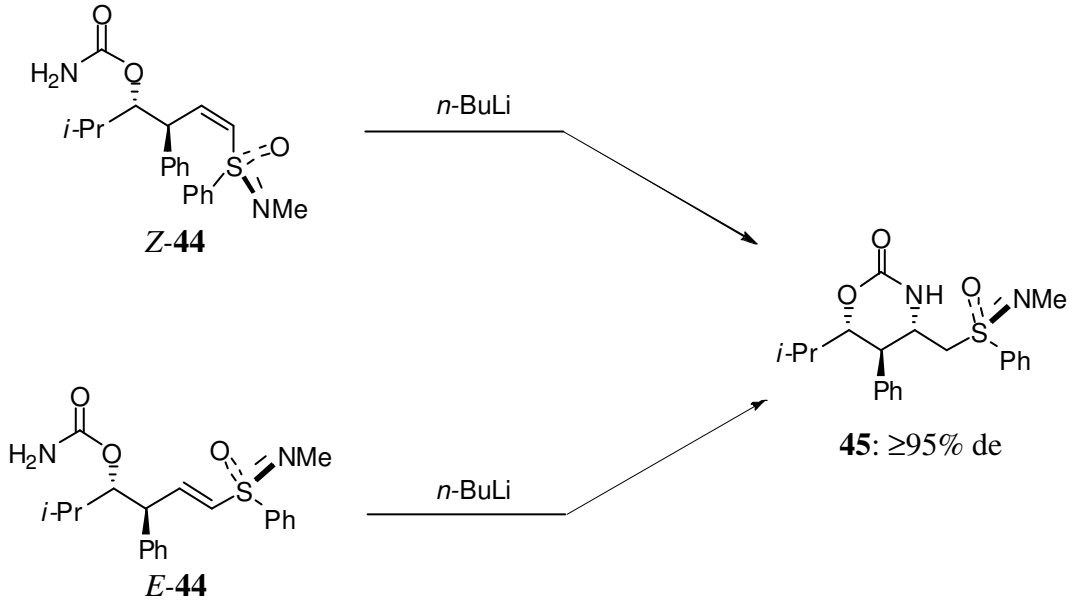
n	Yield of oxazinone **29** (from alcohol **28**)
1	**29a**: 79% (from **28a**), ≥98% de
2	**29b**: 77% (from **28b**), ≥98% de

2.6.2 Discussion

Formation of diastereomerically pure oxazinone **29b** (n=2) from the mixture of carbamates *Z*-**29b** and *E*-**29b** points to a stereoselective cyclization of both carbamates with the same sense and with similar degrees of asymmetric induction (stereoconvergence). We did not test

this hypothesis with our carbamates, but we based our reflection on studies carried out by GAIS et al. with *Z*-**44** and *E*-**44** (Scheme 14).[18]

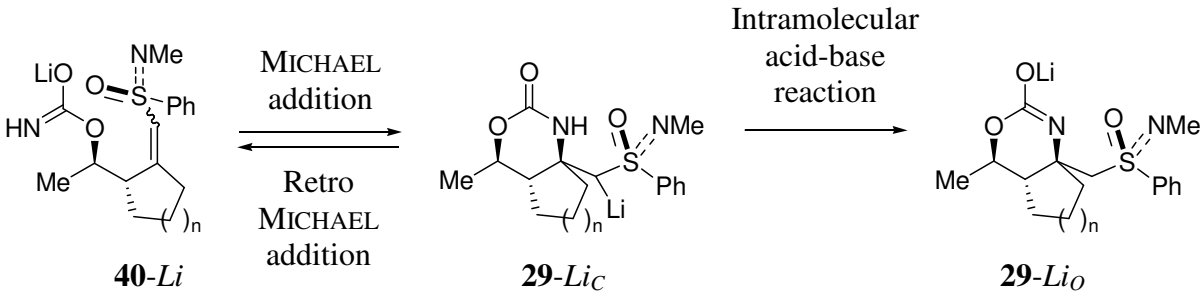
Treatment of *Z*-**44** with *n*-BuLi under the same conditions as used in the case of *E*-**44** resulted in a highly stereoselective cyclization reaction (≥ 95% de) to give oxazinone **45** as a single diastereoisomer in good yields.



Scheme 14. Stereoconvergence of the aza-MICHAEL addition starting from a mixture of *E*/*Z*-carbamates

These results confirm that the formation of *E*/*Z*-mixtures in the case of carbamate **40b** is not detrimental to the success of the highly stereoselective aza-MICHAEL addition leading to oxazinone **29b**.

The stereochemical aspects of the intramolecular aza-MICHAEL addition have to be investigated (Scheme 15). The formation of oxazinone **29** from the corresponding carbamate starts most probably with the deprotonation of the amino group and formation of the lithium salt **40**-*Li*. This lithium salt undergoes cyclization to give the *C*-lithiated sulfoximine **29**-Li_C. Since the acidity of the carbamate-NH is much higher than those of alkyl sulfoximines, lithiated sulfoximine **29**-Li_C would be expected to undergo transmetalation with formation of the *O*-lithiated oxazinone **29**-Li_O. This transmetalation may be crucial for the success of the intramolecular amination, since the lithiated oxazinone **29**-Li_O, should be less prone to retro-MICHAEL addition than the lithiated sulfoximine **29**-Li_C.[18]



40-*Li* **29**-Li_C **29**-Li_O

Scheme 15. Cyclization of sulfonimidoyl-substituted lithiated homoallylic carbamates

We were able to obtain an X-ray crystal structure of **29a**, which permitted to confirm the configuration of the three contiguous stereogenic centers (Figure 11).

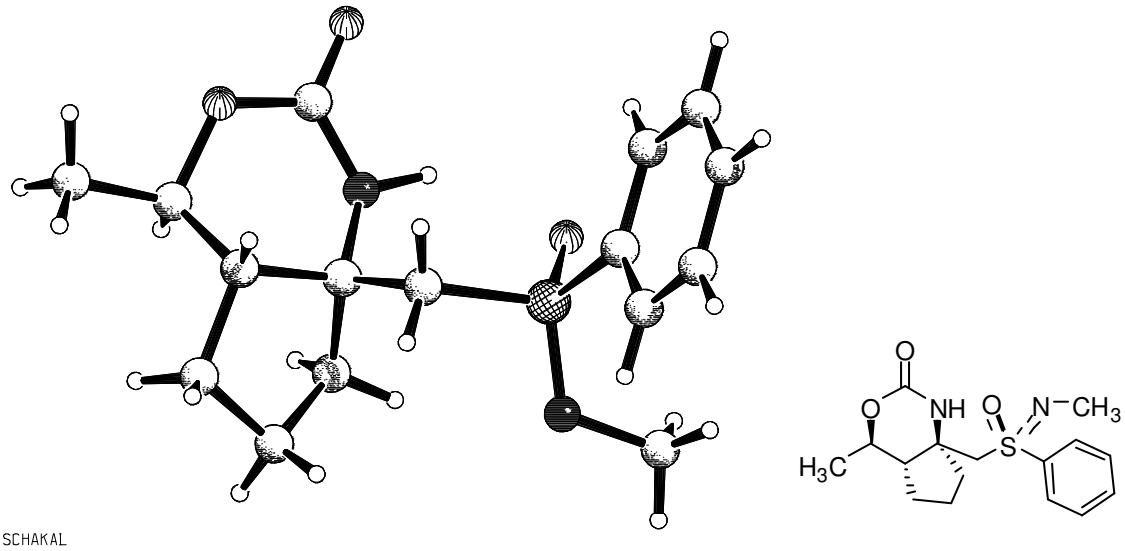


Figure 11. Structure of **29a** in the crystal

The highly selective formation of bicyclic oxazinones **29** from **40** implies that the C=C double bond of the lithiated carbamates is attacked by the N-atom from the *Si* face (Figure 12). This can be explained by invoking transition state models of type **TS-1** for the *Z*-isomers *Z*-**40a** and *Z*-**40b** and **TS-3** for the *E*-isomer *E*-**40b**, resulting in the bicyclic oxazinones with the cis ring fusion. The alternative transition state models **TS-2** and **TS-4** which would give isomeric bicyclic oxazinones with a trans ring fusion, are highly strained and destabilized by an unfavorable approach of the nitrogen atom to the MICHAEL system.[18]

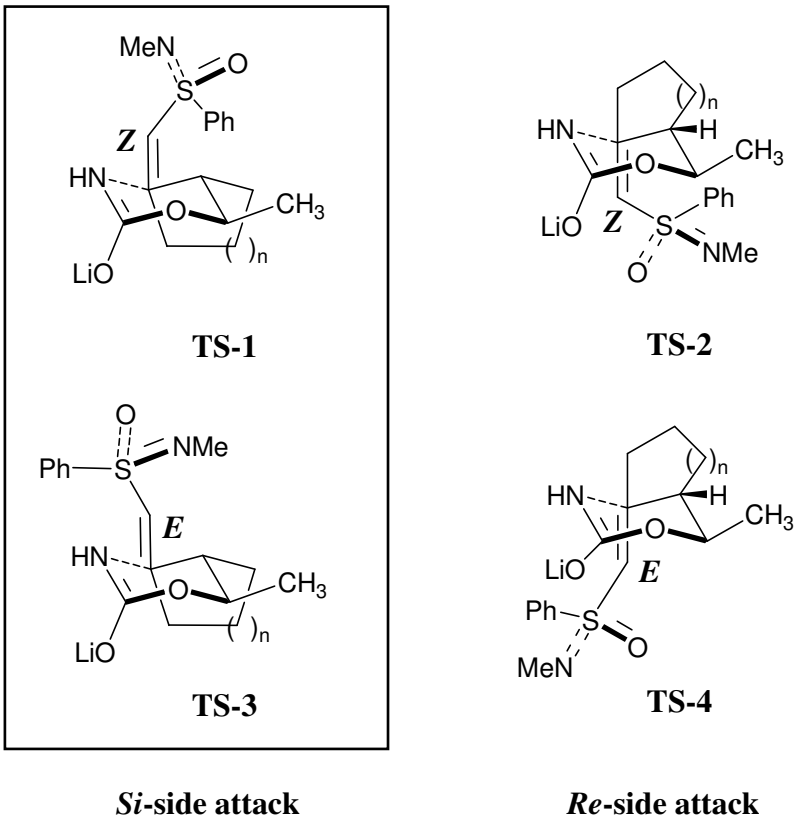


Figure 12. Transition state models for the aza-MICHAEL addition of **40**-*Li*

2.7 Possible structural variations of the carbocycle and the side chain

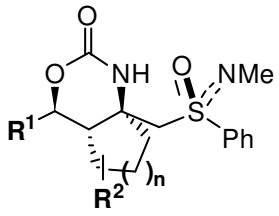


Figure 13. Variation of the carbocycle and side-chain substitution pattern

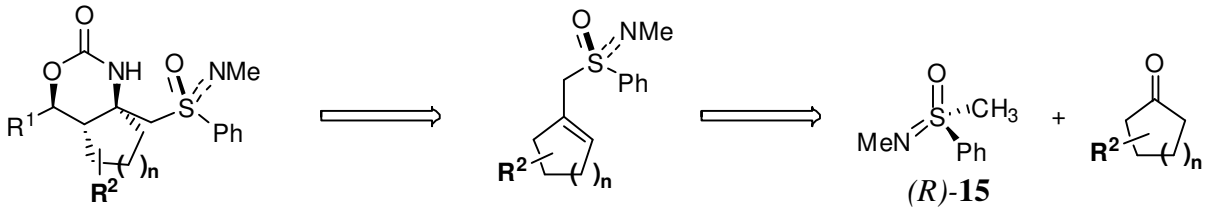
The size of the carbocycle ( )$_n$ as well as the substituent R^2 are determined by the structure of the allylic sulfoximine, whereas the susbtituent R^1 is introduced by the aldehyde in the hydroxyalkylation reaction (Figure 13).

Based on previous results of GAIS et al., which are the possible variations of the target molecule?

2.7.1 Variations of the carbocycle

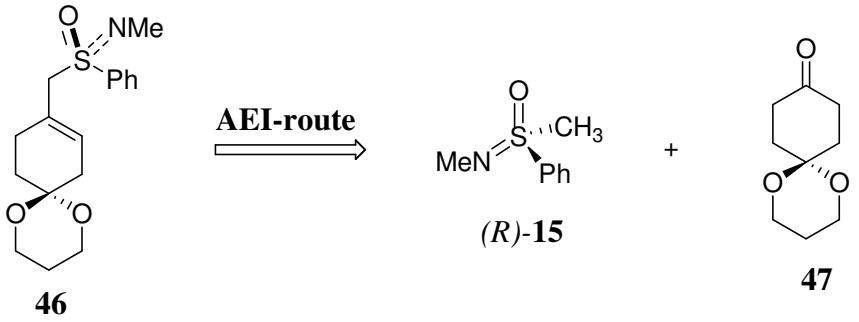
The size of the carbocycle depends on the allylic sulfoximine being used (Scheme 16). In this work, we used successfully the five-membered and the six-membered allylic sulfoximines **27a** (n=1) and **27b** (n=2), respectively.

Other cyclic allylic sulfoximines having for example a four-membered ring (n=0), a seven-membered (n=3) or an eight-membered ring (n=4) are available.[33]



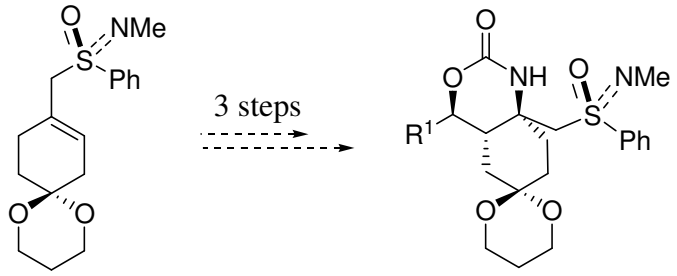
Scheme 16. Variations of the carbocycle

KÜPKER prepared the bicyclic sulfoximine **46** using *N*,*S*-dimethylsulfoximine **15** and ketone **47** (Scheme 17).[38]



Scheme 17. Synthesis of allylic sulfoximine **46**

The use of the allylic sulfoximine **46** could perhaps give oxazinones of type **48** having a protected carbonyl group in the carbocycle (Scheme 18).



46 **48**

Scheme 18. Possible synthesis of functionalized oxazinones

2.7.2 Hydroxyalkylation with other aldehydes

Since the γ-hydroxyalkylation of titanated allylic sulfoximines had been introduced, a number of different aldehydes have been used leading to a range of substituted homoallylic alcohols. We carried out the reaction with acetaldehyde, but it should be possible to carry out the reaction with a variety of aldehydes.[26,37,38]

It should be noticed that the use of a chiral aldehyde does not influence the diastereoselectivity of the reaction (Figure 14).[38]

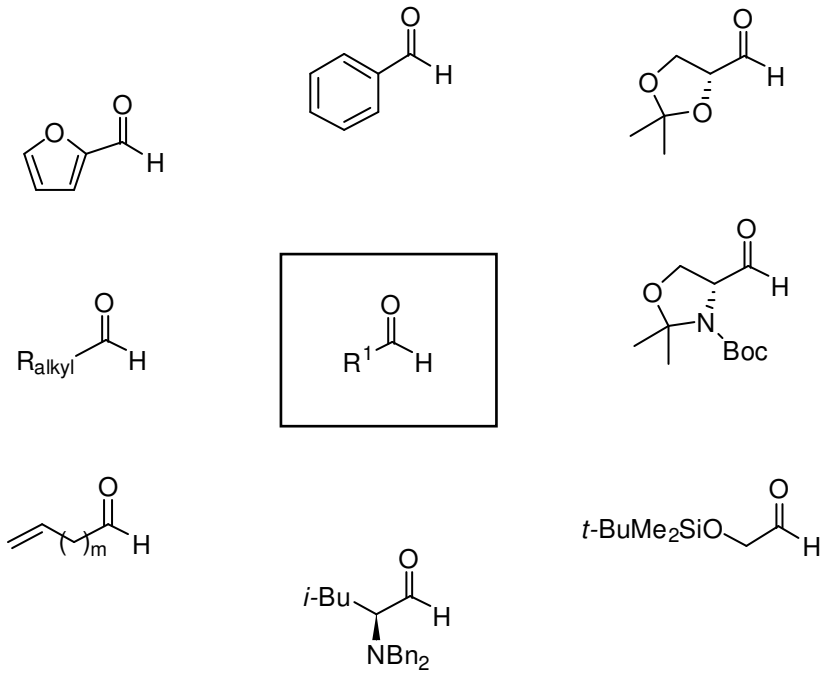


Figure 14. Examples of aldehydes successfully used in the γ-hydroxyalkylation of titanated allylic sulfoximines

3. The Ring-closing metathesis route

3.1 The plan

Having achieved an efficient synthesis of the functionalized carbocycle **29** which carries three contiguous stereogenic centers and the tertiary carbon atom bearing a nitrogen atom, we focused on the construction of the heterocycle having a double bond at the β,γ- position.

The ring-closing metathesis (RCM) belongs to the best methods for the construction of complex cyclic molecules,[39] particulary natural products. This well-developed methodology should be applied for the synthesis of azaspirocycle **49** from oxazinone **29a** (Figure 15).

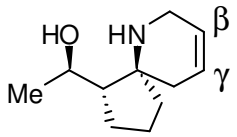
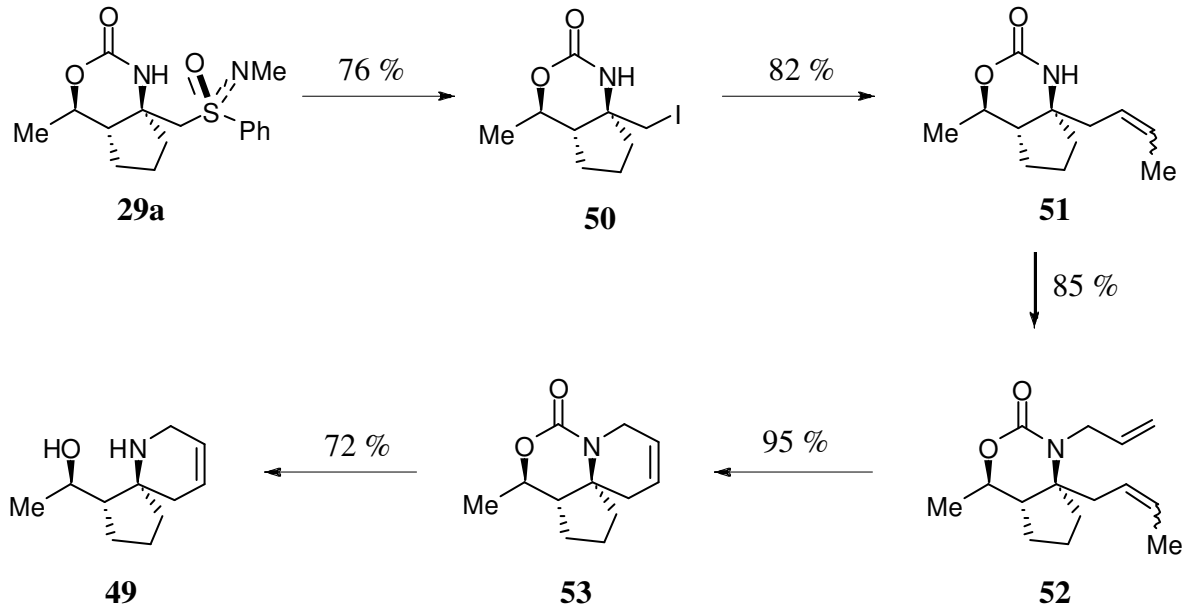


Figure 15. Azaspirocycle **49** containing a double bond in the heterocycle

3.2 Synthesis of amino alcohol 49 from sulfoximine 29a

Sulfoximine **29a** was successfully transformed into the desired azaspirocycle **49** in 5 steps with 36% overall yield (Scheme 19).

The sulfoximine moiety of **29a** was replaced by an I-atom, which was then substituted by propenyl cuprate to give alkene **51**. Allylation of the nitrogen atom followed by a ring-closing metathesis furnished tricycle **53**. Deprotection of the carbamate led to the desired spirocycle **49**.

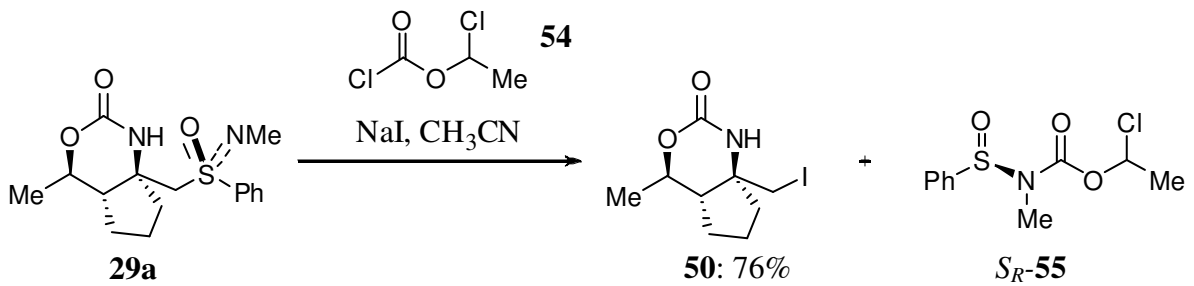


Scheme 19. Synthesis of azaspirocycle **49** from sulfoximine **29a**

In the following chapters the steps leading to azaspirocycle **49** will be detailed.

3.3 Iodide substitution

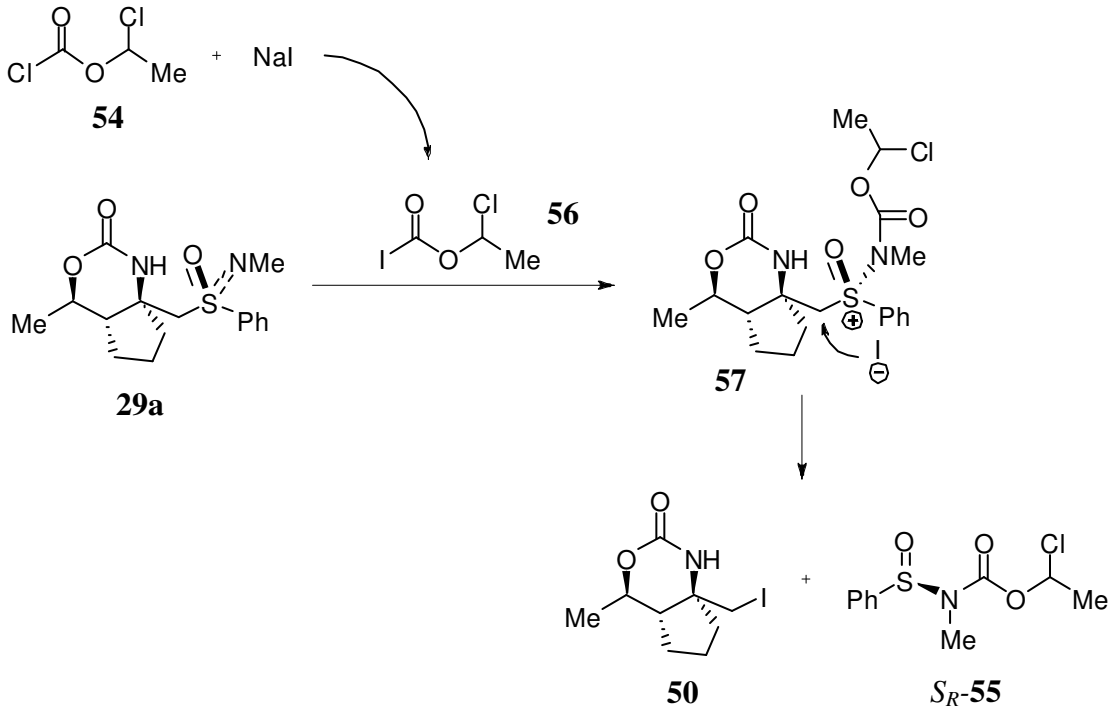
It is known that the sulfoximine group can be replaced by chlorine or iodine.[18] This can be achieved by reaction with chloro- and iodoformic esters, respectively. Because of their potential conversion to the corresponding alkylzinc iodides[40] and ready cross-coupling reaction[27], we decided to synthesize the iodo derivative **50** (Scheme 20).



Scheme 20. Replacement of the sulfoximine group by an I-atom

We could successfully synthesize iodide **50** from sulfoximine **29a** by the haloformate method. Chloroformate **54** reacts in situ with an excess of sodium iodide to give the corresponding iodoformate **56**,[41] which can acylate the nitrogen of the sulfoximine group. It generates the

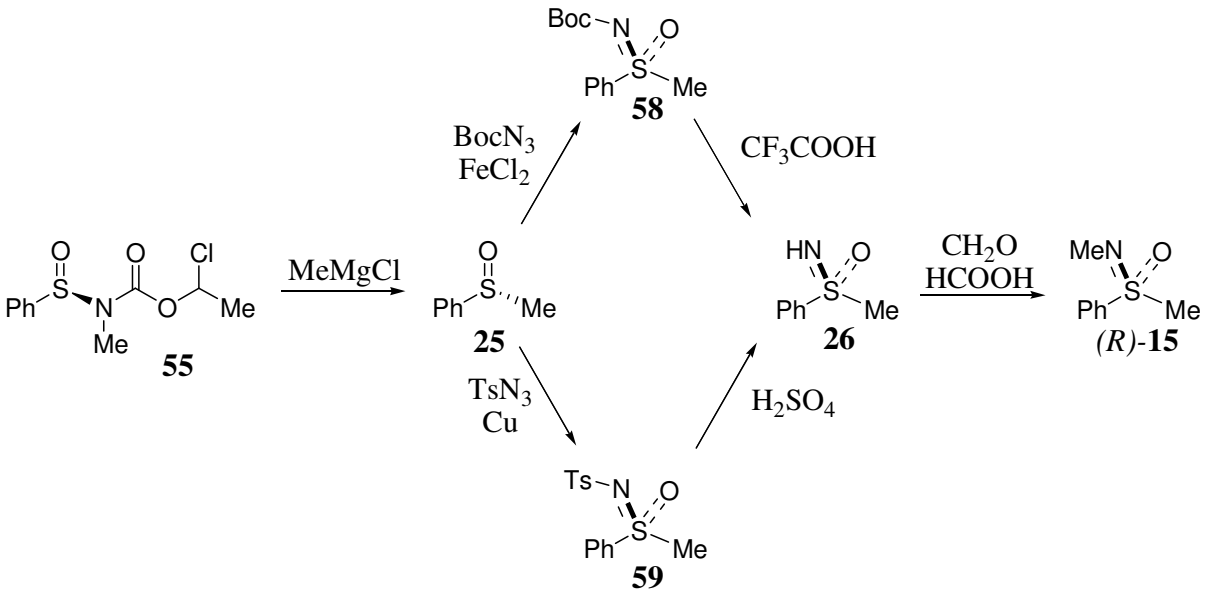
corresponding N-acylaminosulfoxonium salt **57** which undergoes a facile substitution by the I^- ion because of the nucleofugacity of the aminosulfoxonium group (Scheme 21).



Scheme 21. Possible mechanism for the iodide substitution of the sulfoximine group

The conversion of sulfinamide S_R-**55** (≥ 98% ee in regard to the *S* atom) to the starting *(R)*-(+)-*N*,*S*-dimethyl-*S*-phenylsulfoximine *(R)*-**15** (≥ 98% ee) has already been described in the literature:

Reaction of methylmagnesium chloride with sulfinamide *(R)*-**55** gives sulfoxide **25** (≥ 98% ee).[42] Now there are two possibilities to obtain the sulfoximine. On one hand sulfoxide **25** can be treated with Boc-azide in presence of iron dichloride to furnish the Boc-protected sulfoximine **58**.[43] On the other hand sulfoxide **25** can be treated with Ts-azide in presence of copper to give the Ts-protected sulfoximine **59**.[44] Deprotection of **58** and **59** with trifluoroacetic acid and sulphuric acid, respectively, gives sulfoximine **26**. Sulfoximine **26** can be cleanly N-methylated under ESCHWEILER-CLARK conditions to give enantiomerically pure *(R)*-**15** (Scheme 22).[30]

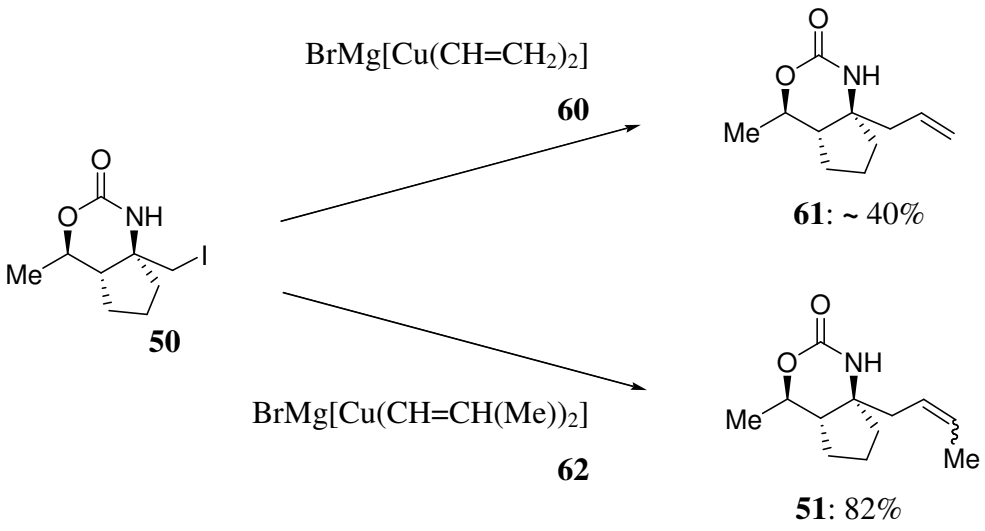


Scheme 22. Recycling of sulfinamide **55** into sulfoximine *(R)*-**15**

3.4 Cuprate substitution

Organocopper reagents are used frequently in organic chemistry as alkylating agents. They are prepared in situ and show in general a higher functional group tolerance than corresponding Grignard or organolithium reagents.[45]

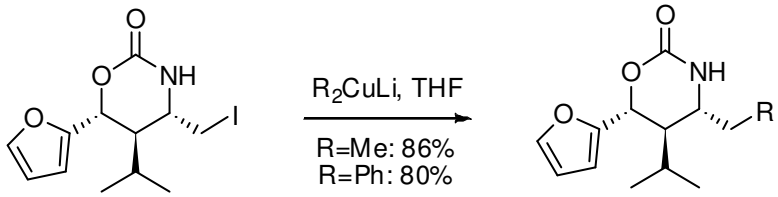
Organocopper reagents are softer than Grignard reagents because copper is less electropositive than magnesium. Therefore the C-Cu bond is less polarized than the C-Mg bond, giving the carbon atom less of a partial negative charge suggesting less nucleophilicity for carbon.



Scheme 23. Cuprate substitution on β-amido iodide **50**

Treatement of **50** with the vinyl cuprate **60** gave a mixture of unidentified products together with terminal alkene **61**, which was isolated in best cases in only 40% yield. Purification was difficult because of the many impurities. All attempts to optimize the yield of **61** failed. Interestingly, the reaction of **50** with the propenyl cuprate **62** gave the desired alkene **51** in 82% yield (Scheme 23).

Later KÖHLER reported cuprate substitution on a similar β-amido iodide (Scheme 24).[27]



Scheme 24. Cuprate substitution on a β-amido iodide

3.5 Ring-Closing Metathesis

The ring-closing metathesis is a very useful tool for the synthesis of cyclic natural products and was already successfully applied to the synthesis of azaspirocycles (Figure 16).

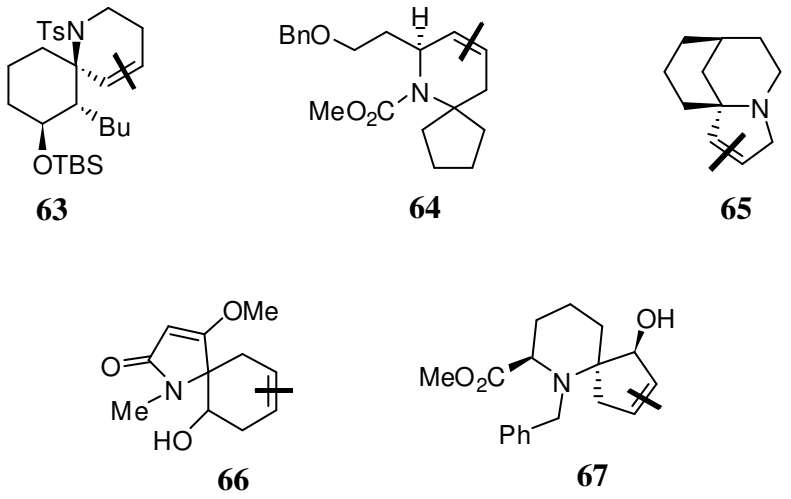


Figure 16. Construction of azaspirocycles using ring-closing metathesis

TANNER et al. developed a method for the synthesis of spirocyclic alkaloids combining [2,3] sigmatropic rearrangement and ring-closing metathesis. RCM of the corresponding diene gave **63**, which was used as precursor for a formal total synthesis of (±)-perhydrohistrionicotoxin **5**.[46]

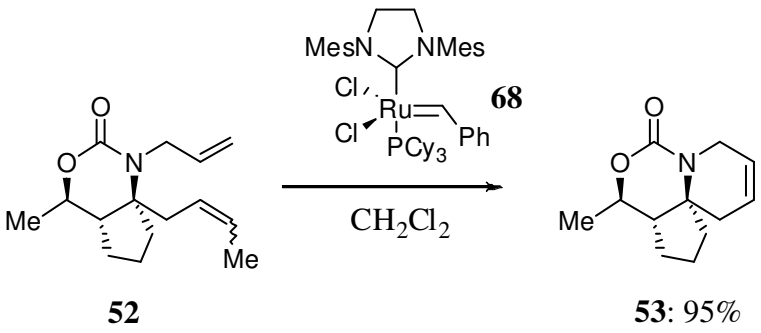
WRIGHT et al. proposed an approach to the spirocyclic core of halichlorine **4** and pinnaic acid **7** by ring-closing metathesis. They showed that the protection of the amine function as its methyl carbamate was important to obtain the ring-closing metathesis product **64** in high yield.[47]

KIBAYASHI et al. proposed an alternative route to the azatricyclic core skeleton of FR901483 based on bridgehead vinylation via an anti-Bredt iminium ion and ring-closing metathesis to furnish **65**.[48]

SIMPKINS et al. developed a chiral base desymmetrization followed by a ring-closing metathesis route to chiral azaspirocycles of type **66**, aiming at the synthesis of core structures related to pinnaic acid **7** and halichlorine **4**.[49]

HUNTER et al. used ring-closing metathesis to provide the crucial spirocycle **67** in the construction of the ring-system of lepadiformine **3**.[50]

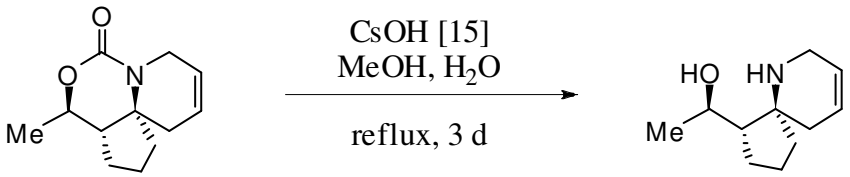
Based on these results an efficient ring-closing metathesis of diene **52** was carried out in CH_2Cl_2 (0.01 M) using 5 mol% of catalyst **68**, which gave tricycle **53** in excellent yield (Scheme 25).



52 **53**: 95%

Scheme 25. Ring-closing metathesis for the construction of the heterocycle

At this stage, the carbocycle, the spiro carbon atom and the heterocycle were built up. The remaining step was the deprotection of the carbamate. It was achieved by refluxing tricycle **53** under strongly basic aqueous conditions, which gave amino alcohol **49** (Scheme 26).[51]



53 **49**: 72%

Scheme 26. Deprotection of the carbamate under basic conditions

3.6 Structural variations of the target molecule

Only **49** was synthesized but it should be possible to obtain other derivatives as well (Figure 17). Changing the ring size of the allylic sulfoximine would allow to control the size of the carbocycle, and the substituent R^1 could be varied by using different aldehydes in the γ-hydroxyalkylation reaction.

Instead of using propenylcuprate (which gives m = 1), it should also be possible to use allyl cuprate (which would give m = 2) for example.

Instead of using allyl bromide for the alkylation of the N-atom (which gives p = 1) also homoallyl bromide (which would give p = 2) could be employed.

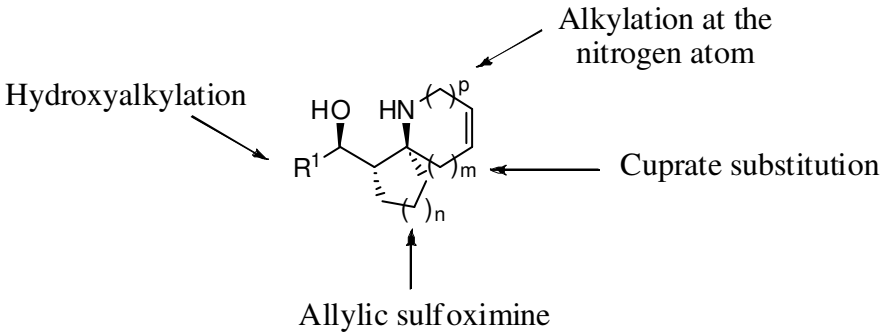


Figure 17. Possible variations of the target molecule

A new method for the asymmetric synthesis of azaspirocycles having a double bond in the heterocycle has been developed. Azaspirocycle **49** having the double bond at the β,γ-position has been successfully prepared and it should be possible to obtain azaspirocycles with different ring sizes and with the double bond at other positions in the heterocycle.

4. Cycloalkylation and removal of the sulfoximine group

4.1 The plan

4.1.1 Target molecule

Oxazinone **29** already contains the carbocycle with three contiguous stereogenic centers and the tertiary carbon atom bearing a nitrogen atom in the α position. It was of interst to see whether an access to azaspirocycles carrying a functional group at the δ-position of the nitrogen atom could also be opened (Figure 18).

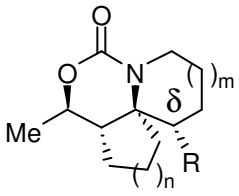
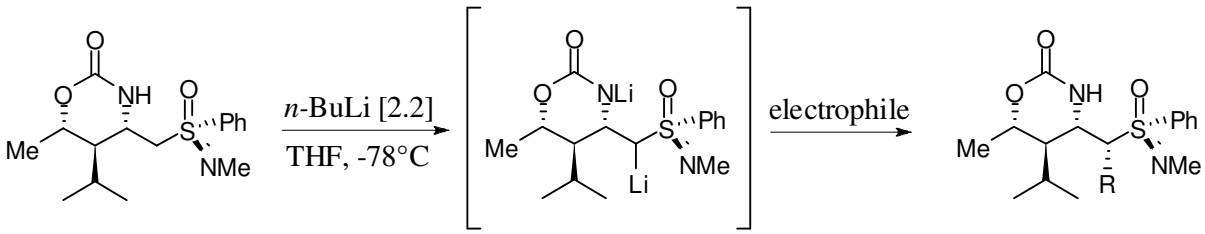


Figure 18. Target molecule

4.1.2 Dilithiated sulfoximines in the literature

Previously GAIS et al. showed that sulfoximines similar to **29** can be deprotonated using 2 equivalents of *n*-butyllithium. At first the nitrogen atom is deprotonated then the carbon atom bearing the sulfoximine group. Reaction with electrophiles occurs at the stabilized α-sulfonimidoyl carbanion (Scheme 27).[18]



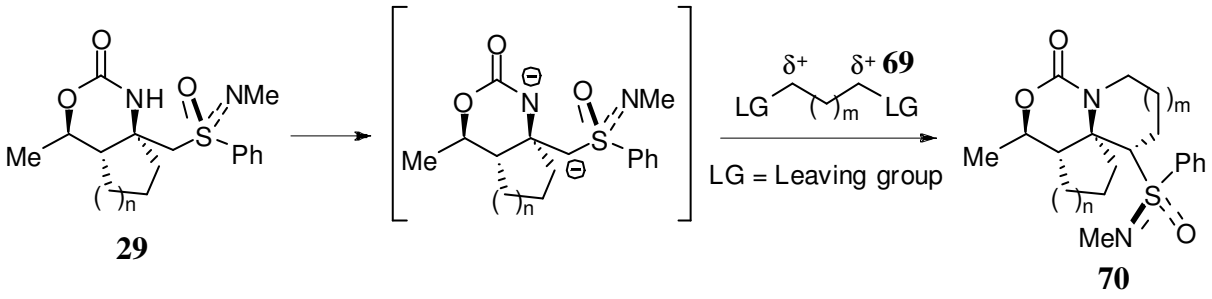
R = C(Me,H)OH, Me, CH_2OBn, CO_2Me

Scheme 27. Alkylation of a dilithiated sulfoximine

This route was developed to provide a new access to enantio- and diastereopure β-substituted and β,β-disubstituted δ-hydroxy β-amino acids and to γ-amino alcohols.[18]

4.1.3 From dilithiated sulfoximines to the synthesis of the heterocycle

It was planed to achieve a cycloalkylation reaction, which should proceed as follows: sulfoximine **29** should be doubly deprotonated at the N-atom and the α-position to the sulfoximine group leading to the corresponding dianion, which should react with a biselectrophile of type **69** giving tricycle **70** (Scheme 28).



Scheme 28. Cycloalkylation reaction

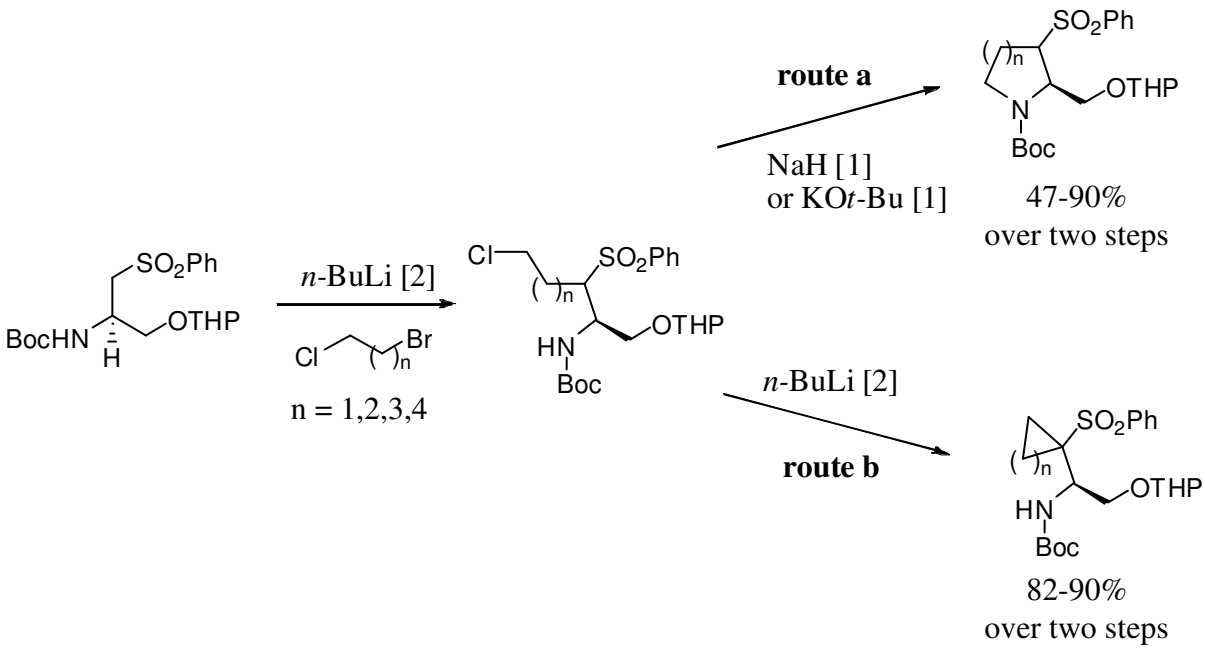
4.2 Cycloalkylation: Similar examples in the literature

4.2.1 With sulfone and carbamate

SASAKI et al. described the synthesis of two different types of cyclic α-amino acids: cycloalkylglycines and N-heterocyclic α-amino acids through reaction of sulfonyl anions and/or carbamate anions with dihaloalkanes (Scheme 29).[52]

By addition of an appropriate base, two distinct types of anion can be formed, carbamate and sulfonyl anions. Since a sulfonyl anion should be much more reactive than a carbamate anion, creation of such dianionic species followed by addition of an α,ω-dihaloalkane would first afford monoalkylation products.

Then two different routes are possible. Cyclization can take place either by reaction with the carbamate anion to give an N-heterocyclic compound (route a) or by reaction with the tertiary sulfonyl anion to give a cycloalkyl compound (route b). No information is given about the diastereoselectivity in regard to the newly created stereogenic center.

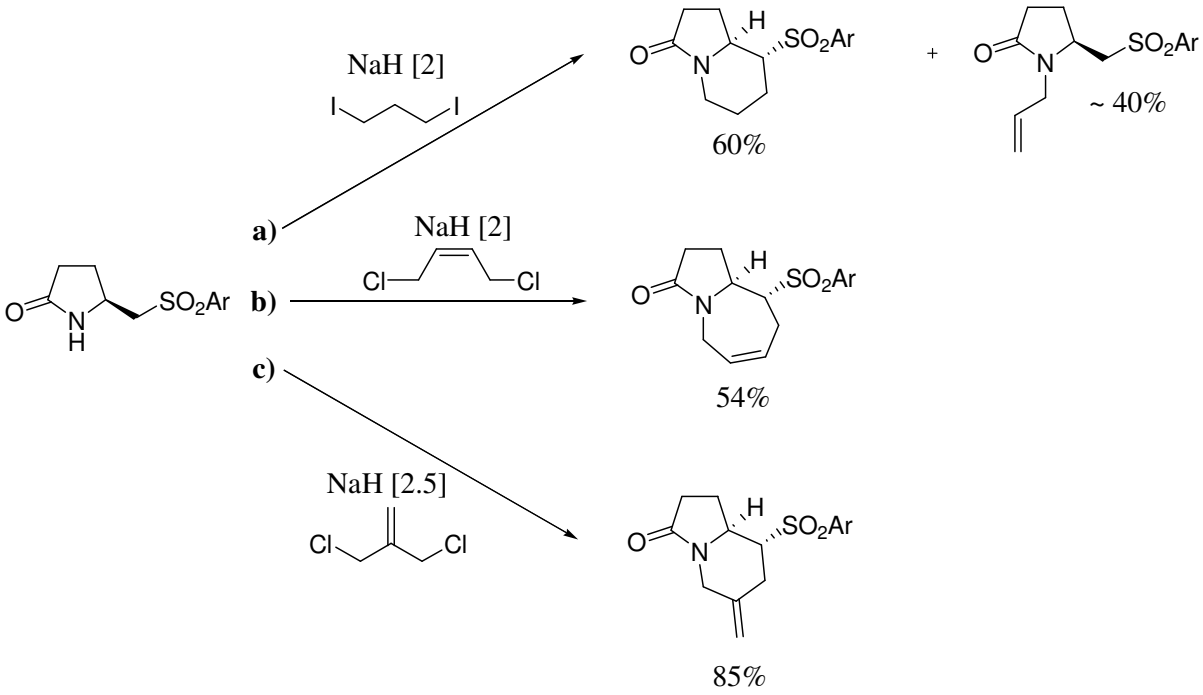


Scheme 29. Versatile method for the synthesis of N-heterocyclic α-amino acids and cycloalkylglycines by SASAKI et al.

4.2.2 With sulfone and amide

NÁJERA et al. reported the diastereoselective preparation of indolizidines by dialkylation of a chiral pyrrolidinone at the nitrogen atom and at the α-sulfonyl position by using several 1,3- and 1,4-biselectrophiles, after deprotonation with 2 equivalents of NaH. The methodology was applied to the synthesis of (–)-δ-coniceine (Scheme 30).[53,54]

They assumed that first of all the N-atom reacted with the biselectrophile. This notion was supported by isolation of around 40% of elimination product in reaction a). Elimination is not possible with biselectrophiles used in reaction b) and c).



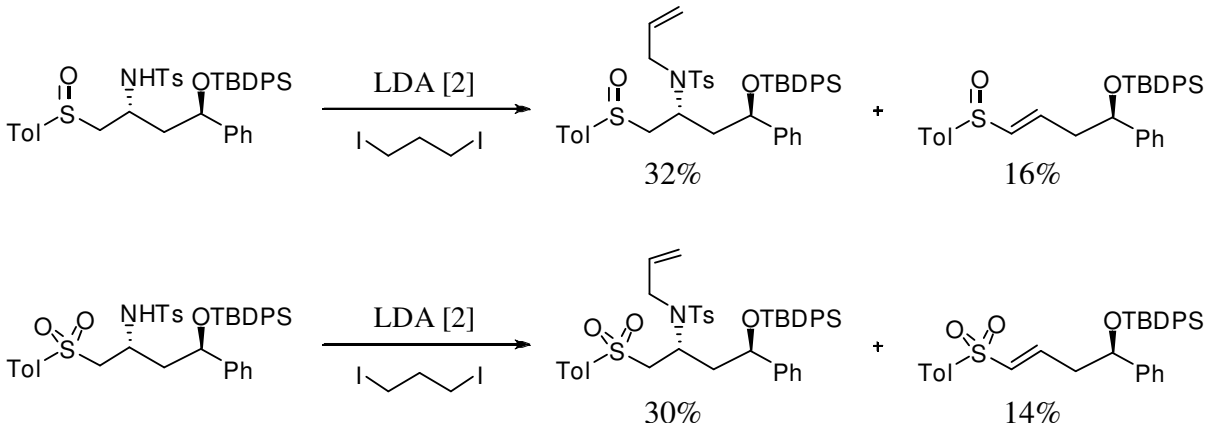
Scheme 30. Diastereoselective synthesis of indolizidine derivatives by NÁJERA

4.2.3 With sulfoxide/sulfone and sulfonamide

RAGHAVAN et al. planed the construction of the piperidine ring of allosedamine via dialkylation of the dianion derived from a β-aminosulfoxide with a suitable 1,3-biselectrophile (Scheme 31).[55]

Generation of the dianion using LDA and its subsequent treatment with 1,3-diiodopropane, with the intention of elaborating the piperidine ring, was not successful. The products isolated were the *N*-allylation product and the elimination product. Attempted formation of the piperidine ring starting from the corresponding sulfone failed also. Again the *N*-allylated and the elimination product were the only compounds obtained.

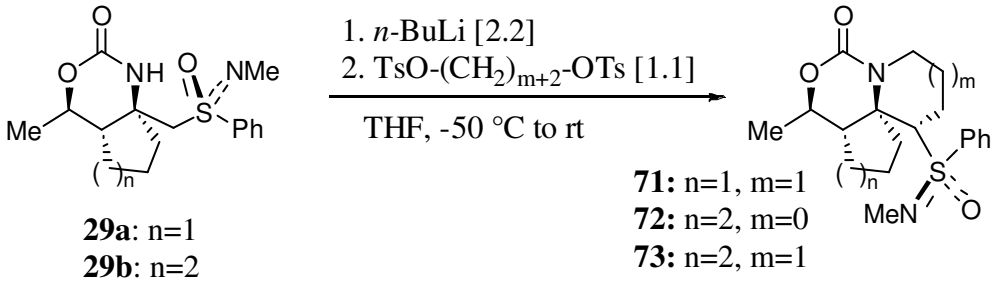
However it could be argued that the use of LDA is not compatible with the existence of the dianion, so that at first only deprotonation at the nitrogen atom occurs and this anion reacts with the 1,3-diiodopropane. Then, with the remaining LDA, elimination takes place either to give the *N*-allylated products or the elimination products.



Scheme 31. Attempted cycloalkylation of β-aminosulfoxide and -sulfone by RAGHAVAN et al.

4.3 Cycloalkylation: Results

The synthesis of the heterocycle through cycloalkylation of the C,N-dianions of **29** with ditosylates of the type TsO-$(CH_2)_{m+2}$-OTs was studied (Scheme 32).



Scheme 32. Cycloalkylation of C,N-dianions

Treatment of the 5-membered cyclic sulfoximine **29a** with 2.2 equivalents *n*-BuLi in THF at low temperatures generated the corresponding (C,N)-dianion which was stable in solution. Upon treatment with TsO-$(CH_2)_3$-OTs tricycle **71** having a 6-azaspiro[4.5]decane skeleton was formed with high diastereoselectivity (Table 6).

Double deprotonation of the 6-membered cyclic sulfoximine **29b** and treatment of the corresponding (C,N)-dianion with TsO-$(CH_2)_2$-OTs afforded tricycle **72** having a 1-azaspiro[4.5]decane skeleton with high selectivity.

Finally, reaction of the (C,N)-dianion derived from the 6-membered cyclic sulfoximine **29b** with TsO-$(CH_2)_3$-OTs furnished tricycle **73** having a 1-azaspiro[5.5]undecane skeleton with high diastereoselectivity.

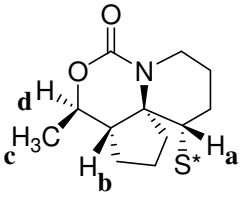
Table 6. Result of the cycloalkylation reactions

Starting material	Product	Isolated yield	Chemical yield	de
29a	**71**	75%	75%	≥ 98%
29b	**72**	57%	73%	≥ 98%
29b	**73**	59%	72%	≥ 98%

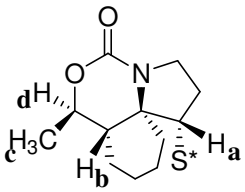
4.4 Cycloalkylation: Discussion

4.4.1 Determination of the configuration at the newly formed stereogenic center

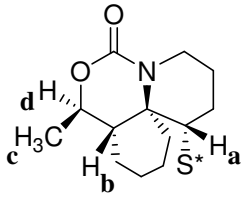
The determination of the configuration of the newly formed stereogenic center was accomplished using the coupling constants and NOE experiments (Figure 19).



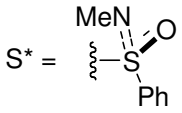
71



72



73



For the sake of clarity, the sulfoximine moeity is replaced by S*

Figure 19. Determination of the configuration of the newly formed stereogenic center

At first, using as a major argument the ^3J coupling constants between H_a and the vicinal hydrogen atoms, it is possible to determine the position of H_a in the heterocycle.

In case of tricycles **71** and **73**, the 6-membered ring heterocycle seems to adopt a chair conformation, in which H_a is in axial position and the sulfoximine group in equatorial position. In case of tricycle **72**, the 5-membered ring heterocycle seems to adopt an envelope

or a half-chair conformation, in which H_a is in pseudo-axial and the sulfoximine in pseudo-equatorial position.

Considering the bulkiness of the sulfoximine group, it is not surprising that this substituent adopts an equatorial or pseudo-equatorial position.

Then, using NOE experiments, we were able to determine the spacial environment of H_a. In the three cases, H_a showed an NOE with H_b and/or H_c. Since we know the absolute configuration at the other carbon atoms and H_b and H_c point to the concave face formed by the oxazinone ring and the heterocycle, H_a has to be on the same side. Thus we were able to determine the configuration of the newly formed stereogenic center (Table 7).

Table 7. Decisive criteria for the determination of the configuration

Compounds	^3J coupling constants of H_a	Coupling constants between H_b and H_d	Decisive NOE
71	13.2 Hz 3.3 Hz	J = 10.2 Hz	NOE: $H_a \leftrightarrow H_b$ $H_a \leftrightarrow H_c$
72	11.6 Hz 8.4 Hz	J = 10.4 Hz	NOE: $H_a \leftrightarrow H_b$
73	12.9 Hz 4.1 Hz	J = 4.4 Hz	NOE: $H_a \leftrightarrow H_b$ $H_a \leftrightarrow H_c$

Finally an X-ray crystal structure analysis of **71** confirmed the configuration deduced from the NMR experiments (Figure 20).

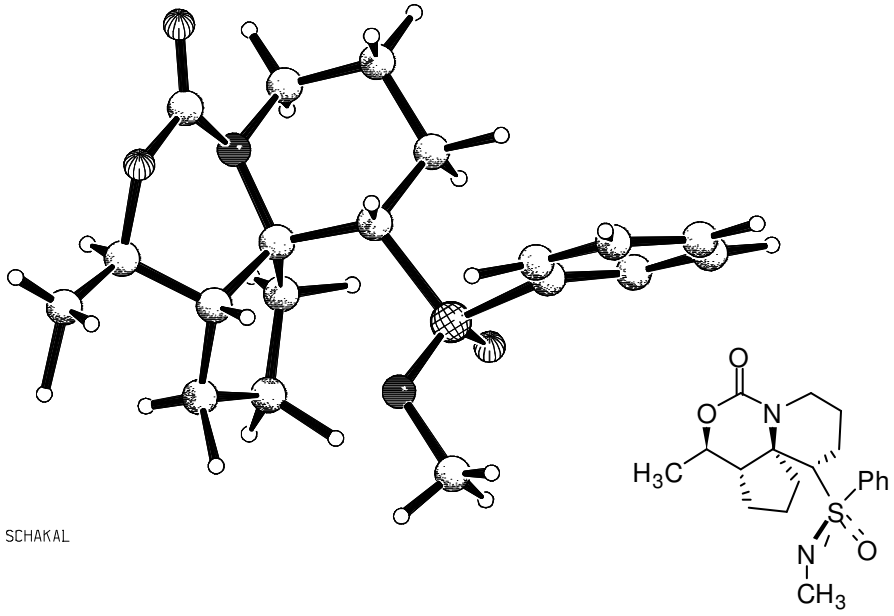
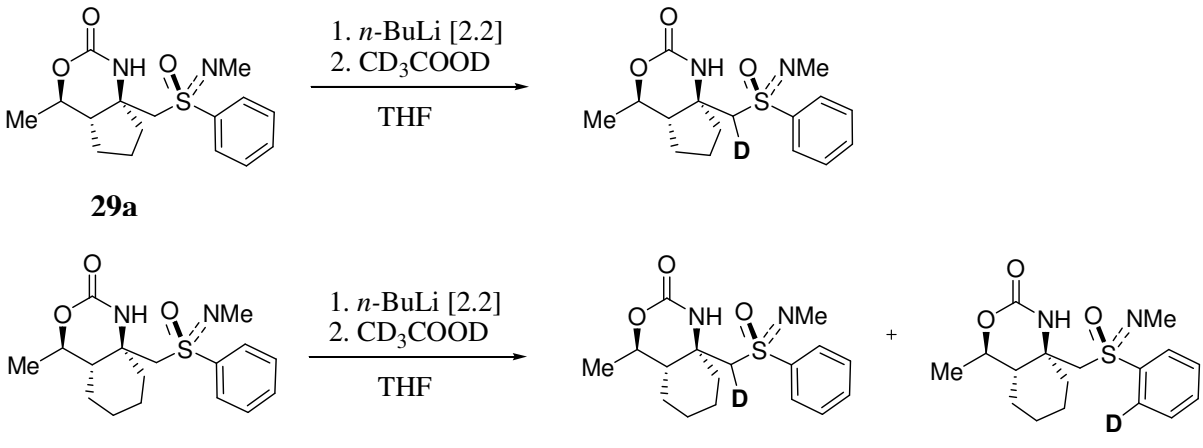


Figure 20. Structure of **71** in the crystal

4.4.2 Rationalization of the observed conversions

Dilithiation of the 5-membered ring oxazinone **29a** and reaction with a biselectrophile gave tricycle **71** in 75% yield. The same procedure applied to the corresponding 6-membered oxazinone **29b** furnished **72** and **73** in 57% and 59%, respectively. The yields based on conversion of **71**, **72** and **73** were almost the same.

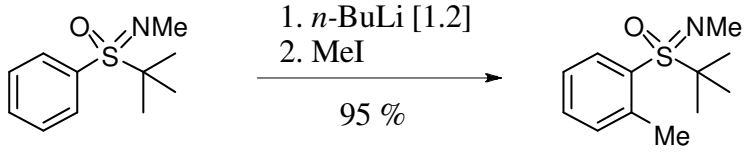
In order to understand the reason why the conversion was lower in the case of oxazinone **29b**, experiments with deuterated acetic acid were carried out (Scheme 33).



Scheme 33. Dilithiation of oxazinones followed by deuteration

Oxazinones **29a** and **29b** were deprotonated with 2.2 eq. of *n*-BuLi and the mixtures were treated with deuterated acetic acid. **29a** was only deuterated at the α-position of the sulfoximine group, whereas in the case of **29b** deuteration at the *ortho* position of the phenyl ring was also observed.

It is known in the literature that phenylsulfoximines can be deprotonated at the *ortho* position of the phenyl ring. The directed *ortho* lithiation reaction is a very powerful method for the functionalization of aromatic compounds. PAPAMICAËL and DUPAS showed that the sulfoximine group is an excellent *ortho* directing group in lithiation reactions. Several electrophiles like methyl iodide were used to afford the corresponding *ortho* functionalized aryl sulfoximines in good yields (Scheme 34).[56]

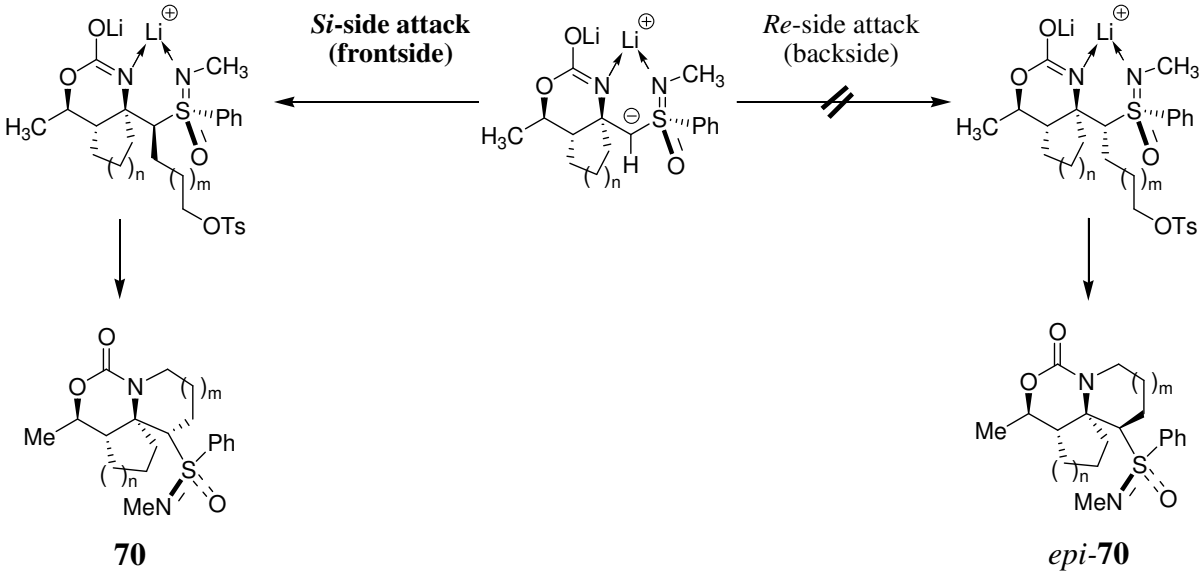


Scheme 34. Sulfoximine as *ortho* directing group in a lithiation reaction

By the undesired *ortho* lithiation of the phenyl ring in case of **29b** some of the *n*-BuLi is consumed and consequently upon work up starting material is recovered. Therefore in the 6-membered ring case, yields are not as good as in the the 5-membered ring case. Anyway the yields based on conversion are good for this highly diastereoselective cycloalkylation reaction.

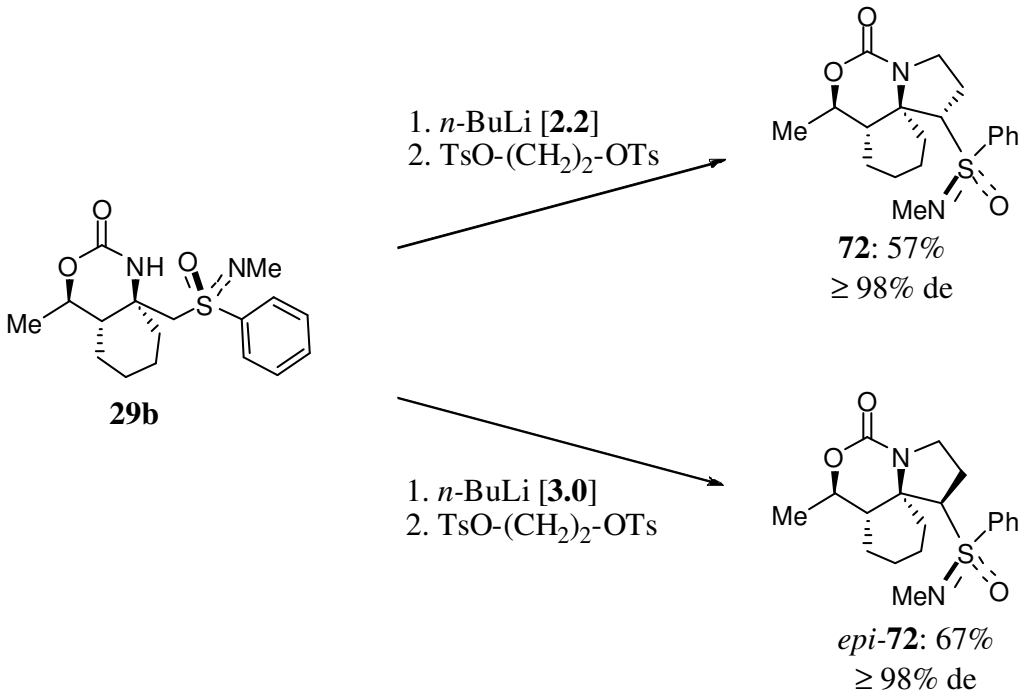
4.4.3 Rationalization of the stereoselectivity outcome

The selective formation of the *S*-configured tricycles can be rationalized by assuming a chelate structure for the (C,N)-dianion, in which the nitrogen and the oxygen of the sulfoximine group coordinate to the lithium cations (Scheme 35). The ditosylate preferably attacks at the *Si*-side of the α-carbon of the sulfoximine group giving **70** rather than *epi*-**70** steming from a *Re*-side attack. The preference of the *Si*-side attack seems to be due to the carbocycle and the phenyl group pointing towards and thus shielding the *Re*-side. Then the heterocycle is closed by substitution of the remaining tosylate group by the carbamate nitrogen.



Scheme 35. Attempted rationalization of the selectivity of the cycloalkylation

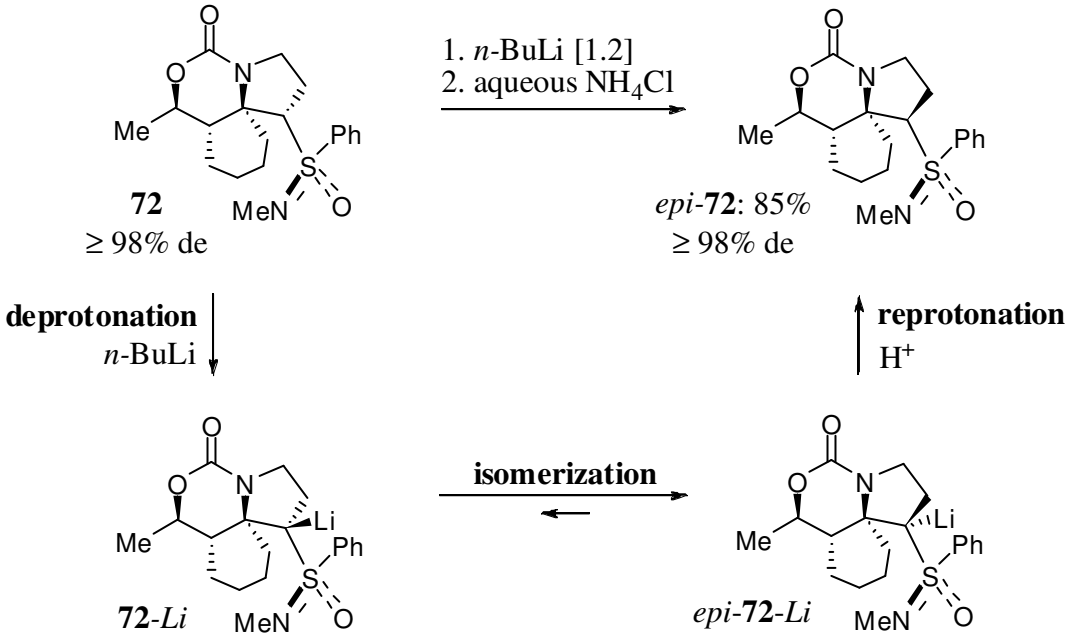
In an attempt to optimize the conversion of **29b**, an interesting observation was made (Scheme 36). The use of 2.2 equivalents *n*-BuLi gave the *S*-configured tricycle **72**, whereas the use of 3.0 equivalents *n*-BuLi gave the epimeric sulfoximine *epi*-**72** having the *R*-configuration at the carbon atom in α-position to the sulfoximine group.



Scheme 36. Highly diastereoselective syntheses of **72** and *epi*-**72**

In order to explain this result, we postulate that at first oxazinone **29b** is doubly deprotonated with 2 equivalents of *n*-BuLi, then cyclization occurs to give tricycle **72**, which should thus be the kinetic product (Scheme 37). The remaining equivalent of *n*-BuLi deprotonates **72** at the α-position to the sulfoximine group to give carbanion **72**-*Li*, which is most likely endowed with a pyramidalized *C* atom. α-Sulfonimidoyl carbanions are configurationally labile, and thus, carbanion **72**-*Li* is expected to undergo an isomerization with formation of the epimeric carbanion *epi*-**72**-*Li*. The epimer should be thermodynamically prefered over **72**-*Li* because of the relief of steric interaction between the sulfoximine group and the carbocycle. Finally, protonation of **72**-*Li* preferentially occurs from the direction of pyramidalization and gives *epi*-**72**.

Another experiment confirmed this mechanism. Treatment of **72** (≤ 98% de) with 1.2 equivalents of *n*-BuLi gives *epi*-**72** (≤ 98% de). Thus **72** seems to be the kinetic product and *epi*-**72** the thermodynamic one.

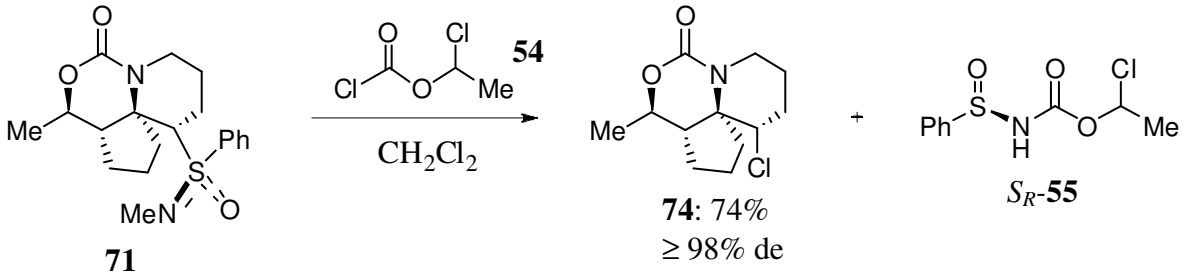


Scheme 37. Diastereoselective isomerization of **72** to *epi*-**72**

4.5 Chloride substitution of the sulfoximine group of the tricycle

4.5.1 Results

The application of tricycles **71**, **72**, *epi*-**72** and **73** to the synthesis of azaspirocyclic natural products requires a substitution of the sulfoximine group. This was accomplished, for example, by the treatment of sulfoximine **71** with $ClCO_2CH(Cl)Me$ in CH_2Cl_2 at room temperature. Chloride **74** was formed in high diastereoselectivity and good yield as well as sulfinamide **55** (Scheme 38).



Scheme 38. Chloride substitution of a secondary sulfoximine

4.5.2 Determination of the absolute configuration

The configuration of **74** was determined by a combination of TOCSY and NOE experiments. First TOCSY experiments were carried out in order to assign the signals of the protons, particulary the CH_2-groups of the carbocycle and of the heterocycle. Then on the basis of coupling constants and through NOE experiments the configuration at the C-atom carrying the chlorine atom could be assigned (Figure 21).

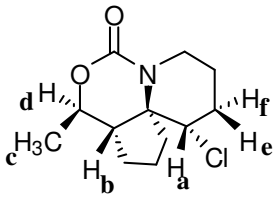


Figure 21. Configuration of **74**

According to the coupling constants the heterocycle seems to adopt a chair conformation and H_a should be in axial position (Table 8). According to NOE experiments H_a must point in the same direction than H_b and H_c.

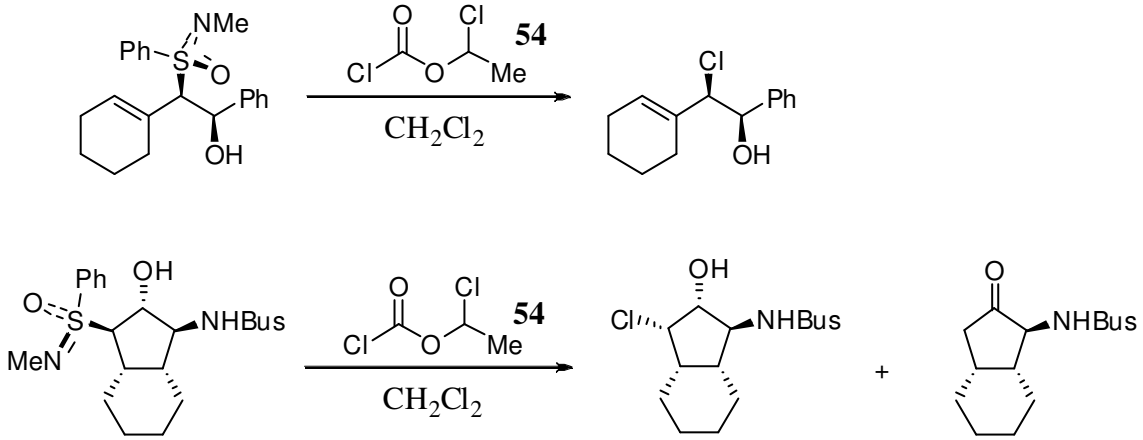
Table 8. Decisive criteria for the determination of the absolute configuration of chloride **74**

Information	Interpretation
$^3J_{Ha\text{-}Hf}$ = 11.9 Hz $^3J_{Ha\text{-}He}$ = 4.0 Hz	H_a is in axial position
NOE: $H_a \leftrightarrow H_b$ NOE: $H_a \leftrightarrow H_c$	H_a must point in the same direction than H_b and H_c

The results of the NMR experiments are similar to those found in the case of sulfoximine **71**, therefore it is not surprising that **74** has the same configuration than **71**. However it was unexpected that the chlorine substitution proceeds selectively under retention of configuration.

4.5.3 Mechanism of the substitution of secondary sulfoximines

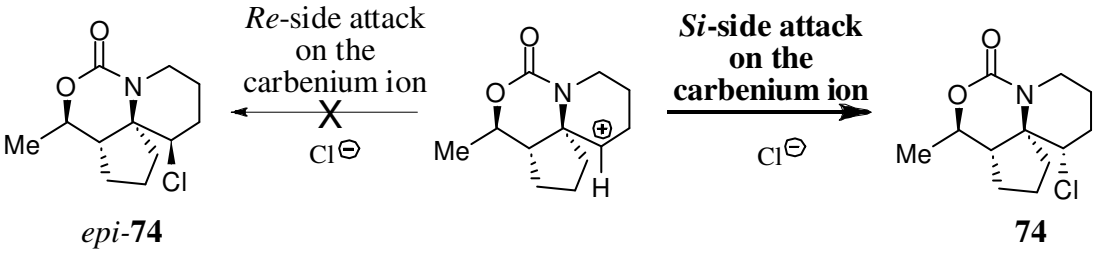
The mechanism of the substitution of sulfoximines with chloroformates is not known. Previously, both retention[42] and inversion[57] had been observed in the substitution of secondary sulfoximines (Scheme 39).



Scheme 39. Chlorine substitution of secondary sulfoximines

The available evidence including the formation of sulfinamide **55** suggests an acylation of sulfoximine **71** at the N-atom with formation of the corresponding aminosulfoxonium salt. The formation of chloride **74** from **71** with complete retention of configuration could be result of different pathways. One can imagine a sequence of two S_N2 reactions but there is no evident neighbouring group which could exercise an effect. On the other hand, it could be a

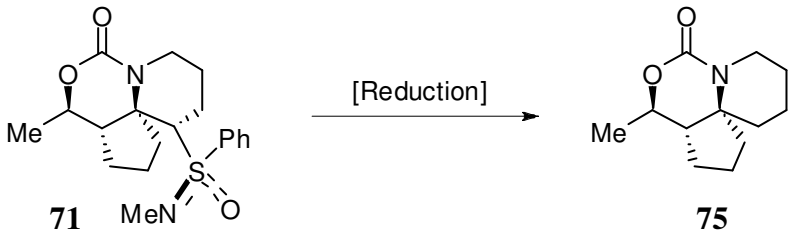
S_N1 reaction with intermediate formation of a carbenium ion. However, it is difficult to see why the carbenuim ion should be attacked selectively from the *Si* side which seems to be the sterically more hindered one because of the carbocycle (Scheme 40). A third possibility would be a S_Ni mechanism.



Scheme 40. S_N1 pathway for the chlorine substitution

4.6 Reduction of the sulfoximine moiety

An access to more simple azaspirocycles could be opened by reductive cleavage of the carbon-sulfur bond. It is known that the sulfoximine group has a low redox potential, so that it can be easily reduced. Different reducing agents were tested for this purpose, including aluminum amalgame, LDBB and RANEY nickel[18] (Scheme 41, Table 9).



Scheme 41. Reduction of the sulfoximine group of **71**

Table 9. Screening of reducing agents for the reduction of the sulfoximine group of **71**

Reducing agent	Observations
Al / Hg, THF, H_2O	Complete conversion Isolated yield: 40% Many impurities
LDBB	Complete conversion Desired product not observed Only destruction of the starting material
RANEY nickel	**Complete conversion** **Isolated yield: 96%**

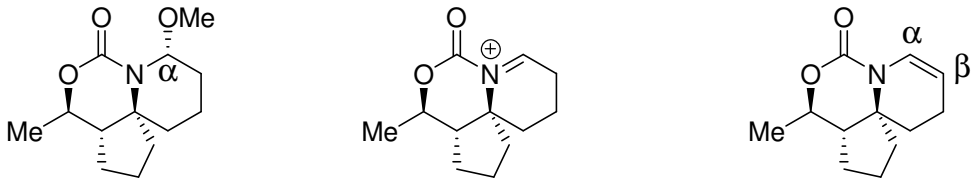
RANEY Nickel was the most suitable agent in this case and we were able to isolate **75** in excellent yield.

5. Functionalization by generation of an N-acyliminium ion

5.1 The plan

Having achieved syntheses of azaspirocycles with functional groups at the β,γ-position in the heterocycle using ring-closing metathesis, and at the δ-position using cycloalkylation, it was of interest whether an access to azaspirocycles carrying a functional group at the α- and/or β-position could also be opened.

We aimed at the preparation of **76** and **78**, which are precursors of the N-acyliminium ion **77**, in order to functionalize easily the α- and/or β-position (Scheme 42).



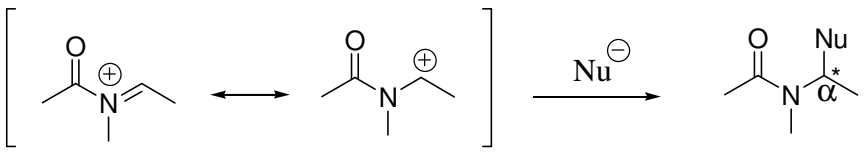
76 **77** **78**

Scheme 42. Structure of precursors **76** and **78** for the N-acyliminium ion **77**

5.2 Importance and reactivity of N-acyliminium ions

5.2.1 Importance of N-acyliminium ions

Reactions between N-acyliminium ions and nucleophiles, also described as amidoalkylation or MANNICH type condensations, have been frequently used to introduce susbtituents at the α-carbon of an amine (Scheme 43).[58]



Scheme 43. Amidoalkylation reaction

A substantial number of valuable and pertinent contributions about N-acyliminium ions have appeared in the literature covering significant improvements in the accessibility of precursors and generation of the reactive species. The control of diastereo- and enantioselectivity of the addition reacton has also been a main focus.

The N-acyliminium ion synthetic method has already been successfully applied to the syntheses of chiral pyrrolidines, chiral piperidines, chiral bicyclic lactams and others.

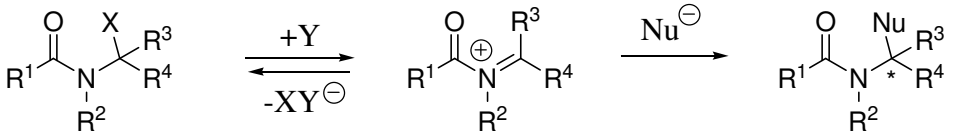
5.2.2 Formation and reactivity of N-acyliminium ions

Because of their limited stability and high reactivity, N-acyliminium ions for synthetic applications are frequently generated in situ from α-haloalkyl-, α-hydroxyalkyl-, α-alkoxy- or α-acyloxyalkyl-substituted amides, lactams, or carbamates.[59]

LEWIS acids ($BF_3.OEt_2$, $TiCl_4$, or $SnCl_4$) and silylating agents (Me_3SiOTf) are routinely used to assist the formation of the electrophile intermediate.

The formation of the N-acyliminium ion, which is generally assumed to be the rate-determining step, is followed by in situ trapping with nucleophiles such as Grignard reagents, organocopper reagents, allyltin reagents, allylsilanes and silyl enol ethers.

This process is known as the α-amidoalkylation reaction. Generally the rate of the amidoalkylation reaction increases with the stability of the N-acyliminium ion that is formed (Scheme 44).

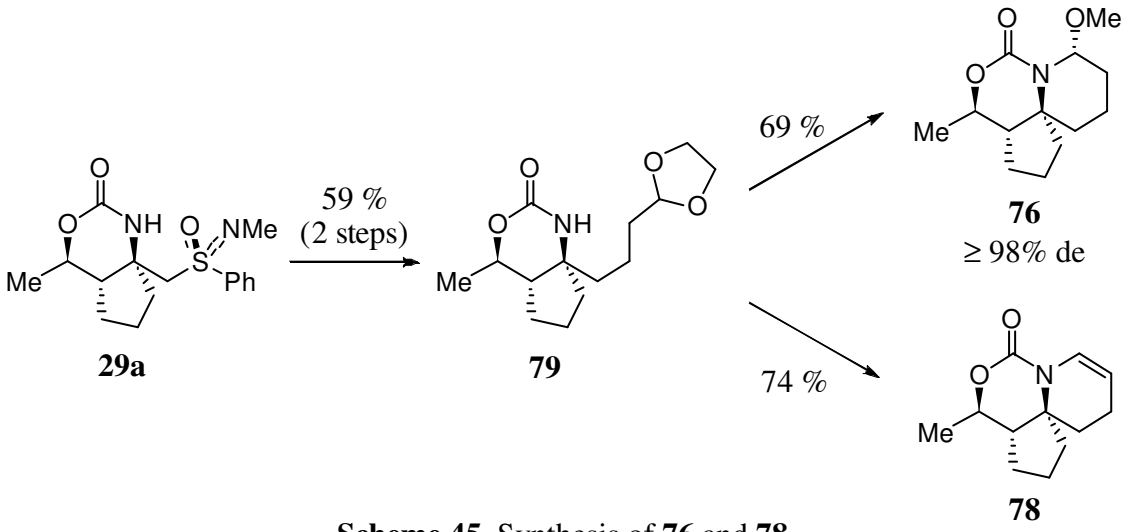


R^1 = H, alkyl, alkoxy, aryl, aryloxy
$R^2 = R^3 = R^4$ = H, alkyl, aryl

Scheme 44. General reaction pathway for the α-amidoalkylation

5.3 Synthesis of precursors 76 and 78 for the N-acyliminium ion 77

We were successful in the synthesis of **76** and **78**, which are both precursors of N-acyliminium ion **77**. The syntheses of **76** and **78** were accomplished in three steps starting from oxazinone **29a** (Scheme 45).

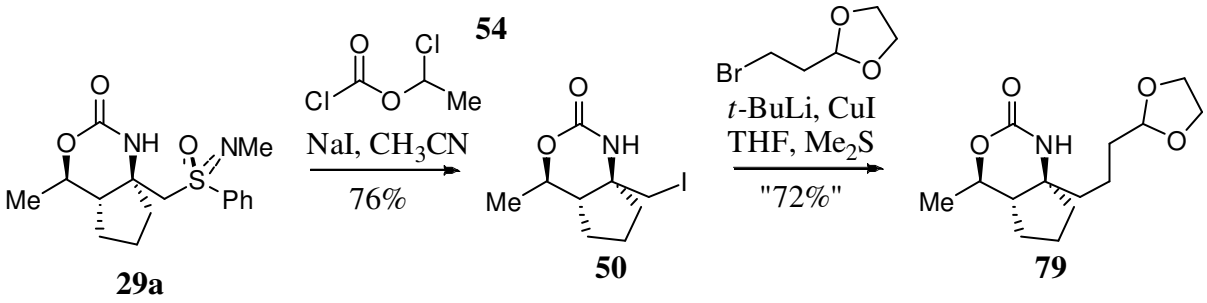


Scheme 45. Synthesis of **76** and **78**

In the following chapters the steps leading to **76** and **78** will be detailed.

5.3.1 Synthesis of the protected acetal

• First plan / The cuprate route



Scheme 46. The cuprate route to acetal **79**

The first step is the substitution of the sulfoximine group of **29a** by iodide, which was described previously. Then the iodo atom should be substituted by an alkyl group containing a protected aldehyde (Scheme 46).

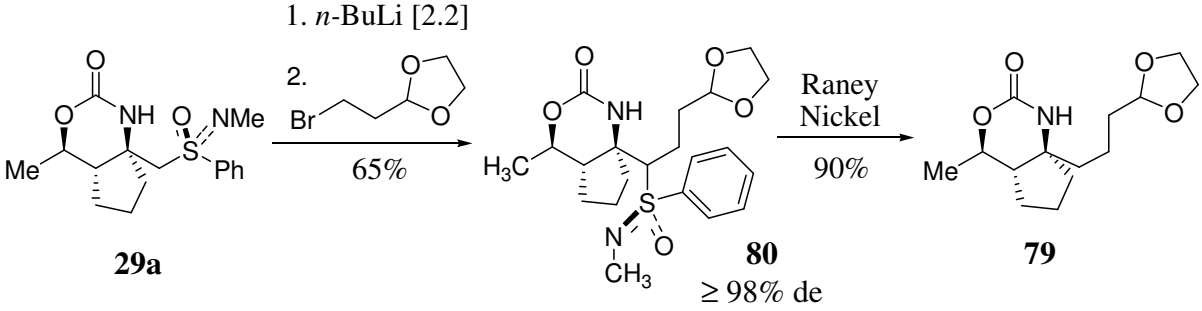
The commercially available 2-(2-bromoethyl)-1,3-dioxolane was chosen for the synthesis.

The procedure for the conversion of a bromide into the corresponding cuprate is well established. At first the bromide has to be treated with 2 equivalents of *t*-butyllithium to furnish via lithium-bromine exchange the corresponding organolithium compound, which can then be transformed into the GILLMAN cuprate using 0.5 equivalent of copper(I). [45,60,61,62]

Iodides are even better substrates for the conversion to the corresponding cuprate because of their better capacity to undergo lithium-halogen exchange.

The problem encountered with the cuprate substitution from **50** to **79** was the upscale. In fact the yield of **79** decreased dramatically on a "larger" scale. An alternative for the synthesis of **79** had to be found.

• Second plan / The double lithiation route



Scheme 47. The double lithiation route to acetal **79**

The alternative for the synthesis of **79** takes benefit of the cycloalkylation methodology developed for the functionalization of the heterocycle at the δ-position (see chapter 4, Scheme 47).

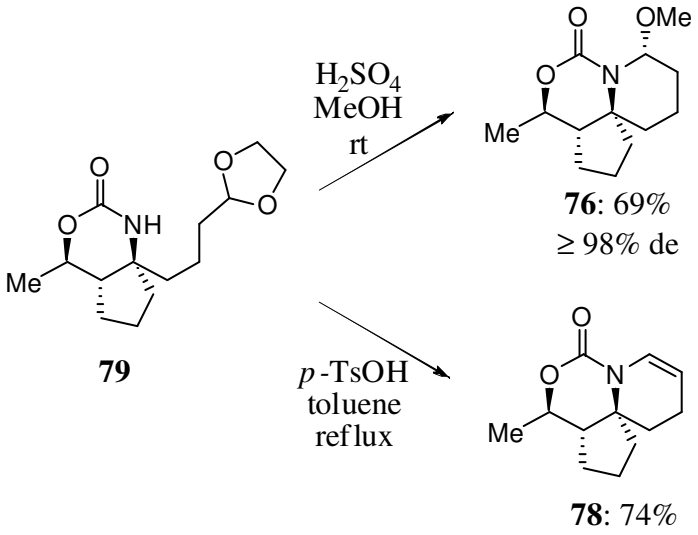
At first the α-position of the sulfoximine group was alkylated with 2-(2-bromoethyl)-1,3-dioxolane and then the sulfoximine group was replaced by a hydrogen atom.

The double lithiation of **29a** followed by the alkylation of the corresponding dianion with 2-(2-bromoethyl)-1,3-dioxolane gave the diastereomerically pure sulfoximine **80** in 65% yield. However 10% of the starting sulfoximine were recovered. For the reduction of the

sulfoximine group RANEY Nickel was used and the reaction furnished the desired product **79** in excellent yield.

5.3.2 Deprotection and cyclization

Deprotection-cyclization of acetal **79** was performed (Scheme 48) under acidic conditions. In the presence of H_2SO_4 and MeOH **76** was isolated in good yield. This reaction proceeds most probably via the formation of the N-acyliminium ion **77** (Scheme 42).
Deprotection of acetal **79** (*p*-TsOH) in absence of a nucleophile gave under elimination of H^+ the desired enamide **78** in good yield.



Scheme 48. Deprotection and cyclization of the cyclic acetal

The configuration of **76** was determined by a combination of TOCSY and NOE experiments. First TOCSY experiments were carried out in order to assign the signals of the protons, particulary the CH_2-groups of the carbocycle and of the heterocycle. Then on the basis of coupling constants and through NOE experiments the configuration at the C-atom carrying the methoxy group could be assigned (Figure 22).

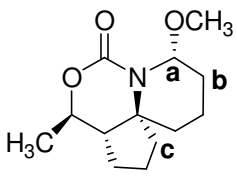


Figure 22. Configuration of **76**

According to the coupling constants the heterocycle seems to adopt a chair conformation, H_a should be in equatorial position and the methoxy group in axial position (Table 10). According to NOE experiments H_a must point in the same direction than the carbocycle.

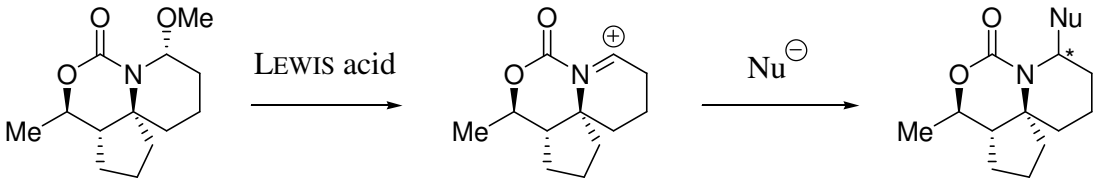
Table 10. Decisive criteria for the determination of the configuration of acetal **76**

Information	Interpretation
$^3J_{Ha\text{-}Hd} = 4.0$ Hz $^3J_{Ha\text{-}Hd'} = 1.8$ Hz	H_a is in equatorial position and OCH_3 (H_b) is in axial position
NOE: $H_b \leftrightarrow H_d$ NOE: $H_b \leftrightarrow H_c$	H_b must point in the same direction than the carbocycle (H_c)

5.4 Applications and structural variations

Acetal **76** and enamide **78** are precursors of N-acyliminium ion **77**. These compounds should, thus, be versatile intermediates for the functionalization at the α- and/or β-position to the N-atom.

(N,O)-acetal **76** could react with a LEWIS acid to give the N-acyliminium ion **77**, which would react at the α-position to the nitrogen atom with nucelophiles (Scheme 49). One example is reported in the next chapter, using $BF_3.OEt_2$ as LEWIS acid and allyltrimethylsilane as nucleophile. Details about this reaction will be given in the next section.

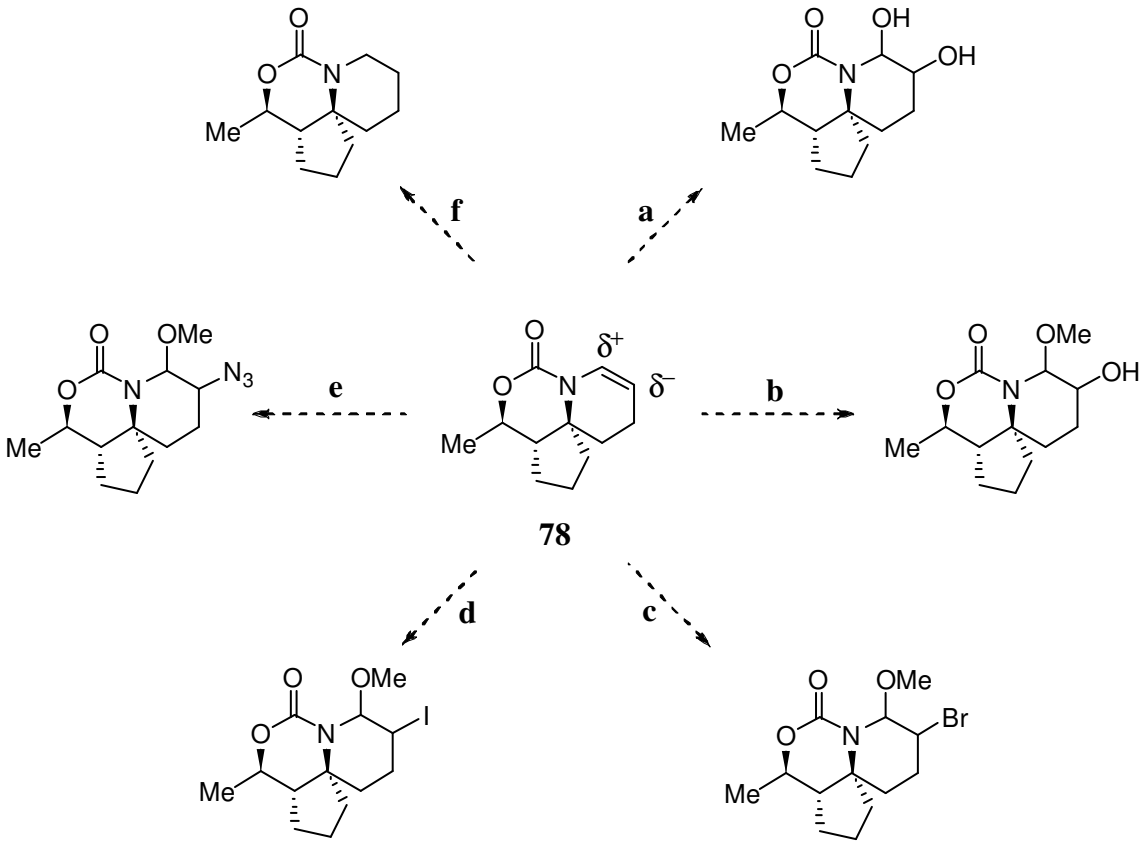


76 **77**

Scheme 49. Functionalization at the α-position using precursor **76**

Enamide **78** is also an interesting precursor; it could lead to the functionalization of the α- and β-position. Similar to enamines, such enamides can react with nucleophiles at the α-position and with electrophiles at the β-position.

Several reactions are reported in the literature (Scheme 50). Via a dihydroxylation reaction (a) two hydroxy groups could be introduced. Epoxidation followed by ring-opening with MeOH would lead to an (N,O)-acetal having a hydroxy group at the β-position (b).The introduction of a bromo and iodo atom at the β-position could be achieved by treatment with NBS (c) and ICl (d), respectively. It should also be possible to introduce an azide at the β-position (e), and finally, reduction of the double bond would lead to a saturated azaspirocycle (f).
It has to be pointed out that in the case of (b), (c), (d) and (e), the presence of the (N,O)-acetal moiety gives rise to further functionalizations and variations at the α-position.



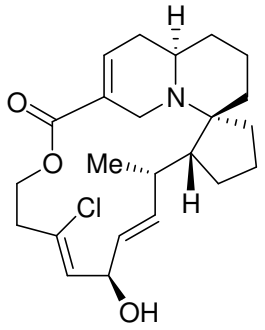
Reaction	Reagents
a[63]	OsO_4, NMO
b[64]	Oxone, $NaHCO_3$, MeOH
c[65]	NBS, MeOH
d[66]	ICl, MeOH
e[67]	NaN_3, $(NH_4)_2Ce(NO_3)_6$, MeOH
f[68]	H_2, Pd, EtOH

Scheme 50. Enamide **78**: A potential intermediate for a modular functionalization at the α- and/or β-position.

6. Studies toward the synthesis of halichlorine and pinnaic acid

6.1 Total and formal syntheses of halichlorine and pinnaic acid in the literature

Several groups have reported their efforts towards the synthesis of halichlorine **4** and pinnaic acid **7** (Figure 23). In 1999, DANISHEFSKY et al. reported the first asymmetric synthesis of this two alkaloids and it is so far the only one for halichlorine.[9] In 2004, HEATHCOCK et al. reported the total synthesis of (±)-**4** and (±)-**7**.[12] KIBAYASHI et al. (2004)[13], ZHAO et al. (2005)[14] and MARTIN et al. (2005)[15] published formal total syntheses of halichlorine **4** and pinnaic acid **7**. In 2007, ZHAO et al. reported a new enantioselective total synthesis of pinnaic acid **7** inspired by their formal total synthesis.[10] In the same year ARIMOTO et al. published a new asymmetric total synthesis of pinnaic acid **7**.[11]



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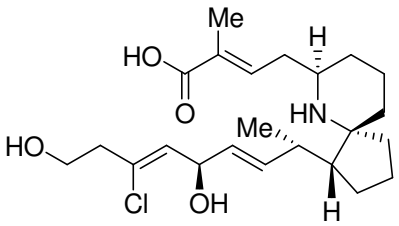
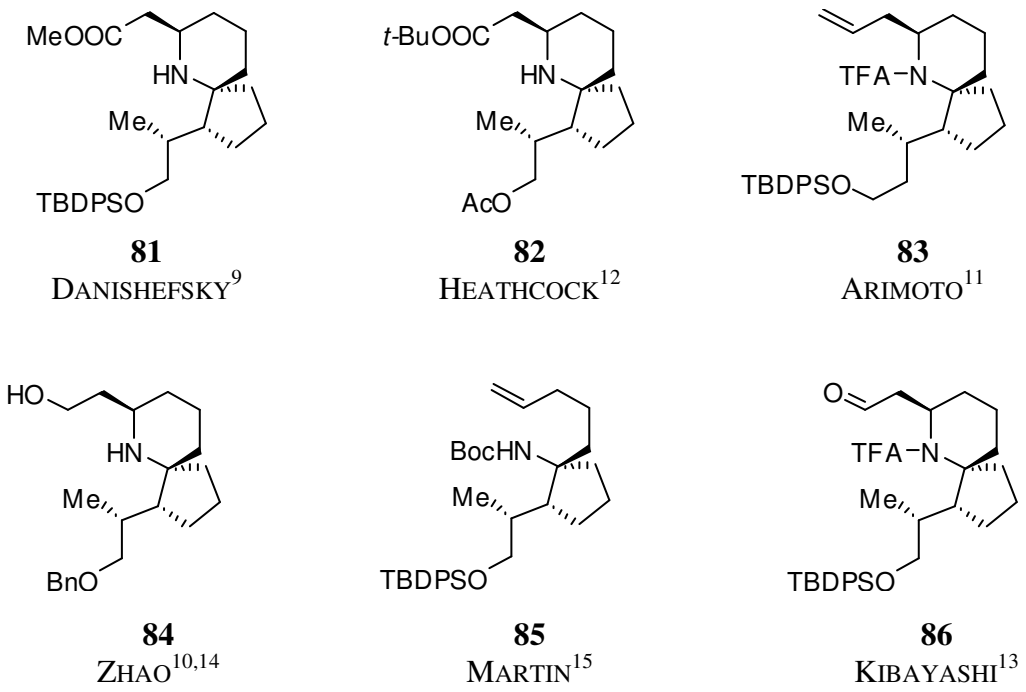


7

Figure 23. Halichlorine **4** and pinnaic acid **7**

In order to plan a formal total synthesis, the intermediates already described in the literature were studied with much attention, and for each synthesis the most interesting structure was selected (Figure 24).



81
DANISHEFSKY[9]

82
HEATHCOCK[12]

83
ARIMOTO[11]

84
ZHAO[10,14]

85
MARTIN[15]

86
KIBAYASHI[13]

Figure 24. Interesting target molecules for our formal total synthesis plans

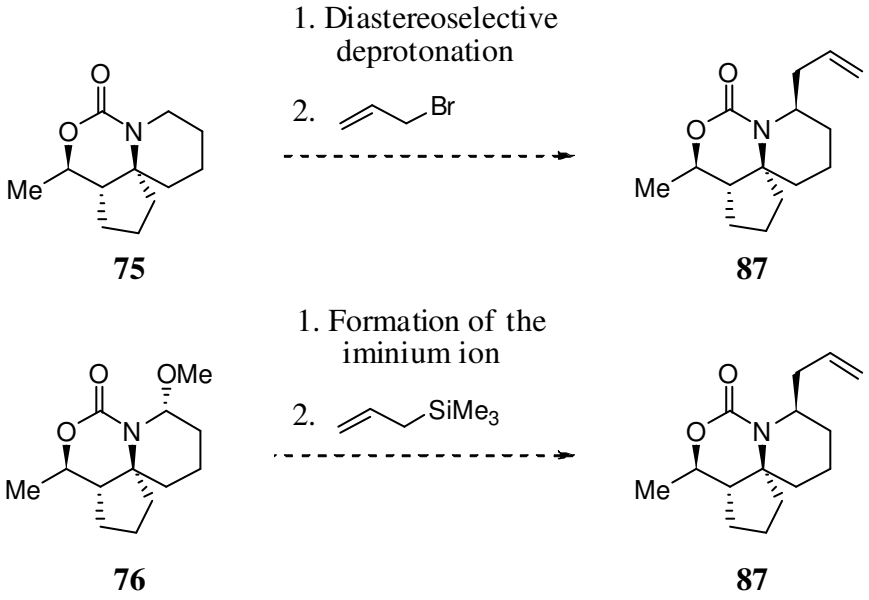
A closer look at the structures of **81**, **82**, **83**, **84** and **86** shows a common skeleton, in which the stereocenter in α-position to the N-atom of the heterocycle is already present. This is not the case in molecule **85**. Finally, two different approaches have been considered. The first one includes the construction of the stereocenter in α-position to the N-atom of the heterocycle, the second one avoids the construction of this stereocenter.

6.2 Formal total synthesis including the construction of the stereocenter in α-position to the N-atom of the heterocycle

6.2.1 The plan

The first challenge is the installation of the new stereogenic center in α-position to the N-atom of the heterocycle. Of course the formal total synthesis should take advantage of the methodology developed previously. Two different ways to introduce the allyl group at the α-position were identified. The first one is the diastereoselective lithiation of **75** alpha to the N-atom and reaction of the corresponding lithiated species with allyl bromide. The second

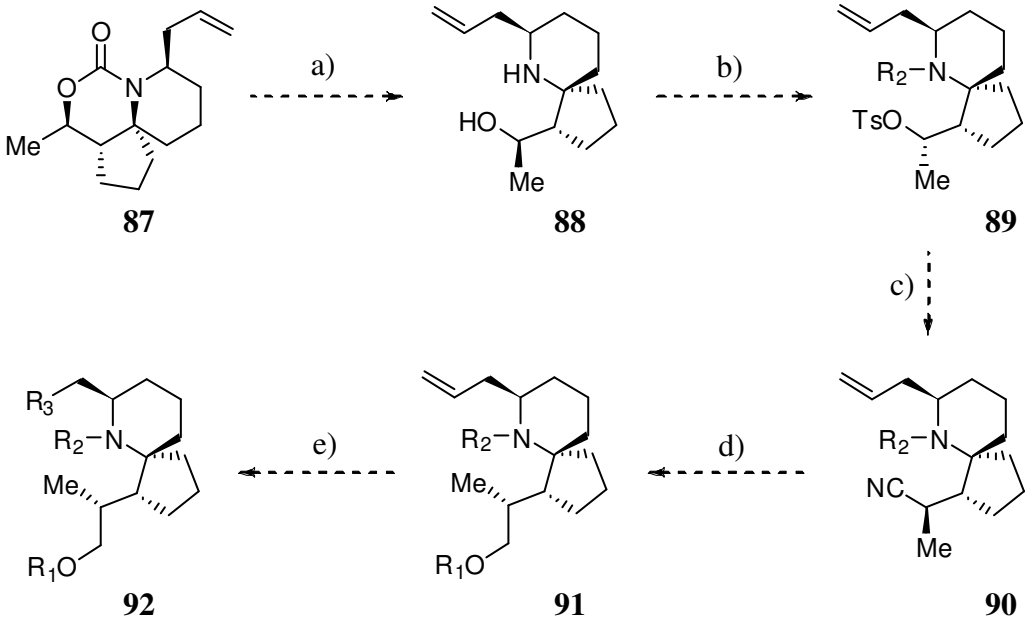
one is the reaction of **76** with a LEWIS acid to form in situ the N-acyliminium ion and its reaction with allyltrimethylsilane. In both cases we expected to get **87** (Scheme 51).



Scheme 51. Possible access to alkene **87**

There were two open questions. Does the reaction work with our system, and if it works, will the desired configuration be obtained?

Given that the synthesis of **87** succeeded with the desired configuration, we envisaged the synthesis shown in Scheme 52.



87 **88** **89** **90** **91** **92**

Scheme 52. Planed formal total synthesis of halichlorine and pinnaic acid

a) At first oxazinone **87** should be hydrolyzed to give the amino alcohol **88**.

b) Then the amino function should be protected selectively. Afterwards the hydroxy group of **88** should be transformed into a good leaving group; tosylation was thought to be a good choice. The tosylation should be performed under modified MITSUNOBU conditions by using *p*-TsOH as a nucleophile. This should give tosylate **89** with inversion of configuration.[69]

c) At this stage another inversion of configuration had to take place. It is known that cyanide substitution of secondary tosylates proceeds via an S_N2 mechanism. Thus nitrile **90** should result.

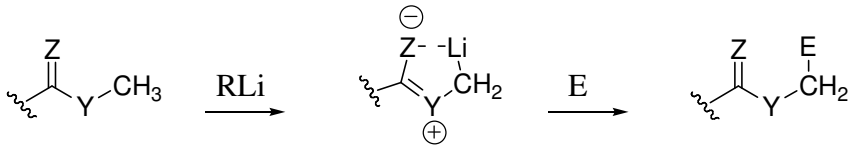
d) The nitrile function of **90** should be reduced into the corresponding primary alcohol. This transformation is known with DIBAL-H in a two steps procedure. The aldehyde is isolated to avoid the formation of the primary amine. Then the hydroxy group should be protected to give **91**.[70]

e) The double bond of **91** should be easily oxidized to the aldehyde or transformed into the primary alcohol under formation of **92**.

6.2.2 Stereoselective deprotonation in α-position to the N-atom

• Principle

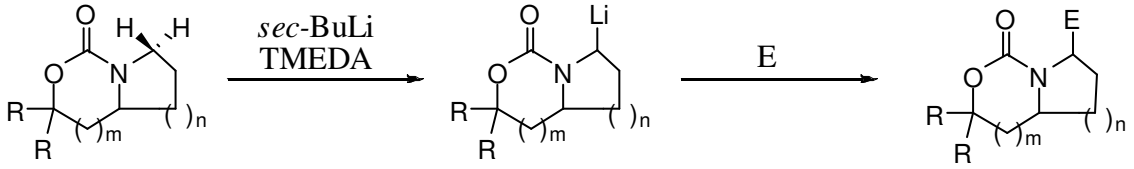
The removal of a proton from a carbon bearing a heteroatom to give an α-heteroatom carbanion is a synthetically useful and mechanistically interesting reaction (Scheme 53). Formation of such organometallic species can be promoted by a local inductive effect when the heteroatom is the positive end of a dipole.[71,72]



Y = must be able to stabilize a positive charge (NCH_3, O, S)
Z = must be able to stabilize a negative charge (N, O, S)
E = electrophile

Scheme 53. General representation of a dipole-stabilized carbanion and subsequent reaction with an electrophile

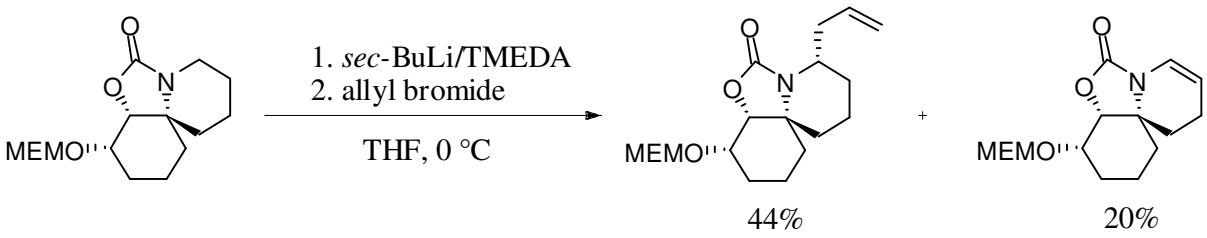
BEAK et al. have been working since a long time in this field, and particulary in the development of methodologies for the enantioselective synthesis by lithiation adjacent to N-atoms and electrophile incorporation (Scheme 54).[73] According to their report about the lithiation-substitution of bicyclic carbamates it seems that lithiations of such carbamates proceed with removal of the proton nearest to the carbonyl oxygen in reactions which are kinetically as well as thermodynamically favored. The fact that the bicyclic carbamates are lithiated with greater efficiency than the corresponding Boc-protected amines also suggests that constraining the position of the proton to be removed to an appropriate angle to the carbamate increases the efficiency of lithiation. The distance between the carbamate carbonyl group and the proton to be removed appears to be important.



Scheme 54. Lithiation-substitution of bicyclic carbamates by BEAK et al.

• Application to the synthesis of natural products

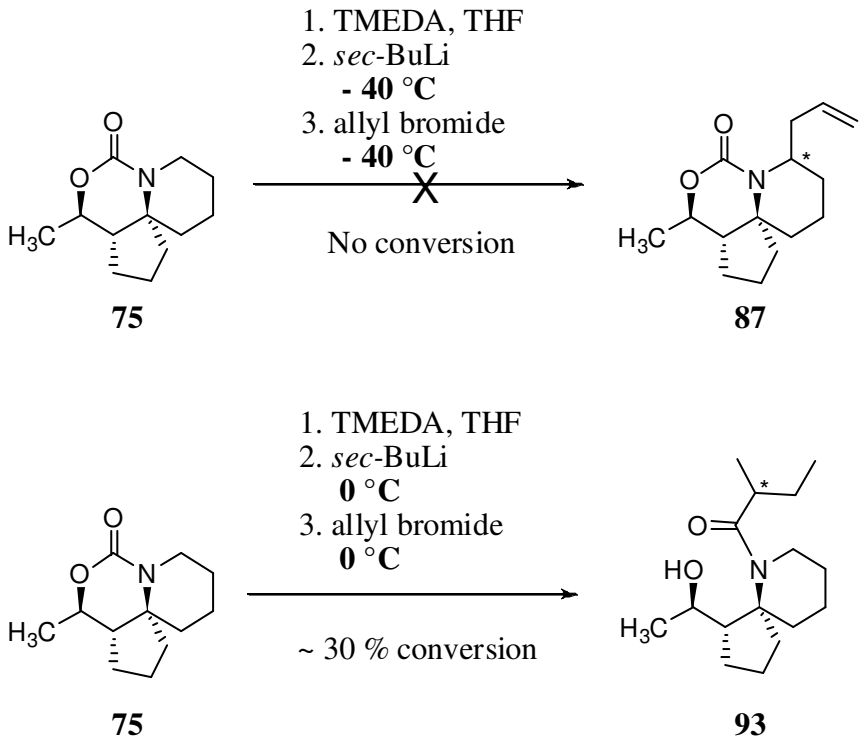
BERA et al. have applied this methodology in an enantioselective synthesis of the 1-azaspiro[5.5]undecane ring system of histrionicotoxin alkaloids (Scheme 55).[74] In order to explain the high diastereoselectivity, it was assumed that the carbonyl group pointing backwards first complexes with *sec*-butyllithium to direct the lithiation to the same face of the ring system.



Scheme 55. Application to the synthesis of azaspirocycles

• Results and discussion

Tricycle **75** was treated with *sec*-butyllithium in presence of TMEDA, then allylbromide was added (Scheme 56). Unfortunately at –40 °C no conversion was observed and starting tricycle **75** was recovered. Increasing the temperature to 0 °C led to consumption of the starting material but the desired alkene **87** was not observed. Amide **93** was isolated and results from the attack of *sec*-butyllithium to the carbamate carbonyl group.



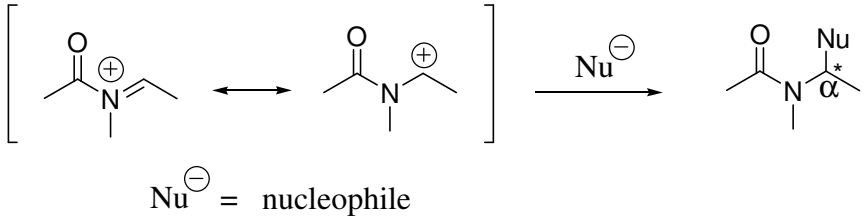
Scheme 56. Tentative of α-lithiation to the N-atom of **75**

BEAK et al. reported that the installation of sterically demanding isopropyl and *tert*-butyl groups nearby the carbamate carbonyl group is necessary to prevent addition of *sec*-butyllithium.[73] In case of **75** the addition of *sec*-butyllithium to the carbamate carbonyl group seems to be favored over the lithiation adjacent to the nitrogen.

6.2.3 Addition to N-acyliminium ions

• Principle

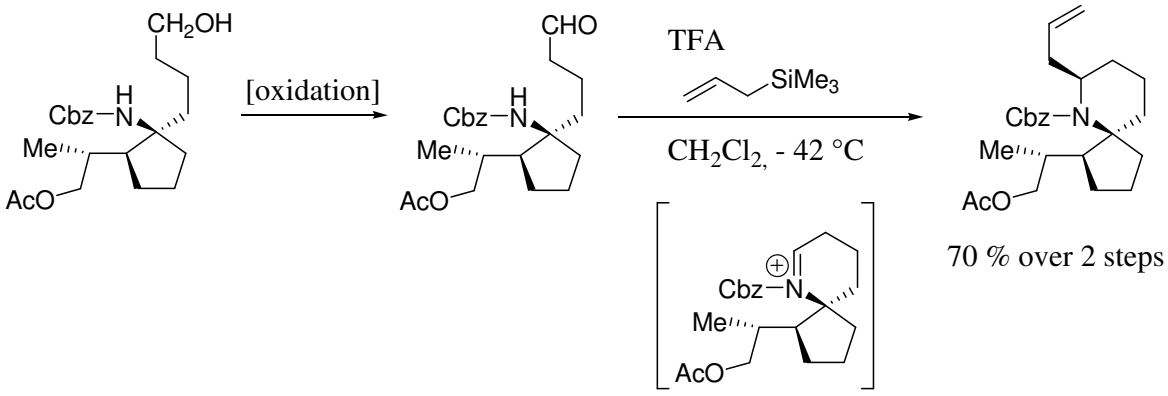
As discussed in chapter 5, reactions between N-acyliminium ions and nucleophiles have been frequently utilized to introduce substituents at the α-carbon of an amine. Because of their limited stability and high reactivity, N-acyliminium ions are frequently generated in situ (Scheme 57).[58,59]



Scheme 57. α-amidoalkylation reaction

• Application to the synthesis of natural products

FORSYTH et al. applied this methodology to the synthesis of the 1-aza-[4.5.0]-spirobicyclic core of halichlorine **4** and pinnaic acid **7** (Scheme 58).[75] The in situ formation and stereoselective allylation of cyclic iminium ions represents a facile reaction sequence for the synthesis of substituted cyclic N-acylamine derivatives from acyclic carbamates. The stereoselectivity of the allylation is consistent with allyl attack occuring on the *Si*-face of the iminium ion.

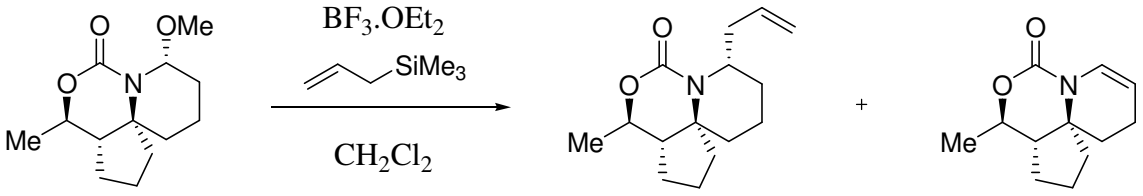


Scheme 58. In situ formation and stereoselective allylation of an iminium ion

• Results and discussion

On the way to halichlorine **4** and pinnaic acid **7**, the introduction of an allyl group in α-position to the N-atom of the heterocycle was required.

The reaction of **76** with $BF_3.OEt_2$ followed by the addition of allyltrimethylsilane to the in situ formed iminium ion **77** led to *epi*-**87** in 71% yield with high diastereoselectivity (≥98% de). An elimination of **76** with formation of enamide **78** was also observed. *epi*-**87** and **78** were isolated in a ratio of 3:1 (Scheme 59).



76 *epi*-**87**: 71% ≥ 98% de **78**: 22%

Scheme 59. Synthesis of alkene *epi*-**87** from acetal **76**

The configuration of *epi*-**87** was determined by a combination of TOCSY and NOE experiments (Figure 25). First TOCSY experiments were carried out in order to assign the signals of the protons, particulary the CH_2-groups of the carbocycle and of the heterocycle. According to NOE experiments H_a, H_c and H_e point in the same direction.

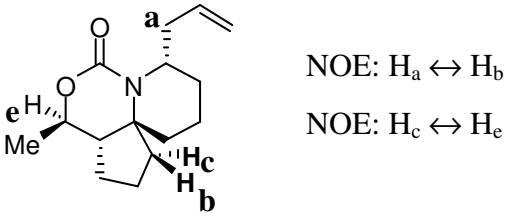


Figure 25. Determination of the configuration of the newly formed sterogenic center in *epi*-**87**

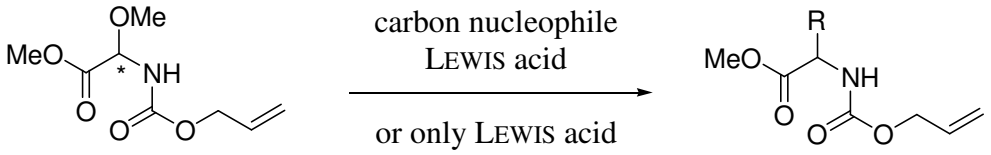
Unfortunately, the route via the N-acyliminium ion did not allow the establishment of the desired configuration of alkene **87**. Such reactions are known to proceed via a S_N1 mechanism. Carbenium ions have been already detected directly in NMR studies and are also chemically proven by experimental observations.[76]

SPECKAMP et al. investigated the reaction of optically pure (+)-**94** with allyltrimethylsilane, 1-phenyl-1-(trimethylsiloxy)ethene and furane, mediated by different LEWIS acids, and obtained in all cases completely racemized products (Scheme 60).[77] This clearly indicates that such reactions proceed via the S_N1 mechanism.

That no S_N2 reaction was found can be attributed to the methoxy group, which is a relatively poor leaving group. Therefore a single-step substitution of this group is not likely.

When optically pure (+)-**94** was mixed with boron trifluoride etherate in absence of a carbon nucleophile, it appeared to racemize rather slowly. Although, after stirring the mixture for

24 h at room temperature, the starting material, recovered in nearly quantitative yield, had almost completely racemized.



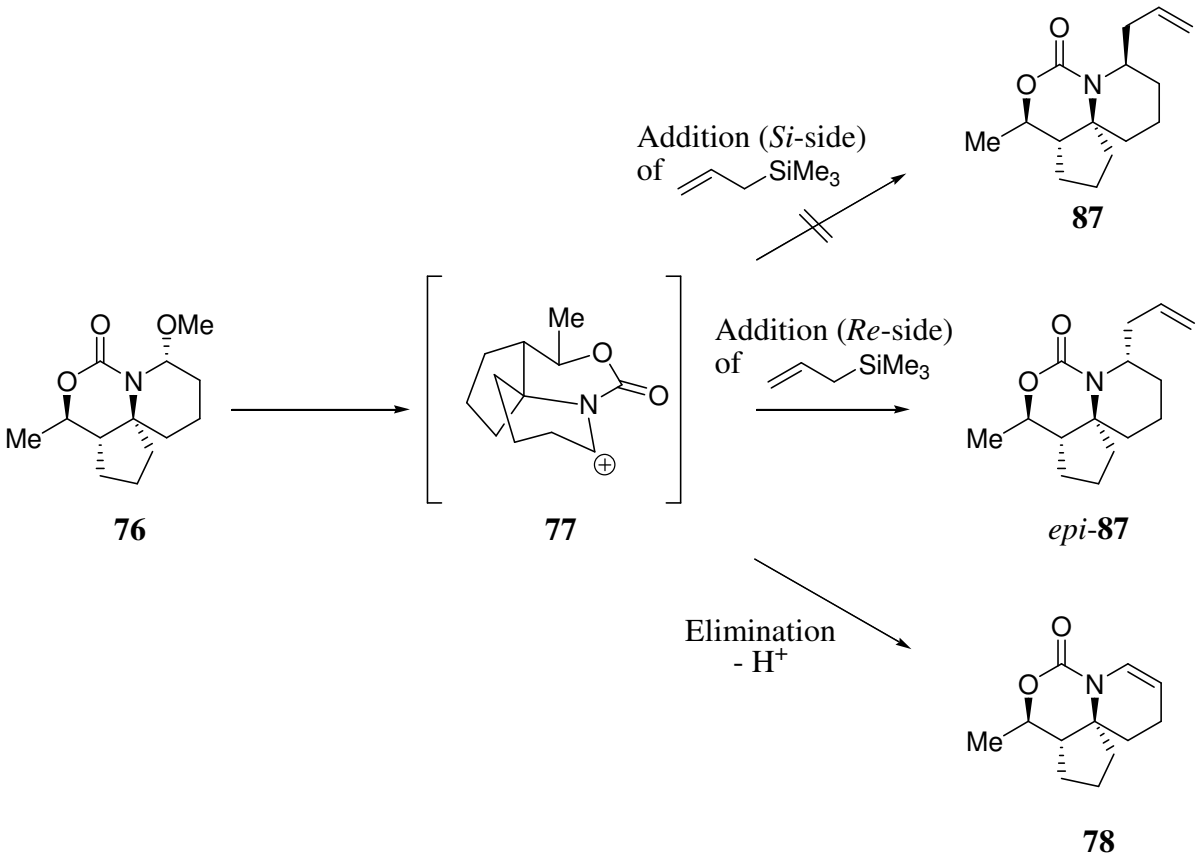
optically pure

94

rac

Scheme 60. Rationalization of the S_N1 mechanism

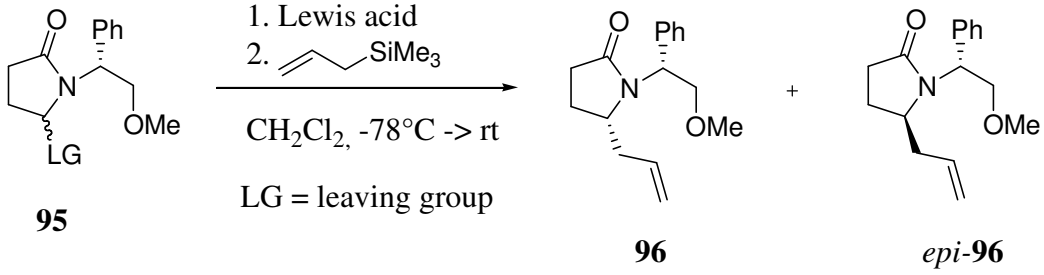
In the case of **76** it is not a S_N2 reaction, probably for the same reasons as in SPECKAMP's case. The methoxy group is a poor leaving group and a single-step substitution of this group is not very favored. We tried to rationalize the selectivity of the reaction but we could not find a reason why the attack of allyltrimethylsilane at the iminium ion should occur preferentially from the *Re*-side (Scheme 61).



Scheme 61. Rationalization of the formation of **87**, *epi*-**87** and **78**

The reaction is highly diastereoselective, but leads to the undesired configuration in terms of the formal total synthesis.

FUJISAWA et al. prepared both enantiomers of amines from a single chiral α-acyloxy amide of type **95** via N-acyliminium ions by simply varying the LEWIS acid (Scheme 62, Table 11). The reasons for this influence of the LEWIS acid are not clear but might be attributed to a different coordination geometry between the intermediate N-acyliminium ion and the LEWIS acid. Finally the ability of the LEWIS acid to form a complex with the oxygen atom in the chiral auxiliary might alter the side for the nucleophile attack. The judicious choice of the leaving group is crucial for enhanced selectivity.[78]



Scheme 62. Influence of the leaving group and of the LEWIS acid

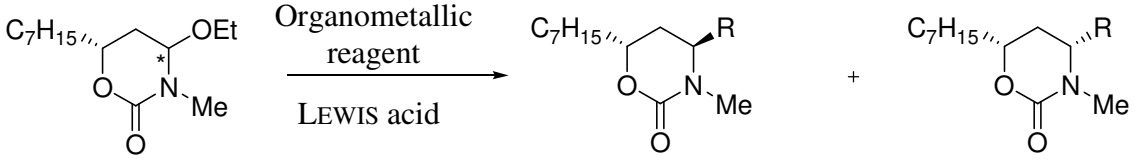
Table 11. Results of the influence of the leaving group and of the LEWIS acid

LEWIS acid	Starting material **95** Leaving group (LG)	Yield (**96**+ *epi*-**96**)	Ratio **96**: *epi*-**96**
$BF_3.OEt_2$	OAc	66%	74:26
$BF_3.OEt_2$	OH	85%	72:28
$SnCl_4$	OAc	91%	16:84
$SnCl_4$	OH	87%	46:54

In the case of alkenes **87** and *epi*-**87** it seems to be difficult to totally invert the stereoselectivity. Alkene *epi*-**87** was obtained as a single isomer in the reaction of acetal **76** with $BF_3.OEt_2$ as a LEWIS acid and OMe as a leaving group. Although in view of this encouraging study a change in favor of alkene **87** might be possible.

YAMAMOTO et al. showed that the reaction of 6-membered α-ethoxycarbamate **97** with organocopper-boron trifluoride reagents proceeds partly via an S_N2-type displacement,

whereas the reaction with allyltributyltin afforded preferentially the product formed via the S_N1-type displacement (Scheme 63, Table 12).[79]



97 *trans*-**98** *cis*-**98**

Scheme 63. S_N1 vs S_N2 displacement: Influence of the organometallic

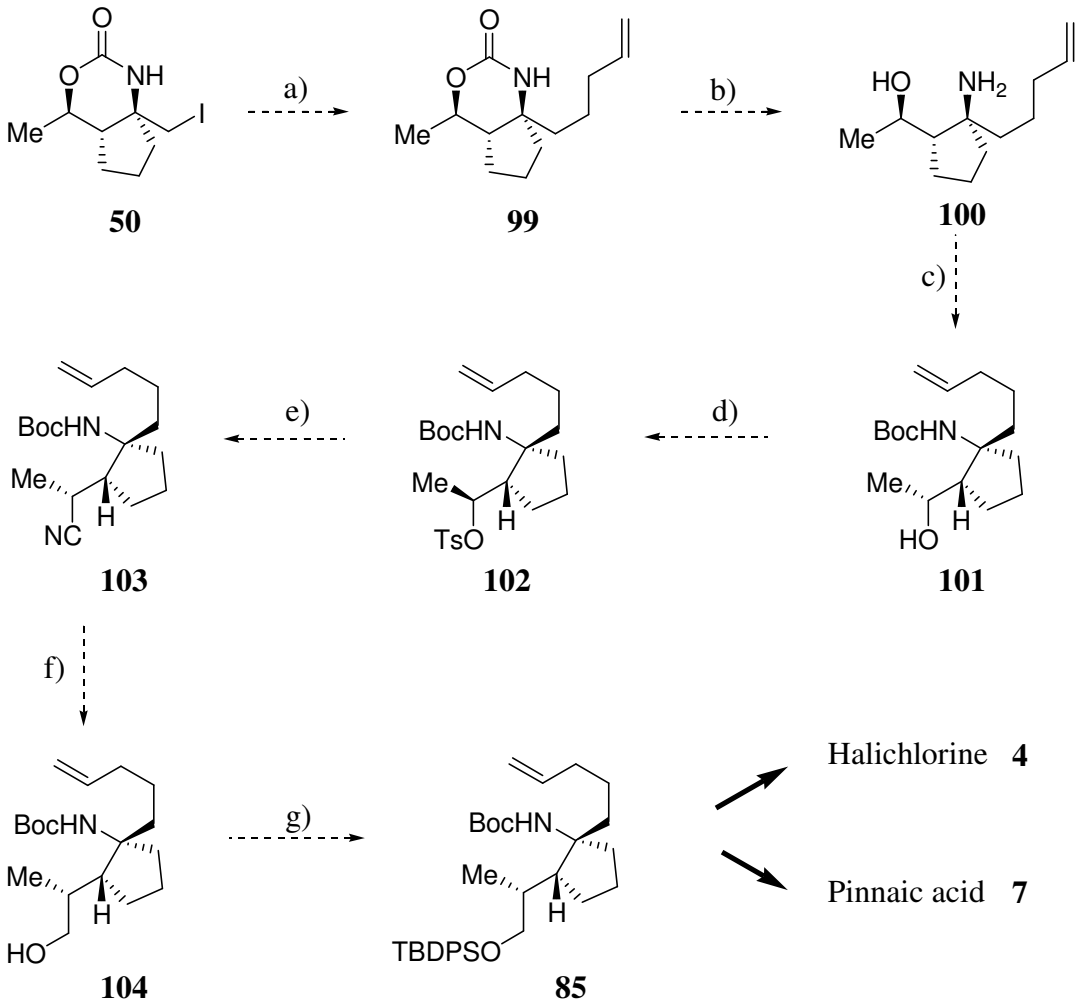
Starting material	Conditions	R	*trans*-**98**	*cis*-**98**	Total yield
trans-**97**	Allyltributyltin $BF_3.OEt_2$	allyl	83%	17%	95%
trans-**97**	Bu_2CuLi $BF_3.OEt_2$	Bu	29%	71%	68%
cis-**97**	Bu_2CuLi $BF_3.OEt_2$	Bu	74%	26%	85%

Table 12. Illustration of the influence of the organometallic in the S_N type displacement

6.3 Formal total synthesis avoiding the construction of the stereocenter in α-position to the N-atom of the heterocycle

6.3.1 The plan

It was not possible to build up the stereocenter in α-position to the N-atom having the desired configuration for the formal total synthesis of halichlorine **4** and pinnaic acid **7**. An alternative avoiding the construction of this stereocenter could take advantage of the formal total synthesis reported by the MARTIN´s group (Scheme 64).[15]



Scheme 64. Planed synthesis of the MARTIN´s intermediate

a) We have already shown that iodide **50** can be substituted by a cuprate; in this case we would have to use a cuprate with a homoallyl substituent to obtain alkene **99**.

b) At this stage the carbamate would have to be deprotected under strongly basic conditions to obtain the amino alcohol **100**.

c) Then the amino function of **100** should be converted into the corresponding Boc carbamate **101**.

d) The hydroxy group of **101** would have to be transformed into a good leaving group; tosylation should be a good choice. The tosylation should be carried out under modified MITSUNOBU conditions by using *p*-toluenesulfonic acid as a nucleophile. This should give tosylate **102**.[69]

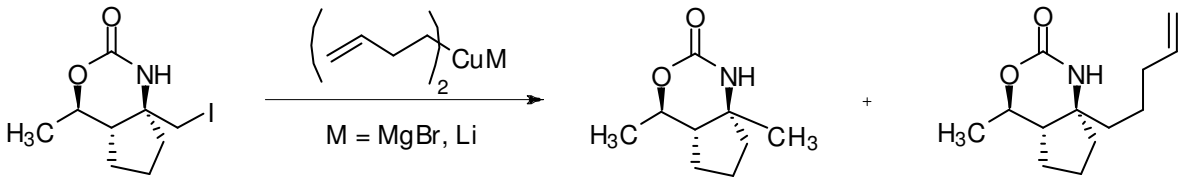
e) At this stage another inversion of configuration should be realized; it is known that cyanide substitution of secondary tosylates proceeds via an S_N2 mechanism. Nitrile **103** should result.

f) The nitrile function of **103** would have to be reduced to the corresponding primary alcohol **104**. The reduction should work with DIBAL-H in two steps with isolation of the intermediary aldehyde to avoid formation of the primary amine.[70]
g) The last step would be the silylation of alcohol **104** to obtain the corresponding TBDPS protected alcohol **85**, which has already been described by the MARTIN´s group.

The synthesis of **85** would represent a formal total synthesis of halichlorine **4** and pinnaic acid **7**.[15]

6.3.2 Results and discussion

The first step of the planed synthesis of **85** caused problems because the desired alkene **99** has never been the major product of the reaction (Scheme 65). Oxazinone **105** was always identified as the major product, whereas alkene **99** was only observed in small amounts according to the ^{1}H NMR spectra of the crude mixtures.



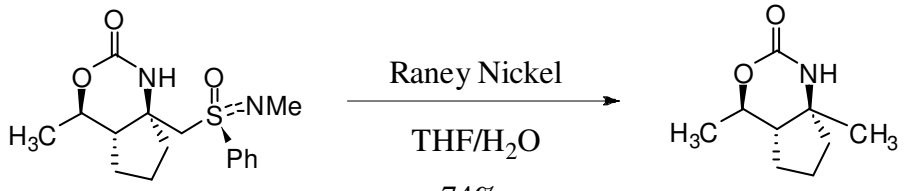
50

105
major product

99
not observed
or in only small
amounts

Scheme 65. Attempted substitution of the I-atom of **50** by a homoallyl group

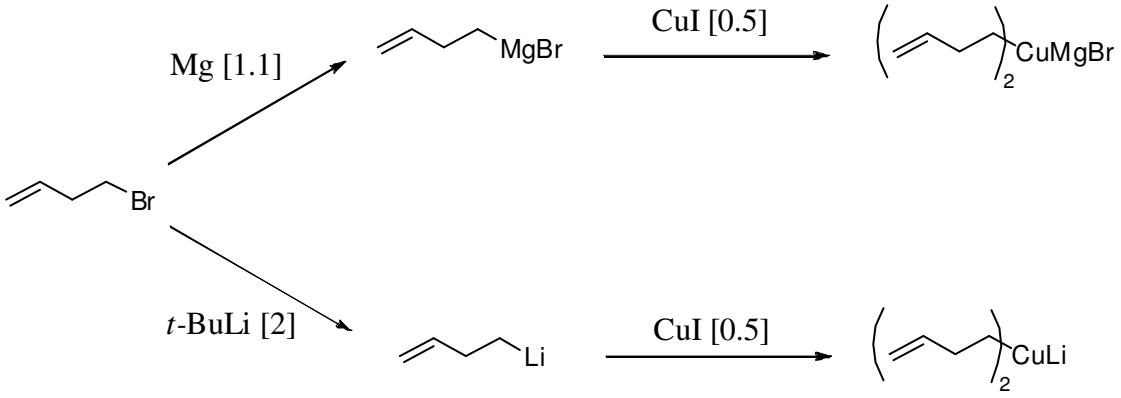
Since alkene **99** and oxazinone **105** could not be obtained in pure form, oxazinone **105** was synthesized by reduction of sulfoximine **29a** with RANEY nickel, in order to confirm the structure and obtain a full characterization (Scheme 66). Treatment of sulfoximine **29a** with freshly prepared RANEY nickel in THF/H_2O furnished oxazinone **105** in 74% yield.



Scheme 66. Reduction of sulfoximine **29a** with RANEY nickel

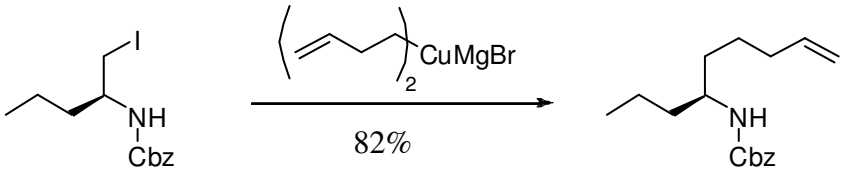
In order to exclude a mistake during the preparation of the cuprate, some titrations and tests were carried out. *t*-Butyllithium and homoallyllithium were titrated with diphenylacetic acid.[80] The freshly prepared homoallylmagnesium bromide was titrated using benzyl alcohol and phenantrolin.[81]

After preparation of the cuprates, a Gilman test using Michler´s ketone was carried out to make sure that no homoallyllithium or homoallylmagnesium bromide remained (Scheme 67).[82]



Scheme 67. Preparation of homoallylcuprates

Considering the example of TAKAHATA et al., it was quite surprising that the substitution of iodide **50** with homoallylcuprate failed (Scheme 68).[83]



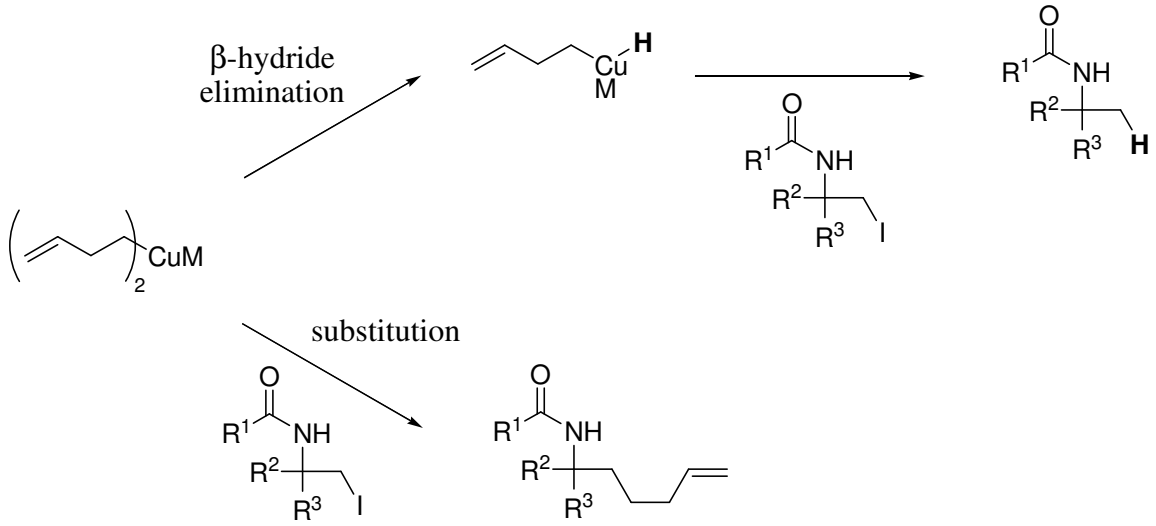
Scheme 68. Substitution of a primary iodide by homoallylcuprate by TAKAHATA et al.

It is known that alkylcuprates are less stable than alkenylcuprates, which is due to their ability to undergo a β-hydride elimination.

The difference between TAKAHATA´s results and ours results from a competition between two pathways: substitution and β-hydride elimination.

In TAKAHATA´s case, R^2 equals alkyl and R^3 equals H, whereas in the case of iodide **50** R^2 and R^3 equal alkyl. Iodide **50** is a hindered substrate and substitutions are known to be more difficult in those cases.

The reaction temperature has to be higher than for substrates having R^3 equals H. But, if the temperature increases, the chances for β-hydride elimination on the alkyl cuprate increase also. Homoallylcuprate undergoes a β-hydride elimination more easily than other alkylcuprates because of the formation of butadiene (Scheme 69).



Scheme 69. Competition between substitution and β-hydride elimination in the reaction of primary alkyliodides and alkylcuprates

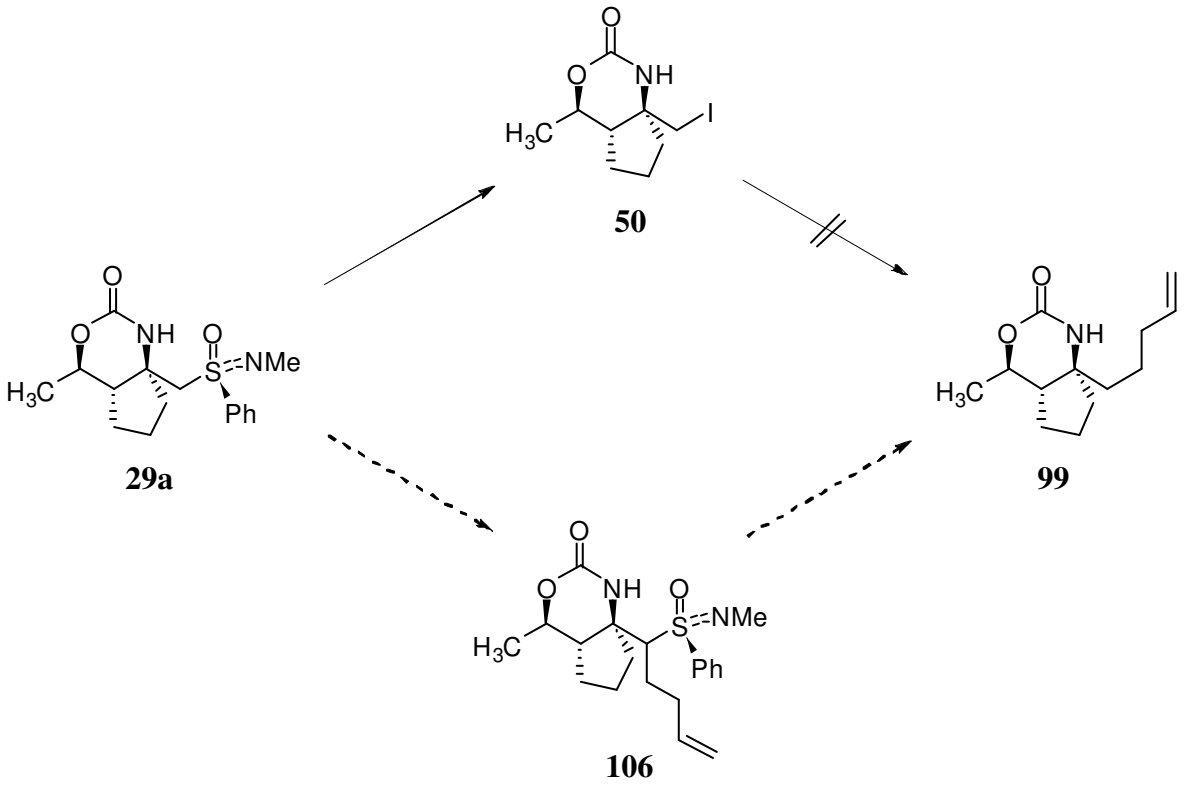
Moreover it is known that complex metal hydrides of copper react very well with alkyl halides to give the corresponding alkane (Scheme 70).[84] This could explain the isolation of the dehalogenated **105**.

Scheme 70. Reaction of complex metal hydrides of copper with alkyliodide

6.3.3 Using the double lithiation methodology

The reaction of doubly lithiated oxazinones with biselectrophiles was described previously (Chapter 4). By using this methodology the substitution of iodide **50** by homoallylcuprate could be avoided.

Only one experiment was carried out. Dilithiation of oxazinone **29a** with 2 equivalents of *n*-butyllithium followed by addition of homoallylbromide gave no conversion. The use of homoallyltosylate could perhaps give better results (Scheme 71).

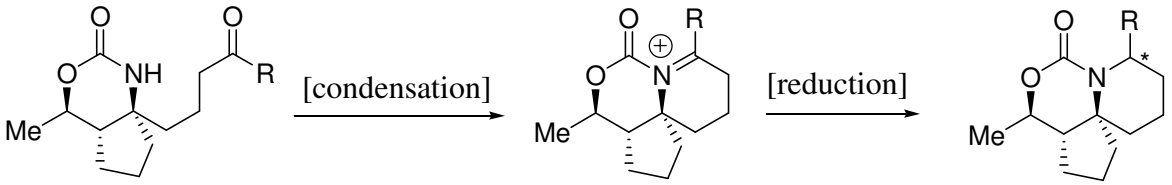


Scheme 71. Studies towards the synthesis of alkene **99**

6.4 Outlook

Another possibility for the construction of the stereogenic center in α-position to the N-atom of the heterocycle would be a route involving the reduction of an N-acyliminium ion (Scheme 72).

Such reactions are described in the literature using different reducing reagents like silanes or borohydrides.[85,86]



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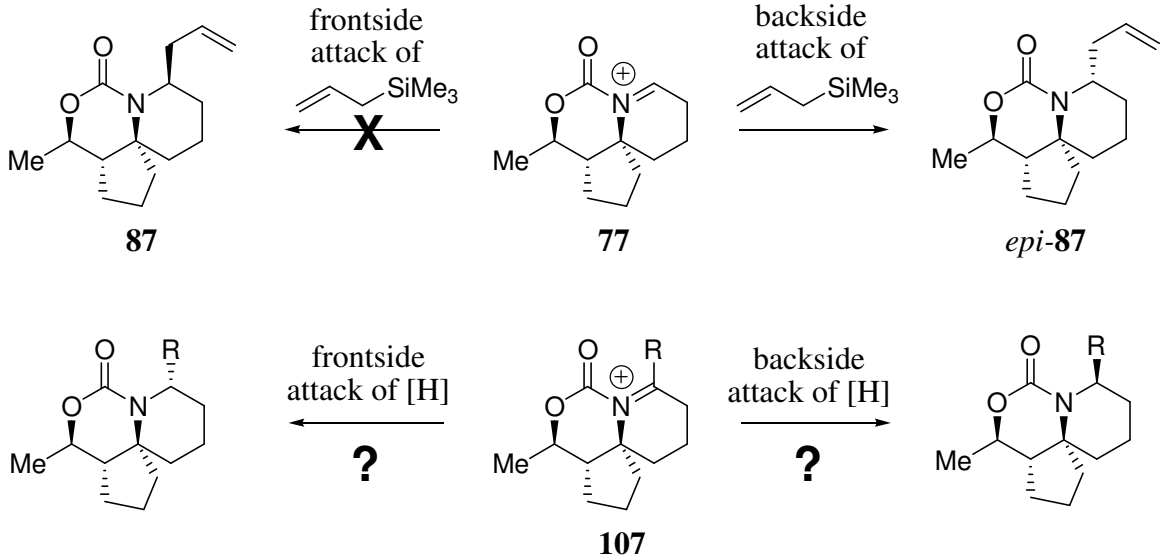
Scheme 72. A new route involving the reduction of N-acyliminium ion **107**

In the following explanations the terms *Si*-face and *Re*-face are not used, because they are different for **77** and **107**. The terms frontside and backside are preferred to enable an easier comparison (Scheme 73).

If the reaction works, which facial selectivity will be observed? In the case of the addition of allyltrimethylsilane to N-acyliminium ion **77**, the nucleophile attacks exclusively from the backside.

There is hope that in the case of N-acyliminium ion **107**, the reducing agent will also prefer to attack from the backside, so that the desired configuration could be obtained.



87 **77** ***epi*-87**

107

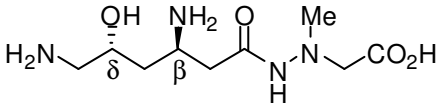
Scheme 73. Comparison between the addition to iminium ion and the reduction of iminium ion in regard to the stereochemistry

7. Synthesis of protected δ-hydroxy-β-amino acids

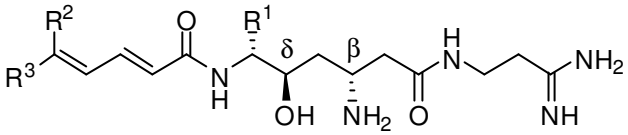
7.1 Introduction to β-amino acids

7.1.1 Importance of β-amino acids

Proteinogenic α-amino acids are constituents of all enzymes which control the metabolism in living matter and are thus an essential prerequiste for life. In contrary, most β-amino acids only occur as constituents of distinct natural products, such as peptides, alkaloids or terpenoids. These compounds are often characterized by potent biological and physiological activities that are crucially based on their β-amino acid substructures. As a consequence, many natural products with a β-amino acid moiety are potential lead structures for the development of new drugs.[87]



108



109

A: R^1=H, R^2=Me, R^3=H
B: R^1=H, R^2=H, R^3=Me
C: R^1=Me, R^2=Me, R^3=H
D: R^1=Me, R^2=H, R^3=Me

Figure 26. Negamycin **108** and the sperabillins **109**

We are particulary interested in δ-hydroxy-β-amino acids. Negamycin **108** and the sperabillins A-D **109** are natural products, which show a δ-hydroxy-β-amino acid subunit (Figure 26).[87]

Negamycin **108** is an unusual hydrazido dipeptide which was isolated in 1970 from *Streptomyces purpeofuscus* and shows activity against multiple drug resistant bacteria by inhibition of the procaryotic protein biosynthesis with miscoding activity.

Sperabillins A-D **109** were isolated from cultures of the bacterium *Pseudimonas fluorescens YK-473*, and are effective against several bacteria including antibiotic resistant ones.

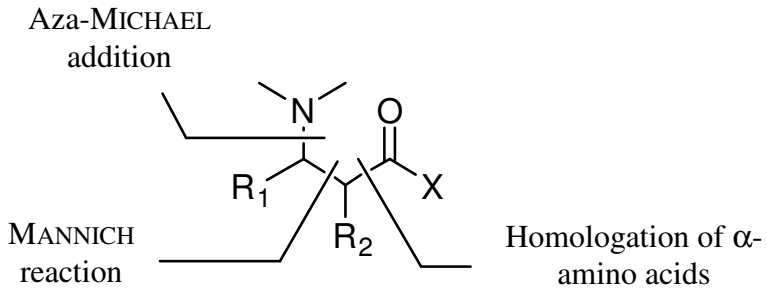
7.1.2 Retrosynthesis of β-amino acids

Because of the importance of β-amino acids a number of synthetic approaches has been developed. There are three general strategies for their construction (Scheme 74).[87]

The first one is the MICHAEL addition of a N-nucleophile. A chiral information can be introduced via the N-nucleophile (e. g. chiral lithium amide), via a chiral MICHAEL system (e. g. EVANS auxiliary strategy) or via a chiral catalyst (e. g. TADDOL).

The second general method is the MANNICH reaction, which can be carried out stereoselectively by using chiral imines or chiral enolates. The use of a chiral catalyst is an efficient method, for example a chiral LEWIS acid (e. g. BOX ligand and copper) or a chiral organocatalyst (e. g. proline).

The last approach is the homologation of α-amino acids like the ARNDT-EISTERT reaction or the use of cyanohydrins. In this case the chiral information is derived from the α-amino acid.



Scheme 74. Retrosynthetic approaches to the synthesis of β-amino acid subunits

These three methods are the most general ones. Of course a lot of further synthetic approaches have been developed in the last decades opening an access to various target systems.

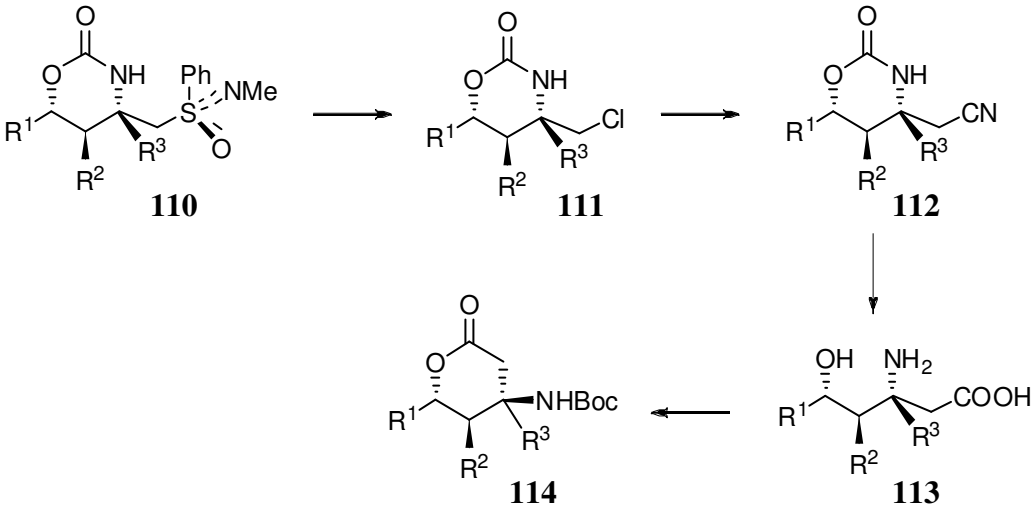
7.2 Toward a selective protection of δ-hydroxy β-amino acids

7.2.1 Methodology developed by GAIS et al.

The approach should take advantage of the methodology developed by Gais and co-workers (Scheme 75).[17,18,51] The route involves a facile substitution of the sulfoximine group of **110** by a chlorine atom to give β-aminochlorides of type **111**. Then the introduction of a cyano group

was achieved through treatment of **111** with KCN, which gave the corresponding β-amino nitriles **112** in very good yield. Finally hydrolysis of **112** followed by Boc-protection of **113** afforded lactones of type **114**.

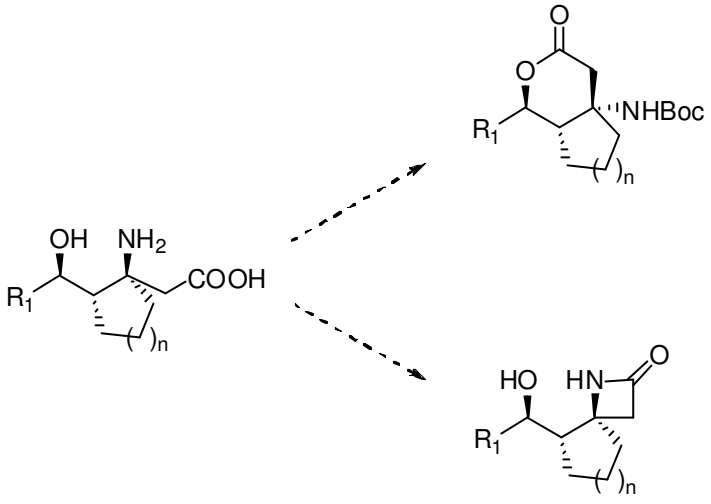
This method works well for acyclic and for cyclic (R^2---R^3) substrates.



Scheme 75. Strategy towards protected β-amino acids of type **114** by the GAIS group

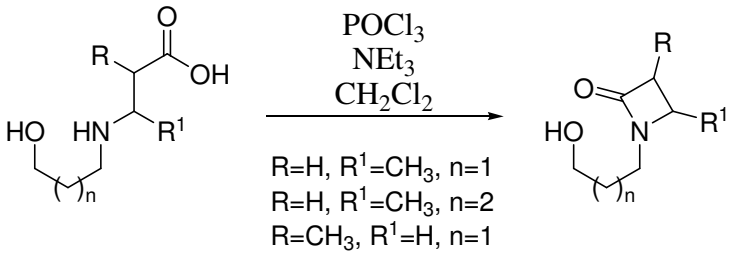
7.2.2 The plan

We were interested in the possibility to protect the amino acid part of **113** as a β-lactam in the presence of the hydroxy group. This would be an entry to functionalized spirocyclic β-lactams (Scheme 76).



Scheme 76. Lactone vs. lactam

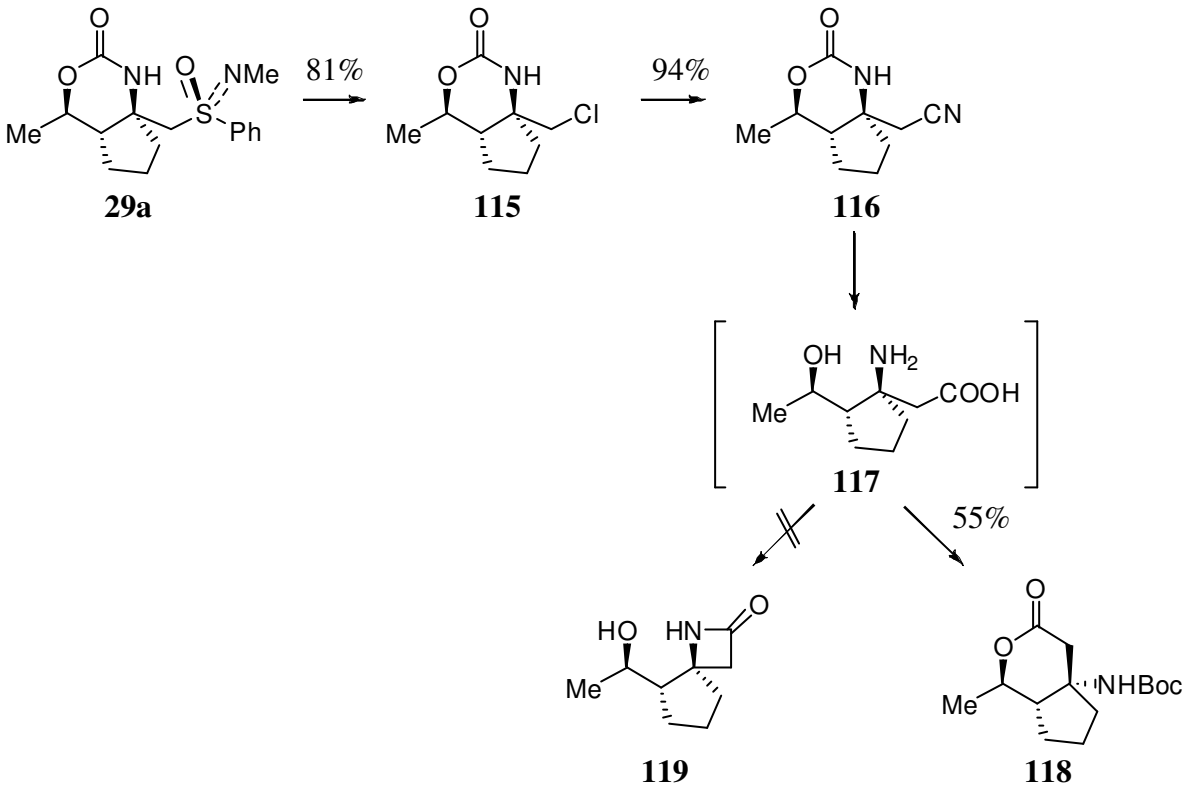
SHARMA et al. described the synthesis of monocyclic β-lactams via cyclodehydration of β-amino acids incorporating a hydroxy group using $POCl_3$ (Scheme 77).[88]



Scheme 77. SHARMA´s approach to β-lactams

7.3 Results

Substitution of the sulfoximine group of **29a** led to the β-amino chloride **115**. Replacement of the chlorine atom by cyanide gave the β-amino nitrile **116**. Hydrolysis of **116** under basic condition afforded the unprotected β-amino acid **117**. Boc-protection and cyclization of **117** gave the desired Boc-protected aminolactone **118** in good yield. Unfortunately the synthesis of β-lactam **119** via a cyclodehydration reaction did not succeed.



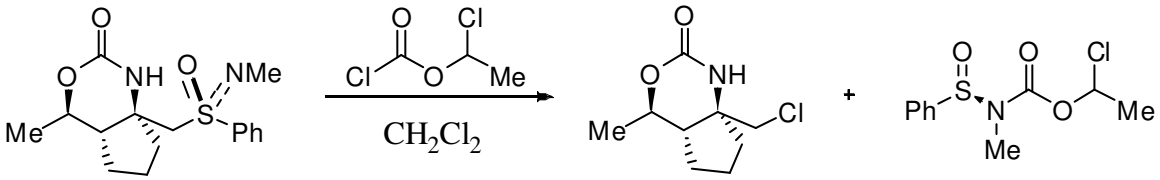
Scheme 78. Attempted selective protection of the δ-hydroxy β-amino acid **117**

In the following chapters the synthesis of **118** and the attempted synthesis of **119** will be discussed in detail.

7.3.1 Substitution of the sulfoximine group by a chlorine atom

The first step was the substitution of the sulfoximine group of **29a** by a chlorine atom. The nitrogen atom of the sulfoximine group was acylated, then the liberated chlorine atom underwent a substitution reaction with the activated aminosulfoxonium salt giving the desired chloride **115** (Scheme 79).

It has already been shown by Gais et al. that chiral auxiliary **15** can be recovered enantiomerically pure in good yields from sulfinamide **55**.[42]



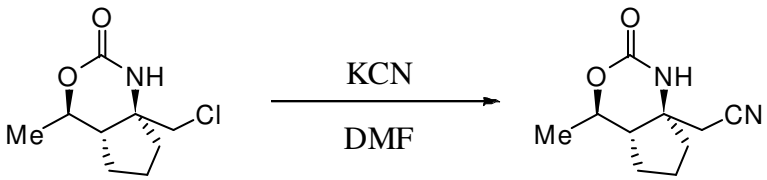
29a **115:** 81% **55**

Scheme 79. Chlorine substitution of sulfoximine **29a**

7.3.2 Substitution of the chlorine atom by cyanide

The second step was the substitution of the chlorine atom of **115** by cyanide. This reaction worked well, nitrile **116** was obtained from chloride **115** in 94% yield (Scheme 80).[18,27]

Earlier KÖHLER investigated the "direct" substitution of sulfoximines similar to **29a** by cyanide but he did not succeed.[89]

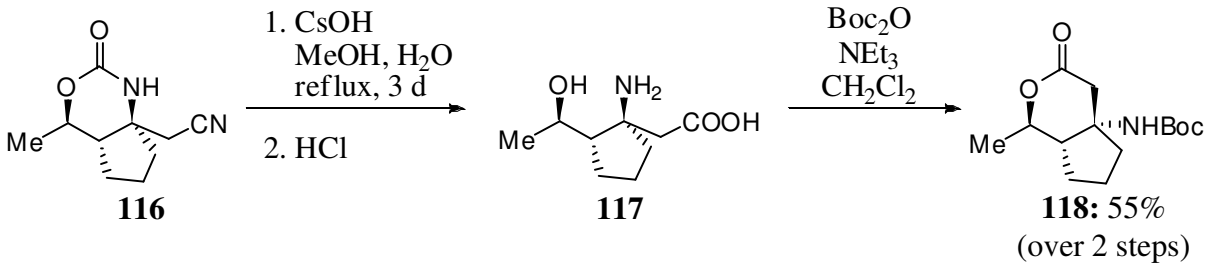


115 **116**: 94%

Scheme 80. Cyanide substitution of chloride **115**

7.3.3 Cyclization to the lactone

Under highly basic conditions both the nitrile function of **116** and the cyclic carbamate were hydrolyzed under formation of the hydroxyl substituted amino acid. After neutralization the unprotected δ-hydroxy β-amino acid **117** was isolated. Treatement of **117** with Boc-anhydride in the presence of triethylamine afforded Boc-protection of the amino function and the activation of the carboxy group, which led to cyclization with formation of lactone **118**.

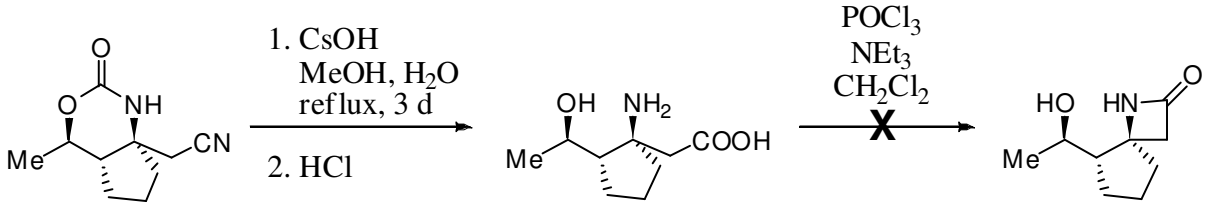


116 **117** **118:** 55% (over 2 steps)

Scheme 81. Cyclization to the Boc-protected lactone **118**

7.3.4 Cyclization to the β-lactam

When unprotected δ-hydroxy-β-amino acid **117** was treated with $POCl_3$ in the presence of triethylamine, which are the conditions SHARMA et al. used for their cyclodehydration, no lactame **119** was formed. The unprotected amino acid **117** could partly be recovered.



116 **117** **119**

Scheme 82. Attempted cyclization of amino acid **117** to the β-lactam **119**

8. Synthesis of cycloalkenyl oxiranes

8.1 Introduction to vinyl oxiranes

8.1.1 Vinyl oxiranes as structural element in natural products

Vinyl oxiranes are found as structural element in natural products, for example in (+)-posticlure **120** and in leukotriene A_4 (LTA_4) **121** (Figure 27).

(+)-Posticlure **120** is a novel trans-epoxide pheromone from the virgin females of the tussock moth *Orgyia postica*.

Leukotrienes are a family of biologically active metabolites of arachidonic acid known to play a role in a number of different pathophysiological processes. Leukotriene A_4 (LTA_4) **121** is a chemically reactive conjugated triene epoxide product derived from 5-lipoxygenase oxygenation of arachidonic acid.

Figure 27. Examples of natual products having a vinyl epoxide building block

8.1.2 Vinyl epoxides as interesting starting materials for further transformations

Vinyl epoxides are useful electrophiles which can react with a range of nucleophiles. Since they are a subset of allylic electrophiles, nucleophilic substitutions can take place through S_N2 and $S_N2´$ attack, and the ability to control the regioselectivity is critical (Figure 28).

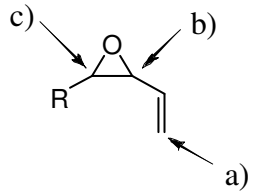
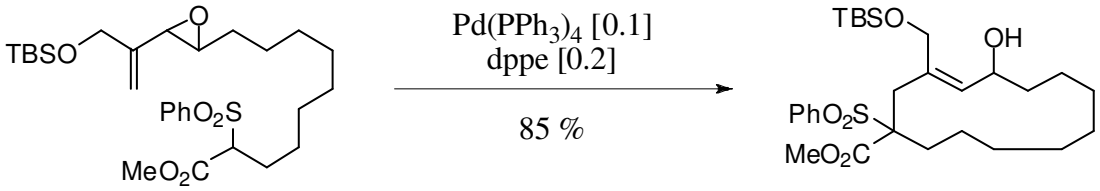


Figure 28. Positions for nucleophilic attack on vinyl epoxides

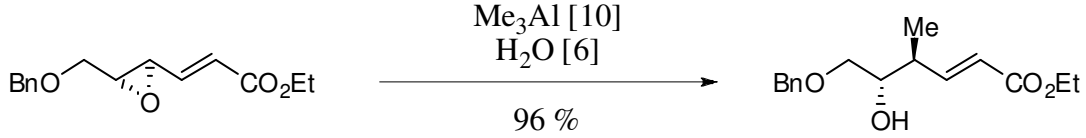
Normally, soft nucleophiles prefer the $S_N2´$ reaction variant via route a), while hard ones participate in the S_N2 attack at the allylic position via route b), although several exceptions are known. During these nucleophilic attacks the vinyl moiety acts as a regiochemical directing element, and attack following route c) is usually not observed. As the epoxide moiety is a small strained-ring system, it is perhaps not surprising that vinyl oxiranes participate in several useful rearrangement reactions.

1,4-Additions ($S_N2´$ pathway) of carbon nucleophiles to vinyl epoxides are well documented and can be accomplished by several different techniques. Palladium-catalyzed allylic alkylation of these substrates with soft carbon nucleophiles (pK_a 10–20) proceeds under neutral conditions and with excellent regioselectivities. For example cyclization of the sulfone using catalytic amounts of $Pd(PPh_3)_4$ and bis(diphenylphosphino)ethane (dppe) under high dilution conditions gives the corresponding macrocycle which is an intermediate in a total synthesis of the antitumor agent roseophilin (Scheme 83).



Scheme 83. Example for $S_N2´$ pathway

The S_N2 reaction alternative is often the major pathway when hard nucleophiles are employed. γ,δ-Epoxy acrylates can be opened regio- and stereselectively at the γ-position with $AlMe_3/H_2O$. This method has been used for iterative construction of polypropionate chains and tertiary stereocenters (Scheme 84).



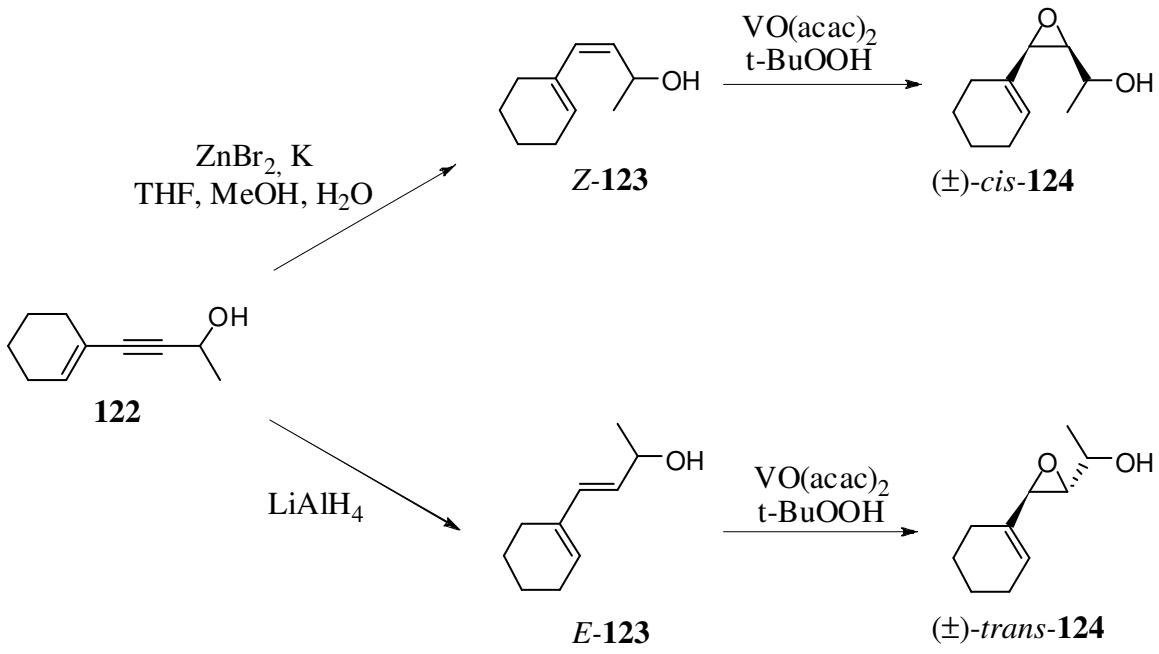
Scheme 84. Example for S_N2 pathway

8.2 Introduction to cycloalkenyl oxiranes

Chiral vinyl oxiranes are valuable intermediates in organic synthesis. Their asymmetric synthesis has been accomplished by several methods, including the epoxidation of allylic alcohols in combination with an oxidation and olefination, the epoxidation of dienes, the chloroallylation of aldehydes in combination with 1,2-elimination, and reactions between sulfur ylides and aldehydes. Although some of these methods are very efficient for the synthesis of alkenyl oxiranes, all of them fail for the preparation of cycloalkenyl oxiranes. There are only a few examples of diastereoselective and enantioselective syntheses of cycloalkenyl oxiranes in the literature.

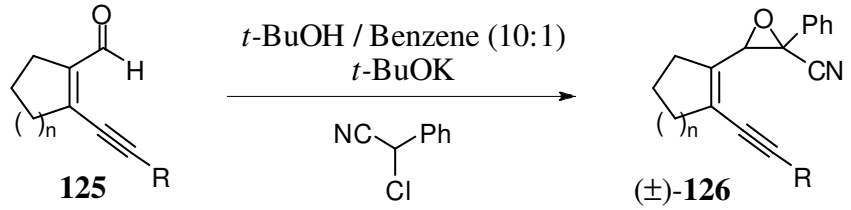
8.2.1 Diastereoselective syntheses of cycloalkenyl oxiranes

WHITE et al. published in 1990 the diastereoselective syntheses of *cis*- and *trans*-vinyl epoxides from enynols, and in one case the method was applied to a cyclic system (Scheme 85). Reaction of **122** with the highly activated RIEKE zinc provided dienol *Z*-**123** having a *Z* double bond. Reduction of **122** with $LiAlH_4$ gave dienol *E*-**123** having an *E* double bond. The allylic double bonds of dienols *Z*-**123** and *E*-**123** were selectively epoxidized using $VO(acac)_2$ and *t*-BuOOH to yield epoxyalcohols (±)-*cis*-**124** and (±)-*trans*-**124**, respectively.[90]



Scheme 85. Diastereoselective syntheses of cycloalkenyl oxiranes by WHITE et al.

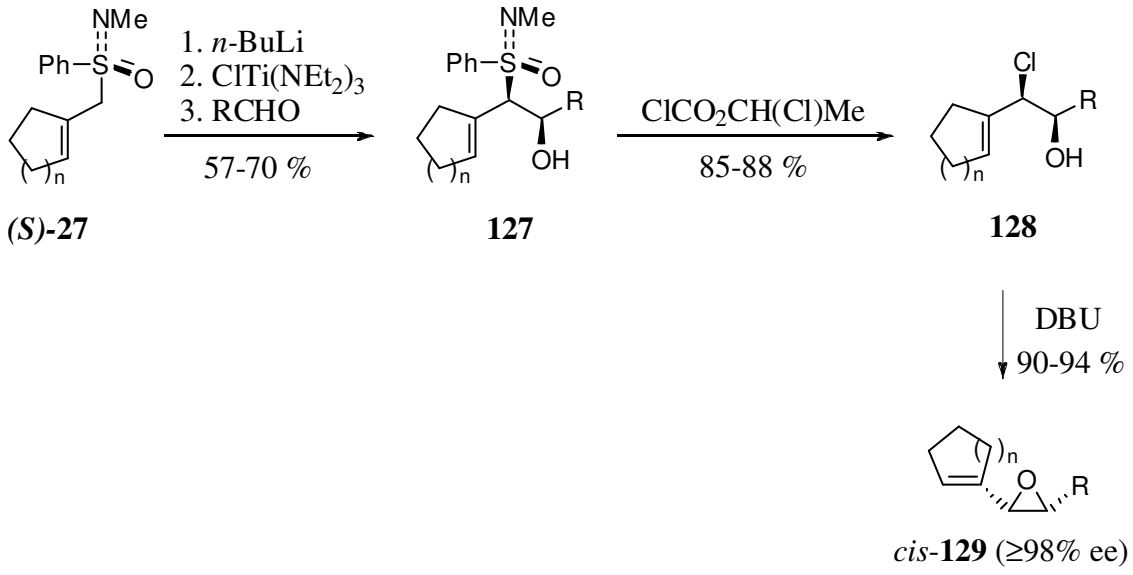
EBERBACH et al. developed a DARZEN condensation of aldehyde **125**, which afforded oxirane **126** with exclusively or predominant *trans*-arrangement of the phenyl and cycloalkene groups (Scheme 86).[91]



Scheme 86. DARZEN condensation to cycloalkenyl epoxides by EBERBACH et al.

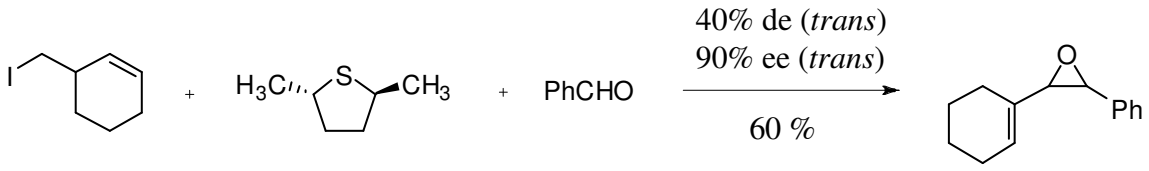
8.2.2 Enantioselective syntheses of cycloalkenyl oxiranes

GAIS et al. published the synthesis of cycloalkenyl oxiranes in three steps from cyclic allylic sulfoximines. Treatment of derivatives of cyclic allylic sulfoximines of type *(S)*-**27**, bearing a tris(diethylamino)titanium group in the α-position, with aldehydes gave the sulfoximine-substituted homoallylic alcohols **127** with high regio- and diastereoselectivity. The sulfoximine group of **127** could be stereoselectively replaced by a Cl-atom with formation of the corresponding chlorohydrins **128**, which upon base treatment gave cycloalkenyl oxirane *cis*-**129**. The epoxides were enantio- and diastereomerically pure (Scheme 87).[42]



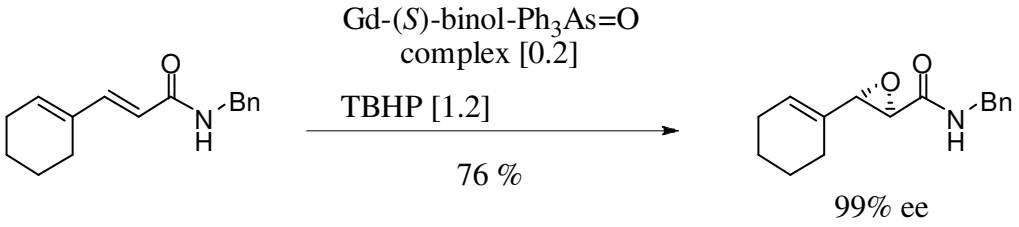
Scheme 87. Asymmetric synthesis of *cis*-cycloalkenyl oxiranes by GAIS et al.

METZNER et al. reported a one-pot epoxidation reaction in which a chiral sulfide, an allyl halide, and an aromatic aldehyde were allowed to react to give a *trans*-vinyl epoxide. This is an efficient approach, as the sulfonium salt is formed and deprotonated in situ to afford the corresponding ylide, which reacts with the aldehyde. They published only one cyclic example: the *trans*-product was isolated in moderate yield, moderate diastereoselectivity and very good enantioselectivity (Scheme 88).[92]



Scheme 88. Asymmetric synthesis of *trans*-cycloalkenyloxiranes using sulfur ylides and aldehydes by METZNER et al.

SHIBASAKI et al. published the regioselective catalytic asymmetric epoxidation of α,β,γ,δ-unsaturated amides with the Gd-(*S*)-binol-Ph_3As=O complex. Only one cyclic example was reported, but yield and enantioselectivity are good and very good, respectively (Scheme 89).[93]

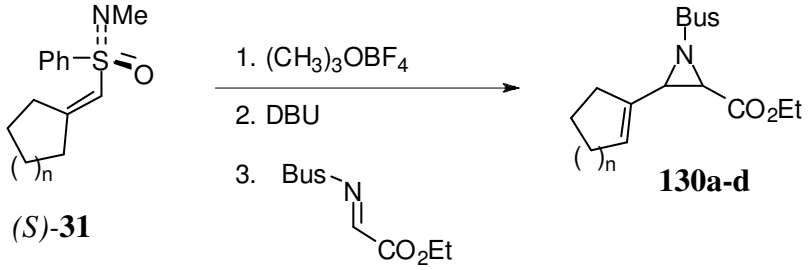


Scheme 89. Catalytic asymmetric epoxidation of α,β,γ,δ-unsaturated amides by SHIBASAKI et al.

8.3 REDDY´s synthesis of cycloalkenyl aziridines

In the GAIS group REDDY described the synthesis of cycloalkenyl aziridines from cyclic vinylic sulfoximines *(S)*-**31** (Scheme 90).[25]

He was able to synthesize cycloalkenyl aziridines as *cis*/*trans* mixtures in good yield and enantioselectivity (Table 13).



Scheme 90. Synthesis of cycloalkenyl aziridines from vinylic sulfoximines

Table 13. REDDY´s results concerning the synthesis of cycloalkenyl aziridines

n	Product	Yield (cis+trans)	cis:trans (de)	ee_{cis}	ee_{trans}
1	**130a**	70%	60:40 (20%)	79%	90%
2	**130b**	73%	60:40 (20%)	76%	56%
3	**130c**	71%	60:40 (20%)	78%	57%
4	**130d**	66%	50:50 (0%)	70%	25%

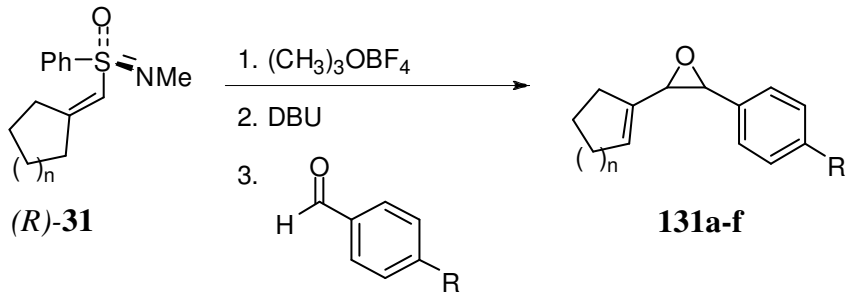
Using REDDY´s procedure it should be possible to synthesize cycloalkenyl oxiranes by replacing the iminoester with aldehydes.

8.4 Synthesis of cycloalkenyl oxiranes

Treatment of the cyclic vinyl sulfoximines **31** with MEERWEIN reagent (Me_3OBF_4) and reaction with aldehydes in presence of DBU led to cyclic alkenyloxiranes **131a-f**.

The reaction was carried out with different vinyl sulfoximines and aldehydes. The cycloalkenyl oxiranes **131a-f** were isolated in moderate yields, high diastereoselectivity and low enantioselectivity (Table 14).

Table 14. Synthesis of cycloalkenyl oxiranes from aldehydes and cyclic vinyl sulfoximines



(R)-**31** **131a-f**

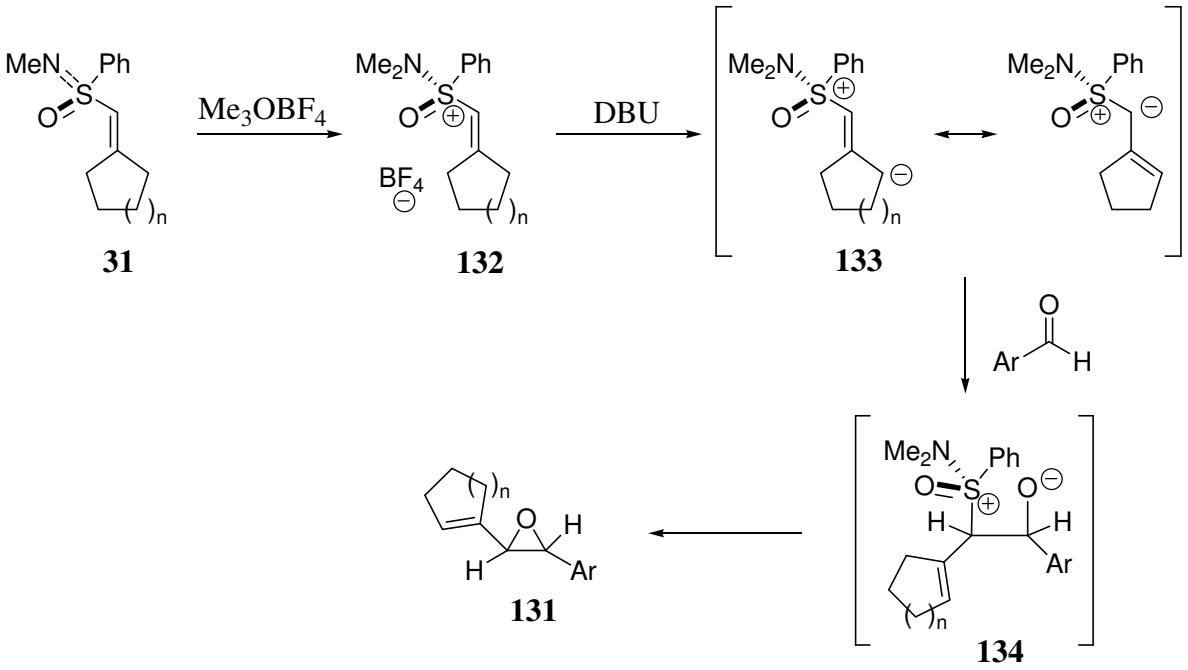
Product	n	R	Yield (cis+trans)	dr (de)	er_{trans} (ee_{trans})
131a	1	H	42%	94:6 (88%)	66 :34 (32%)
131b	2	H	44%	91:9 (82%)	60:40 (20%)
131c	1	Br	27%	93:7 (86%)	63:37 (26%)
131d	2	Br	33%	93:7 (86%)	57:43 (14%)
131e	1	NO_2	34%	94:6 (88%)	66:44 (22%)
131f	2	NO_2	38%	94:6 (88%)	55:45 (10%)

8.5 Discussion

8.5.1 Mechanism

According to REDDY´s work about the cycloalkenyl aziridines, the first step should be the activation of the N-methyl sulfoximine group of the vinyl sulfoximines **31** with MEERWEIN reagent leading to the corresponding (dimethylamino)sulfoxonium salts **132**.[25]

Upon treatment with DBU the salt **132** is deprotonated to generate the corresponding cyclic aminosulfoxonium ylides **133**, which can react with aldehydes via an addition/ring-closing mechanism to give the desired cycloalkenyl oxiranes **131** (Scheme 91).



Scheme 91. Possible mechanism for the formation of cycloalkenyl oxiranes **131** from vinyl sulfoximines and aldehydes

8.5.2 Rationalization of the stereoselectivity outcome

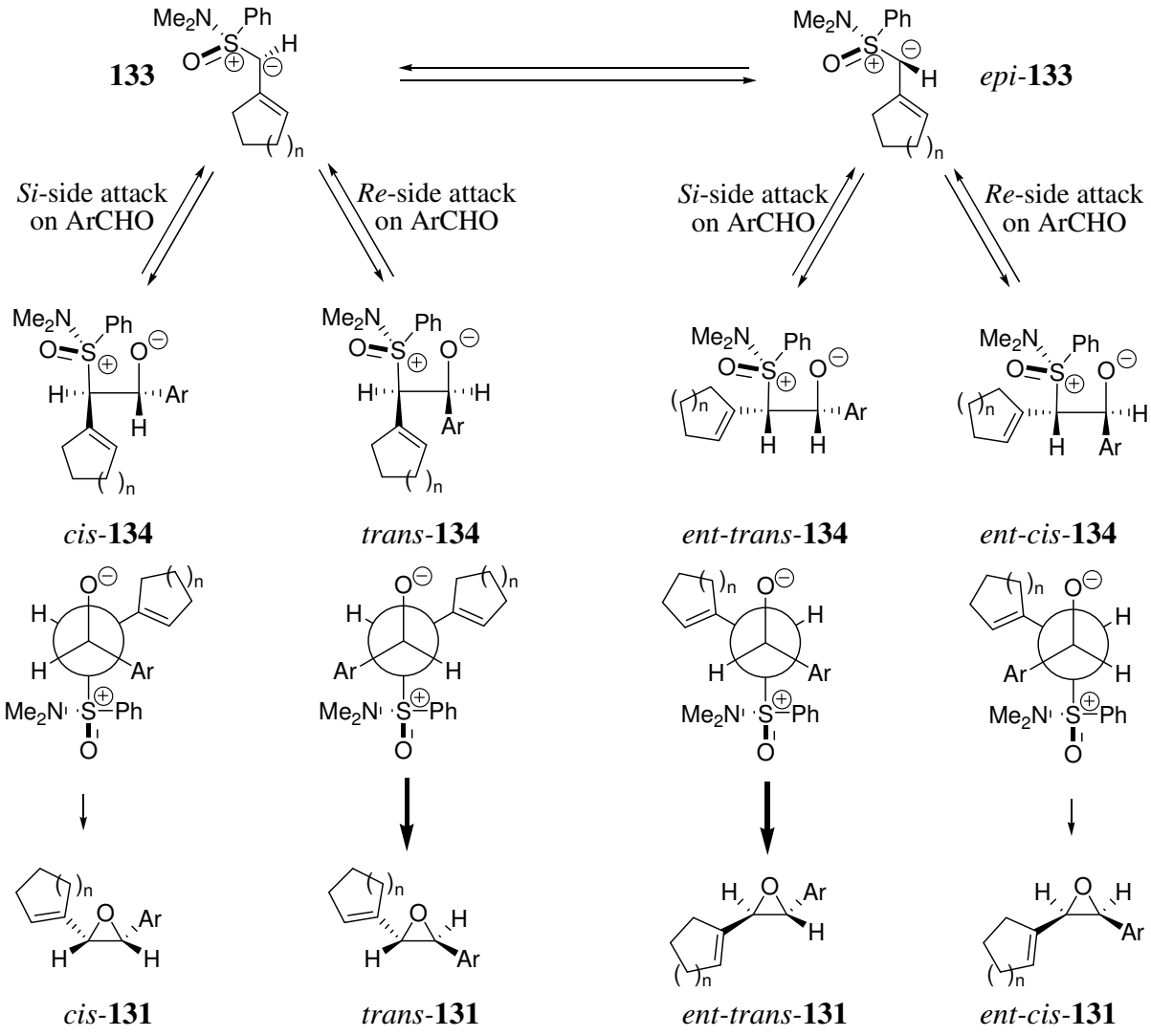
It was assumed that the allylic aminosulfoxonium ylides are not configurationally stable in regard to the center in α-position to the sulfur atom, so that both epimers **133** and *epi*-**133** are in fast equilibrium (Scheme 92). The first step is the addition of the ylide to the aldehyde, which occurs from the *Si*-side or from the *Re*-side of the aldehyde. Reaction of **133** and *epi*-**133** with an aldehyde leads to four theoretically possible betaines *trans*-**134**, *ent-trans*-**134**, *cis*-**134**, *ent-cis*-**134**. This step is reversible so that the betaines are in equilibrium with the ylides. At this stage a new C–C bond is created, only the ring-closure is missing.

According to the literature the ring-closure of alcoholates with a leaving group in α-position should proceed via a S_N2 mechanism. The two bulky groups, the aromatic ring derived from the aldehyde and the cycloalkenyl group derived from the vinyl sulfoximine, seem to play key roles. A closer look to the NEWMAN projections, having the nucleophile and the leaving group in *anti* orientation shows that in *trans*-**134** and *ent-trans*-**134** these two bulky groups are also in *anti* orientation, whereas in the case of *cis*-**134** and *ent-cis*-**134** they are in *gauche* orientation. Therefore it seems likely that the cyclization of *trans*-**134** and *ent-trans*-**134** is

thermodynamically more favored than the cyclization of *cis*-**134** and *ent-cis*-**134**, which is supposed to have a transition state higher in energy.

Cyclization of *trans*-**134** and *ent-trans*-**134** gives oxiranes *trans*-**131** and *ent-trans*-**131**, respectively, whereas cyclization of *cis*-**134** and *ent-cis*-**134** gives oxiranes *cis*-**131** and *ent-cis*-**131**, respectively.

Unfortunately, the reaction gives only poor enantioselectivity. This can be explained with a very low discrimination during the attack of the ylide to the aldehyde.



Scheme 92. Attempted rationalization of the stereoselectivity

8.6 Conclusion and outlook

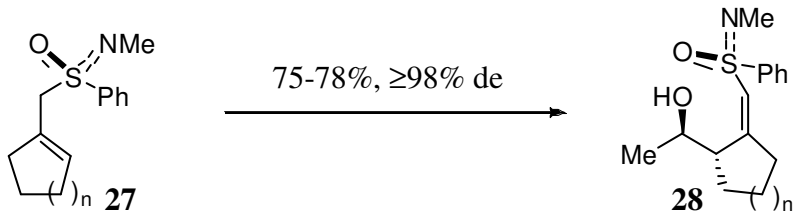
Cycloalkenyl oxiranes are interesting building blocks but the methodologies to synthesize them are limited. A highly diastereoselective synthesis of cycloalkenyl oxiranes was achieved, unfortunately the enantioselectivity was poor and the yields low.

Yields and enantioselectivity might be improved by the use of other vinyl sulfoximines having a different group at the nitrogen atom, which would change the bulkyness and/or the polarity.

9. Conclusion and outlook

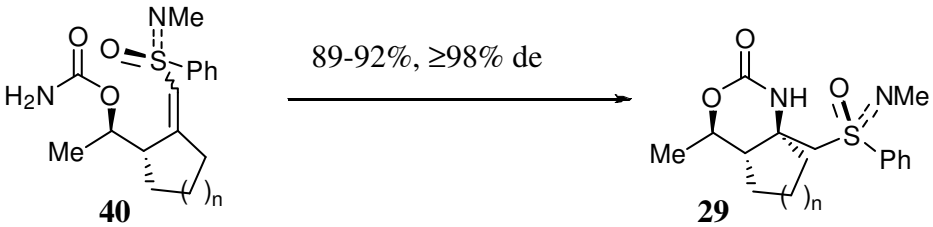
In summary a modular asymmetric synthesis of azaspirocycles using the sulfoximine group as a chiral auxiliary has been developed. A range of azaspirocycles showing flexibility in the ring sizes, as well as in the choice of the substituents were synthesized.

An efficient, modular and diastereoselective strategy for the synthesis of the carbocycle using the titanium-mediated γ-hydroxyalkylation as a key step was developed. Cyclic allylic sulfoximines **27** were transformed into homoallylic alcohols of type **28** while constructing two new stereogenic centers and a double bond (Scheme 93).



Scheme 93. Titanium-mediated γ-hydroxyalkylation

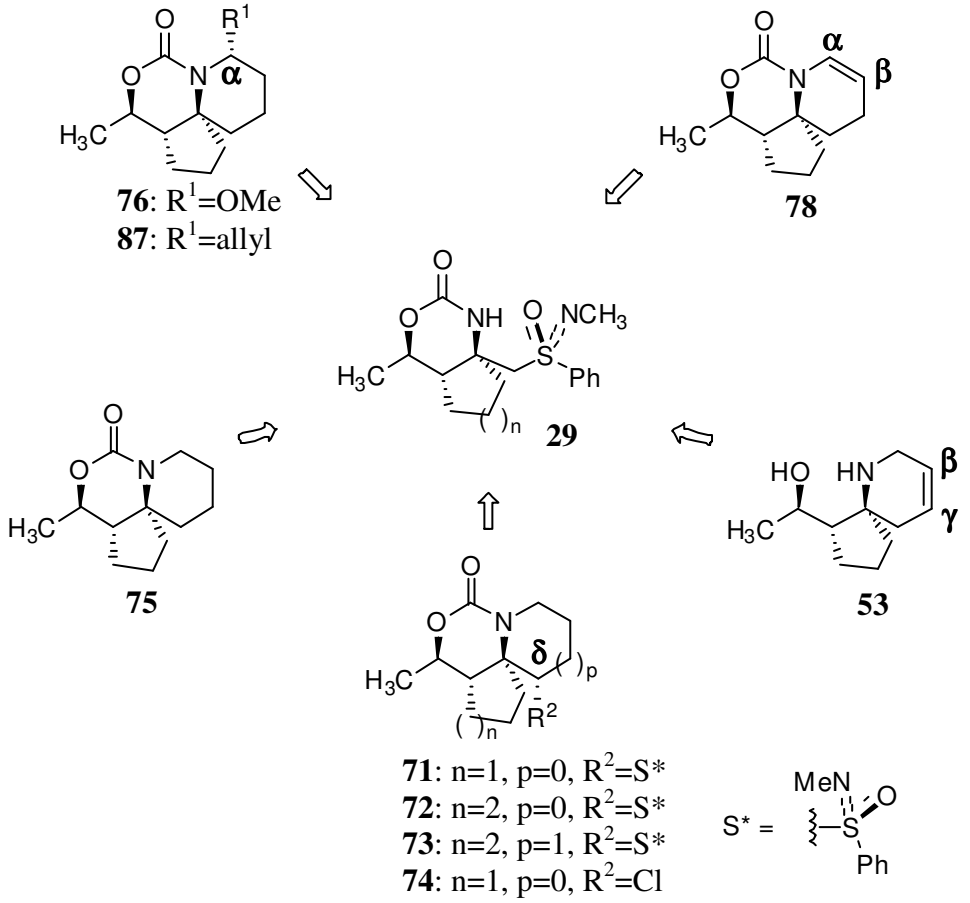
The key step for the installation of the tertiary carbon atom bearing the amino group is based on the use of chiral vinyl sulfoximines as Michael acceptors. The intramolecular aza-MICHAEL addition led to diastereomerically pure oxazinones of type **29** in high yields (Scheme 94).



Scheme 94. Intramolecular aza-MICHAEL addition

Having achieved an efficient synthesis of functionalized carbocycles **29**, which contain three contiguous stereogenic *C* atoms, we focused on the synthesis of the heterocycle. A modular

route to the heterocycle which permitted flexible control of the ring size and substitution pattern could be developed (Scheme 95).



Scheme 95. Modular construction and functionalization of the heterocycle

Synthesis of azaspirocycle **53** having functionalization at the β,γ-position was achieved by ring-closing metathesis.

Using the N-acyliminium ion strategy we were able to synthesize **76**, **78**, and **87** having functionalities at the α and α,β-position.

Cycloalkylation reactions permitted the synthesis of **71**, **72**, **73**, **74** having a variety of substituents at the δ-position, as well as the synthesis of the unfunctionalized azaspirocycle **75**.

An attempt was made to extend this methodology to the synthesis of the azaspirocyclic core of halichlorine **4** and pinnaic acid **7**. Three different approaches were investigated, however these routes were unsuccessful and work is on-going. In one instance, the desired C-C bond forming reaction proceeded but led to the undesired diastereoisomer. As the synthesis of azaspirocycles developed here is very modular, an alternate route could be in theory be easily investigated.

In conclusion the chemistry described here opens a broad avenue for the stereoselective preparation of highly substituted azaspirocycles, being of interest for the synthesis of natural products and derivatives thereof.

B. Experimental Part

1. General remarks

GENERAL INFORMATIONS

All the synthetic operations including reactions, work-ups and chromatographic separations were carried out in a well ventilated hood according to the current safety regulations.
All reactions involving air- or moisture sensitive compounds were carried out under argon using SCHLENK and vacuum line techniques. The glassware employed for those manipulations was oven-dried, and then cooled under argon. Reagents and solvents were transferred under argon using cannulae or syringes.[94]

SOLVENTS

Solvents used for moisture-sensitive reactions were dried and purified according to the standard techniques or purchased from commercial suppliers.[95]

- CH_2Cl_2 was distilled from CaH_2 under argon.
- THF was predried with KOH, filtered through basic Al_2O_3 (2 times) and distilled from sodium-benzophenone under argon.
- Toluene was distilled from sodium under argon.
- DMF was purchased from commercial suppliers (<50 ppm H_2O).
- MeOH was purchased from commercial suppliers (HPLC quality) and stored over molecular sives 4Å.
- Acetone was purchased from commercial suppliers (HPLC quality).

Ethyl acetate (EtOAc), diethyl ether (Et_2O), *n*-hexane, cyclohexane and *n*-pentane for column chromatography were distilled before use. Isopropanol (*i*-PrOH) and methanol (MeOH) were purchased from commercial suppliers (HPLC quality) for column chromatography.

REAGENTS

All reagents were purchased from commercial suppliers and were used without purification, except $ClTi(O\textit{i}\text{-}Pr)_3$, which was distilled prior to use.
Organolithium reagents and GRIGNARD reagents were titrated with diphenylacetic acid and benzylalcohol/phenantrolin, respectively.[80,81]

NMR SPECTRA

NMR spectra were recorded at room temperature using the following spectrometers: Varian VXR 300, Varian Inova 400, and Varian Unity 500.

- **^{1}H NMR spectra**

The chemical shifts are given in ppm relative to tetramethylsilane ($\delta = 0.00$ ppm) as internal standard and referenced to residual solvents signals (methanol, $\delta = 3.31$ ppm; benzene, $\delta = 7.16$ ppm; chloroforme, $\delta = 7.26$ ppm).[96] The following abbreviations are used to designate the multiplicity of the peaks in the ^{1}H NMR spectra: s = singlet, d = doublet, t = triplet, q = quadruplet, qui = quintuplet, m = multiplet, b = broad and combinations thereof. If the assignement could not have been done, the hydrogens are denoted with multipicity (CH, CH_2, CH_3) as determined from 2D NMR spectra as well as DEPT and APT pulse sequences.

- **^{13}C NMR spectra**

The chemical shifts are given in ppm relative to tetramethylsilane ($\delta = 0.00$ ppm) as internal standard and referenced to residual solvents signals (methanol, $\delta = 49.00 \pm 0.01$ ppm; benzene, $\delta = 128.06 \pm 0.02$ ppm; chloroforme, $\delta = 77.16 \pm 0.06$ ppm).[96] The ^{13}C NMR spectra are denoted with u = up and d = down as determined from APT pulse sequence. If the assignement could not have been done, the carbons are denoted with hydrogen multipicity (C, CH, CH_2, CH_3) as determined from from 2D NMR spectra as well as DEPT and APT pulse sequences.

MS

Following spectrometers were used for the recording of mass spectra:
for MS (EI): Finnigan SSQ 7000, 70 eV.
for MS (CI): Finnigan SSQ 7000, 100 eV.
for HRMS (High resolution mass spectra): Varian MAT 95, EI, 70 eV.
Only peaks of $m/z > 80$ and intensity > 10%, except for decisive one, are listed.

IR

IR spectra were recorded on a Perkin Elmer FTIR 1760 S spectrometer as KBr pellets (KBr), neat (capillary) or in chloroform ($CHCl_3$). Absorptions are given in wavenumbers (cm^{-1}).

Only peaks of $\nu > 600$ cm^{-1} are listed, s = strong (70–100% absorption), m = medium (30–70% absorption) and w = weak (10–30% absorption).

ELEMENTAL ANALYSIS

Elemental analyses were performed on a Heraeus CHN-O-Rapid instrument. All values are given in mass percentages.

OPTICAL ROTATION

Perkin-Elmer Model 241, measurements were made at approximately 22 °C, specific rotations are in (deg·mL)/(dm·g), and the concentration *c* is in $g.10^{-2}$. mL.

MELTING POINTS

Melting points were measured in open glass capillaries with a Büchi apparatus, the values are uncorrected.

CHROMATOGRAPHY

♦ Thin layer chromatography (TLC)

Support: Merck silica gel 60 F_{254} plates were used.

Detection: First the TLC plates were submitted to UV ($\lambda = 254$ nm) and then one of the following color reagents was used:

- Anisaldehyde: 6 mL anisaldehyde, 3 mL concentrated H_2SO_4 and 250 mL EtOH
- Ninhydrin: 1 g ninhydrin, 25 mL acetic acid and 475 mL *n*-BuOH
- $KMnO_4$: 3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5% NaOH, 300 mL H_2O

♦ Column chromatography

Purification by flash column chromatography was carried out in glass columns using Merck silica gel 60, particle size 0.040–0.063 mm (230–400 mesh).

♦ High performance liquid chromatography (HPLC)

Analytical HPLC on achiral phases was performed on a Waters 600E instrument with UV detector 481 (254 nm) at 22 °C.

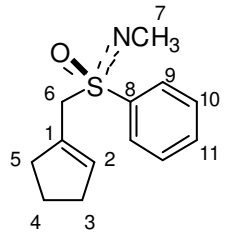
Analytical HPLC on chiral phases was performed on a HP 1050 instrument with MW detector (230 nm, 254 nm) at 24 °C.

Preparative HPLC were performed on a Varian SD-1 instrument with a Prostar 320 detector (254 nm) and a Knauer detector (RI).

2. Construction of the carbocycle having an amino-substituted tertiary *C* atom

2.1 Synthesis of the cyclic allylic sulfoximines

2.1.1 (–)-(*R*)-(S-Cyclopent-1-enylmethyl)-N-methyl-S-phenylsulfoximine (27a)



Allylic sulfoximine **27a** was prepared according to the procedure described in the literature. The analytical data were in agreement with those reported.[33]

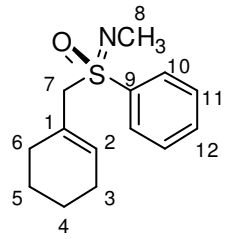
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81 (qui, $^3J_{3\text{-}4} = {}^3J_{5\text{-}4}$ = 7.4 Hz, 2 H, H-4), 2.15–2.45 (m, 4 H, H-3, H-5), 2.72 (s, 3 H, H-7), 3.97 (s, 2 H, H-6), 5.42–4.46 (m, 1 H, H-2), 7.48–7.64 (m, 3 H, H-10, H-11), 7.79–7.84 (m, 2 H, H-9).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6 (u, C-4), 29.8 (d, C-7), 32.7 (u, CH_2), 35.0 (u, CH_2), 58.8 (u, C-6), 129.0 (d, C-10), 129.6 (d, C-9), 131.8 (u, C-1), 132.8 (d, C-11), 135.4 (d, C-2), 137.3 (u, C-8).

Optical rotation for (*S*)-27a, literature: $[\alpha]_D$ = +62.3 ° (*c* 1.37, acetone).

Optical rotation for (*R*)-27a, found: $[\alpha]_D$ = –66.2 ° (*c* 1.46, acetone).

2.1.1 (–)-(*R*)-(S-Cyclohexyl-1-enylmethyl)-N-methyl-S-phenylsulfoximine (27b)



Allylic sulfoximine **27b** was prepared according to the procedure described in the literature. The analytical data were in agreement with those reported.[33]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.57 (m, 4 H, CH_2), 1.79–1.98 (m, 3 H, CH_2), 2.06–2.19 (m, 1 H, CH_2), 2.71 (s, 3 H, H-8), 3.75 (s, 2 H, H-7), 5.29–5.35 (m, 1 H, H-2), 7.50–7.63 (m, 3 H, H-11, H-12), 7.78–7.84 (m, 2 H, H-10).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (u, CH_2), 22.6 (u, CH_2), 25.6 (u, CH_2), 28.8 (u, CH_2), 29.8 (d, C-8), 65.0 (u, C-7), 126.6 (u, C-1), 128.9 (d, C-11), 129.8 (d, C-10), 132.7 (d, C-12), 132.9 (d, C-2), 137.0 (C-9).

Optical rotation for (*S*)-27b: $[\alpha]_D$ = +65.5 ° (*c* 1.13, acetone).

Optical rotation for (*R*)-27b, found: $[\alpha]_D$ = –74.3 ° (*c* 1.30, acetone).

2.2 Titanium mediated γ-hydroxyalkylation of cyclic allylic sulfoximines with acetaldehyde

2.2.1 γ-Hydroxyalkylation of allylic sulfoximine 27a

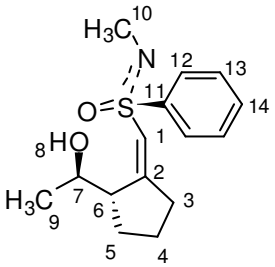
To a solution of allylic sulfoximine **27a** (4.71 g, 20 mmol) in dry THF (200 mL) at –78 °C was added *n*-BuLi (13.2 mL of 1.6 M solution in *n*-hexane, 21 mmol). After stirring the mixture for 10 min at –78 °C, neat $ClTi(O\textit{i}\text{-}Pr)_3$ (10.1 mL, 42 mmol) was added. The resulting mixture was stirred for 10 min at –78 °C, allowed to warm to 0 °C, and stirred for 45 min at this temperature. It was then cooled to –78 °C once more, whereupon acetaldehyde (5.6 mL,

100 mmol) was added. The mixture thus obtained was allowed to warm up to room temperature within 12 h. The solution was then poured into saturated aqueous $(NH_4)_2CO_3$ (50 mL) and H_2O (50 mL) was added. The mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were dried with $MgSO_4$, concentrated in vacuum and the residue was submitted to ^{1}H NMR to determine the diastereoselectivity (84% de). The crude mixture was filtered over silica gel with EtOAc and the solvent was removed in vacuum. The resulting oil was purified by HPLC (Kromasil Si–100, L = 250 mm, ∅ = 40 mm, Et_2O/*i*-PrOH, 95:5, UV 254 nm and RI detectors, R_f(**28a**)<R_f(**36**) to obtain diastereomerically pure alcohol **28a** (4.36 g, 78%) as a colorless solid and diasteromerically pure alcohol **36** (384 mg, 7%) as a colorless oil.

For the determination of the diastereoselectivity with the ^{1}H NMR spectrum of the crude mixture H-1 signals were used.

• **Analytical data of the major isomer**

(*R*)-1-((*S*,*Z*)-2-(((*R*)-N-Methylphenylsulfonimidoyl)methylene)cyclopentyl)ethanol (28a)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, $^3J_{7\text{-}9}$ = 6.1 Hz, 3 H, H-9), 1.60–1.72 (m, 3 H, H-4, H-5, H-8), 1.72–1.95 (m, 2 H, H-4', H-5'), 2.30–2.42 (m, 1 H, H-3), 2.62–2.73 (m, 4 H, H-10, H-3'), 3.49–3.59 (dq, $^3J_{6\text{-}7}$ = 9.9 Hz, $^3J_{9\text{-}7}$ = 6.0 Hz, 1 H, H-7), 3.61–3.69 (m, 1 H, H-6), 6.25 (m, 1 H, H-1), 7.52–7.63 (m, 3 H, H-13, H-14), 7.87–7.92 (m, 2 H, H-12).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (u, CH_2), 23.8 (d, C-9), 29.1 (d, C-10), 30.2 (u, CH_2), 34.1 (u, C-3), 50.6 (d, C-6), 69.4 (d, C-7), 123.7 (d, C-1), 128.7 (d, C-12), 129.3 (d, C-13), 132.7 (d, C-14), 139.6 (u, C-11), 163.7 (u, C-2).

IR (capillary): ν = 3345 (w), 3203 (w), 3060 (w), 2965 (s), 2875 (m), 2800 (w), 2236 (w), 1628 (m), 1448 (m), 1371 (w), 1234 (s), 1146 (s), 1110 (s), 1081 (s), 1012 (m), 963 (w), 925 (m), 858 (m), 801 (m), 734 (s), 693 (m) cm^{-1}.

MS (EI): *m/z* (%) = 279 [M^+] (3), 262 (20), 235 (18), 189 (25), 187 (15), 157 (13), 156 (59), 155 (46), 154 (10), 129 (22), 126 (10), 125 (100), 124 (11), 123 (14), 110 (12), 109 (25), 108 (14), 107 (88), 97 (10), 91 (12), 81 (15).

Elemental Analysis:

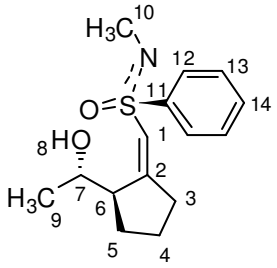
$C_{12}H_{21}NO_2S$ (279.4)	C	H	N
Calculated	64.48	7.58	5.01
Found	64.29	7.40	4.92

Melting point: 65 °C.

Optical rotation: $[\alpha]_D$ = +96.3 ° (*c* 1.16, CH_2Cl_2).

• **Analytical data of the minor isomer**

(*S*)-1-((*R*,*Z*)-2-(((*R*)-N-Methylphenylsulfonimidoyl)methylene)cyclopentyl)ethanol (36)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (d, $^3J_{7\text{-}9}$ = 6.0 Hz, 3 H, H-9), 1.58–1.85 (m, 4 H, H-4, H-5), 2.33–2.44 (m, 1 H, H-3), 2.62–2.73 (m, 4 H, H-3', H-10), 3.46–3.56 (dq, $^3J_{6\text{-}7}$ = 9.6 Hz, $^3J_{9\text{-}7}$ = 6.0 Hz, 1 H, H-7), 3.61–3.70 (bt, $^3J_{7\text{-}6}$ = 9.0 Hz, 1 H, H-6), 6.14 (bd, ^4J = 1.1 Hz, 1 H, H-1), 7.52–7.63 (m, 3 H, H-13, H-14), 7.79–7.85 (m, 2 H, H-12).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (u, C-4), 23.6 (d, C-9), 29.2 (d, C-10), 30.1 (u, C-5), 34.4 (u, C-3), 50.3 (d, C-6), 68.4 (d, C-7), 122.7 (d, C-1), 128.4 (d, C-12), 129.4 (d, C-13), 132.7 (d, C-14), 139.4 (u, C-11), 164.0 (u, C-2).

IR ($CHCl_3$): ν = 3971 (w), 3455 (m), 3184 (w), 3061 (w), 2967 (s), 2875 (s), 2803 (m), 1629 (s), 1447 (s), 1372 (m), 1302 (w), 1237 (s), 1150 (s), 1109 (s), 1081 (s), 1011 (m), 964 (m), 933 (w), 878 (s), 854 (s), 817 (m), 753 (s), 692 (s), 664 (w) cm^{-1}.

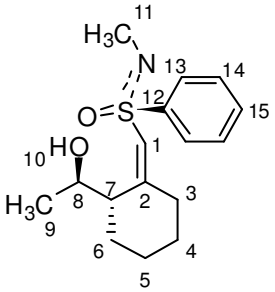
MS (EI): *m/z* (%) = 279 [M^+] (19), 262 (33), 249 (12), 235 (12), 189 (13), 187 (10), 157 (11), 156 (53), 155 (27), 154 (10), 129 (12), 126 (11), 125 (100), 123 (15), 110 (12), 109 (24), 108 (11), 107 (54), 91 (11), 81 (18).

2.2.2 γ-Hydroxyalkylation of allylic sulfoximine 27b

To a solution of allylic sulfoximine **27b** (4.99 g, 20 mmol) in dry THF (200 mL) at –78 °C was added *n*-BuLi (13.2 mL of 1.6 M solution in *n*-hexane, 21 mmol). After stirring the mixture for 10 min at –78 °C, $ClTi(O\textit{i}\text{-}Pr)_3$ (10.1 mL, 42 mmol) was added neat. The resulting mixture was stirred for 10 min at –78 °C, allowed to warm to 0 °C, and stirred for 45 min at this temperature. It was then cooled to –78 °C once more, whereupon acetaldehyde (5.6 mL, 100 mol) was added. The mixture thus obtained was allowed to warm up to room temperature over 12 h. The solution was then poured into saturated aqueous $(NH_4)_2CO_3$ solution (50 mL) and water (50 mL) was added. The mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were dried with $MgSO_4$, concentrated in vacuum and submitted to ^{1}H NMR to determine the diastereoselectivity (74% de). The crude mixture was filtered over silica gel with EtOAc and solvent was removed in vacuum. The resulting material was purified by washing with Et_2O (3 × 40 mL) to obtain diastereomerically pure alcohol **28b** (4.40 g, 75%) as a colorless solid.

For the determination of the diastereoselectivity with the ^{1}H NMR spectrum of the crude mixture H-1 signals were used ($\delta_{H\text{-}1}$ = 6.17 ppm for the minor isomer).

Analytical data of (*R*)-1-((*S*,*Z*)-2-(((*R*)-N-Methylphenylsulfonimidoyl)methylene)cyclohexyl)ethanol (28b)



^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, $^3J_{8\text{-}9}$ = 5.9 Hz, 3 H, H-9), 1.27–1.60 (m, 4 H, CH_2), 1.68–1.81 (m, 1 H, CH_2), 1.82–1.95 (m, 1 H, CH_2), 2.05–2.13 (m, 1 H, CH_2), 2.35–2.55 (m, 1 H, CH_2), 2.60 (s, 3 H, H-11), 3.60–3.70 (m, 1 H, H-7), 3.90–4.05 (dq, $^3J_{9\text{-}8}$ = 5.9 Hz, $^3J_{7\text{-}}$

$_8$ = 11.9 Hz, 1 H, H-8), 5.27 (bs, 1 H, H-10), 6.30 (bd, ^4J = 2.0 Hz, 1 H, H-1), 7.52–7.64 (m, 3 H, H-14, H-15), 7.86–7.93 (m, 2 H, H-13).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3 (u, CH_2), 23.2 (d, C-9), 27.4 (u, CH_2), 28.3 (u, CH_2), 29.2 (d, C-11), 33.0 (u, CH_2), 45.8 (d, C-7), 67.1 (d, C-8), 126.7 (d, C-1), 128.9 (d, C-13), 129.3 (d, C-14), 132.7 (d, C-15), 139.7 (u, C-12), 160.7 (u, C-2).

IR (KBr): ν = 3467 (s), 3059 (m), 2934 (s), 1863 (s), 2796 (m), 1611 (s), 1447 (s), 1376 (m), 1229 (s), 1130 (s), 1070 (s), 928 (m), 853 (s), 820 (s), 751 (m), 689 (s), 602 (s) cm^{-1}.

MS (EI): *m/z* (%) = 293 [M^+] (3), 201 (12), 171 (11), 169 (16), 156 (78), 138 (11), 125 (100), 123 (28), 107 (25), 95 (24).

Elemental Analysis:

$C_{16}H_{23}NO_2S$ (293.4)	C	H	N
Calculated	65.49	7.90	4.77
Found	65.31	8.15	4.80

Melting point: 111 °C.

Optical rotation: $[\alpha]_D$ = +11.2 ° (*c* 1.00, CH_2Cl_2).

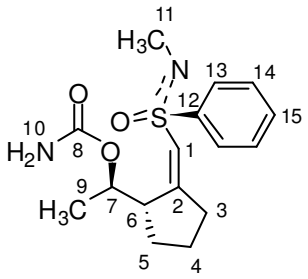
2.3 Synthesis of the carbamate from the alcohol

2.3.1 Carbamate from alcohol 28a

To a solution of alcohol **28a** (1.26 g, 3.90 mmol) in CH_2Cl_2 (50 mL) at room temperature was added trichloroacetyl isocyanate (0.60 mL, 5.07 mmol). The solution was stirred until TLC showed complete conversion (5 h). Then MeOH (25 mL) and $(NH_4)_2CO_3$ (1.87 g, 19.5 mmol) were added and the mixture was stirred at room temperature for 12 h. Saturated aqueous NH_4Cl (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases were dried with $MgSO_4$ and the solvents were removed in vacuum.

The residue was purified by column chromatography on silica gel (EtOAc) to give carbamate *Z*-**40a** (1.06 g, 84%) as a colorless solid.

Analytical data of (*R*)-1-((*S*,*Z*)-2-(((*R*)-N-Methylphenylsulfonimidoyl)methylene)cyclopentyl)ethyl carbamate (*Z*-40a)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98–1.17 (m, 1 H, CH_2), 1.23–1.40 (m, 5 H, H-9, CH_2), 1.42–1.58 (m, 1 H, CH_2), 1.70–1.85 (m, 1 H, CH_2), 2.32–2.47 (m, 1 H, CH_2), 2.68 (s, 3 H, H-11), 4.00–4.09 (m, 1 H, H-6), 4.84–4.98 (dq, $^3J_{6\text{-}7}$ = 9.4 Hz, $^3J_{9\text{-}7}$ = 6.2 Hz, 1 H, H-7), 6.05 (bs, 2 H, H-10), 6.56 (bd, ^4J = 1.7 Hz, 1 H, H-1), 6.95–7.12 (m, 3 H, H-14, H-15), 8.00–8.07 (m, 2 H, H-13).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0 (d, C-9), 21.1 (u, CH_2), 28.9 (u, CH_2), 29.1 (d, C-11), 34.4 (u, CH_2), 45.8 (d, C-6), 69.8 (d, C-7), 123.8 (d, C-1), 129.0 (d, CH), 129.1 (d, CH), 131.7 (d, CH), 140.4 (u, C-12), 158.0 (u, C), 160.6 (u, C).

IR (KBr): ν = 3424 (s), 3176 (m), 3061 (w), 2965 (s), 2874 (m), 2801 (m), 1722 (s), 1608 (m), 1450 (m), 1381 (s), 1325 (s), 1236 (s), 1149 (s), 1076 (s), 852 (s), 797 (m), 752 (m), 692 (m) cm^{-1}.

MS (EI): *m/z* (%) = 322 [M^+] (3), 278 (31), 263 (17), 262 (100), 125 (30), 107 (11).

HRMS:

$C_{16}H_{22}N_2O_3S$ (322.4)	[M^+]
Calculated	322.13512
Found	322.13518

Melting point: 45 °C

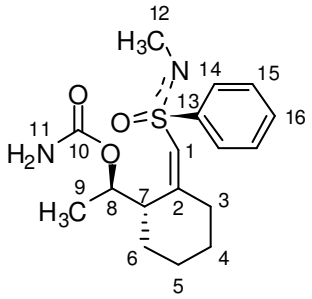
Optical rotation: $[\alpha]_D$ = +17.7 ° (*c* 1.02, CH_2Cl_2).

2.3.2 Carbamate from alcohol 28b

To a solution of alcohol **28b** (700 mg, 2.39 mmol) in CH_2Cl_2 (20 mL) at room temperature was added trichloroacetyl isocyanate (0.37 mL, 3.11 mmol). The solution was stirred until TLC showed complete conversion (5 h). Then MeOH (10 mL) and $(NH_4)_2CO_3$ (1.15 g, 12.0 mmol) were added and the mixture was stirred at room temperature for 12 h. Saturated aqueous NH_4Cl (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried with $MgSO_4$ and the solvents were removed in vacuum. The residue was purified by column chromatography on silica gel (EtOAc) to give carbamate *Z*-**40b** (587 mg, 73%, R_f = 0.2) as a colorless solid and carbamate *E*-**40b** (72 mg, 9%, R_f = 0.35) as a colorless oil.

• **Analytical data of the major isomer (*Z*)**

(*R*)-1-((*S*,*Z*)-2-(((*R*)-N-Methylphenylsulfonimidoyl)methylene)cyclohexyl)ethyl carbamate (*Z*-40b)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06–1.20 (m, 1 H, CH_2), 1.21–1.39 (m, 4 H, H-9, CH_2), 1.40–1.52 (m, 2 H, CH_2), 1.61–1.70 (m, 1 H, CH_2), 1.84–1.94 (m, 1 H, CH_2), 2.01–2.11 (m, 1 H, H-3), 2.41–2.52 (ddt, ^3J = 13.5 Hz, ^3J = 5.0 Hz, ^4J = 1.9 Hz, 1 H, H-3´), 2.68 (s, 3 H, H-12), 3.67 (m, 1 H, H-7), 4.90 (bs, 2 H, H-11), 5.05–5.15 (dq, $^3J_{7\text{-}8}$ = 10.4 Hz, $^3J_{9\text{-}8}$ = 6.0 Hz, 1 H, H-8), 6.29 (d, ^4J = 1.6 Hz, 1 H, H-1), 7.53–7.63 (m, 3 H, H-15, H-16), 7.91–7.97 (m, 2 H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9 (d, C-9), 20.4 (u, CH_2), 28.2 (u, CH_2), 28.4 (u, CH_2), 29.4 (d, C-12), 33.7 (u, C-3), 41.6 (d, C-7), 69.7 (d, C-8), 125.6 (d, C-1), 128.8 (d, C-14), 129.1 (d, C-15), 132.3 (d, C-16), 140.6 (u, C-13), 157.0 (u, C), 159.7 (u, C).

IR (KBr): ν = 3480 (s), 3172 (w), 3059 (w), 2935 (s), 2865 (s), 2801 (m), 1720 (s), 1612 (s), 1451 (s), 1381 (s), 1326 (s), 1238 (s), 1144 (s), 1111 (s), 1072 (s), 1010 (s), 921 (w), 854 (s), 816 (m), 754 (m), 692 (m) cm^{-1}.

MS (EI): *m/z* (%) = 336 [M^+] (6), 292 (12), 276 (25), 156 (100), 138 (16), 137 (11), 125 (50), 123 (15), 121 (13), 93 (20), 91 (14).

HRMS:

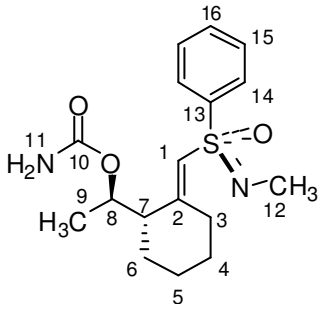
$C_{17}H_{24}N_2O_3S$ (336.4)	[M^+]
Calculated	336.15077
Found	336.15075

Melting point: 52–54 °C

Optical rotation: $[\alpha]_D$ = +182.1° (*c* 1.06, EtOAc).

• Analytical data of the minor isomer (*E*)

(*R*)-1-((*S*,*E*)-2-(((*R*)-N-Methylphenylsulfonimidoyl)methylene)cyclohexyl)ethyl carbamate (*E*-40b)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, $^3J_{8\text{-}9}$ = 6.3 Hz, 3 H, H-9), 1.32–1.56 (m, 3 H, CH_2), 1.59–1.80 (m, 3 H, CH_2), 1.97–2.09 (m, 1 H, H-3), 2.26–2.35 (m, 1 H, H-7), 2.64 (s, 3 H, H-12), 2.96–3.06 (m, 1 H, H-3´), 4.80 (bs, 2 H, H-11), 4.92–5.02 (dq, $^3J_{7\text{-}8}$ = 9.6 Hz, $^3J_{9\text{-}8}$ = 6.0 Hz, 1 H, H-8), 6.44 (bs, 1 H, H-1), 7.50–7.59 (m, 3 H, H-15, H-16), 7.90–7.96 (m, 2 H, H-14).

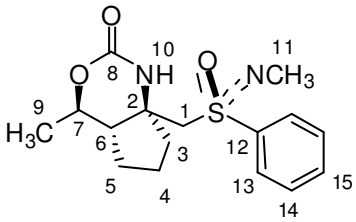
^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7 (d, C-9), 21.3 (u, CH_2), 26.3 (u, CH_2), 27.0 (u, CH_2), 28.8 (d, C-12), 29.6 (u, C-3), 50.8 (d, C-7), 70.0 (d, C-8), 125.3 (d, C-1), 128.4 (d, C-14), 129.1 (d, C-15), 132.5 (d, C-16), 140.2 (u, C-13), 156.0 (u, C), 160.5 (u, C).

IR (KBr): ν = 3906 (w), 3747 (w), 3675 (w), 3418 (s), 3194 (m), 3056 (w), 2936 (s), 2866 (m), 2801 (w), 2344 (w), 1798 (m), 1723 (s), 1621 (m), 1449 (m), 1384 (s), 1322 (m), 1237 (s), 1144 (s), 1108 (s), 1070 (s), 1004 (m), 923 (w), 855 (s), 819 (w), 755 (m), 693 (m), 602 (m) cm^{-1}.

MS (EI): *m/z* (%) = 336 [M^+] (11), 276 (22), 244 (21), 227 (37), 200 (15), 197 (14), 196 (46), 195 (24), 181 (10), 167 (15), 156 (100), 141 (12), 138 (14), 137 (14), 125 (94), 123 (13), 121 (14), 119 (10), 109 (12), 107 (11), 105 (12), 95 (29), 93 (26), 91 (30).

2.4 Intramolecular aza-MICHAEL addition

2.4.1 (4*R*,4a*S*,7a*R*)-4-Methyl-7a-(((*R*)-N-methylphenylsulfonimidoyl)methyl)hexahydrocyclopenta[*d*][1,3]oxazin-2(1*H*)-one (29a)



To a solution of alcohol **28a** (1.97 g, 6.11 mmol) in CH_2Cl_2 (50 mL) at room temperature was added trichloroacetyl isocyanate (1.09 mL, 7.94 mmol). The solution was stirred until TLC showed complete conversion (5 h). Then MeOH (25 mL) and $(NH_4)_2CO_3$ (2.93 g, 30.5 mmol) were added and the mixture was stirred at room temperature for 12 h. Saturated aqueous NH_4Cl (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases were dried with $MgSO_4$ and the solvents were removed in vacuum. The crude carbamate **40a** was taken in THF (50 mL), the solution was cooled to –78 °C and *n*-BuLi (5.0 mL of 1.6 M solution in *n*-hexane, 7.94 mmol) was added. Then the mixture was allowed to warm to room temperature within 12 h. Saturated aqueous NH_4Cl (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases

were dried with $MgSO_4$ and solvent was removed in vacuum. The ^{1}H NMR spectrum of the crude mixture gave no indication of the presence of any other diastereomer. Washing of the solid residue with Et_2O (3 × 20 mL) gave sulfoximine **29a** as a colorless solid. Purification of the mother liquor by column chromatography (EtOAc/*i*-PrOH, 9:1) afforded additional **29a** (1.55 g, 79% combined yield) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (d, $^3J_{7\text{-}9}$ = 6.1 Hz, 3 H, H-9), 1.44–1.53 (m, 1 H, H-5), 1.61–1.75 (m, 2 H, H-4, H-6), 1.75–1.85 (m, 1 H, H-4'), 1.86–1.99 (m, 2 H, H-3, H-5'), 2.63–2.70 (m, 4 H, H-11, H-3'), 3.26 (dd, $^2J_{1'\text{-}1}$ = 14.3 Hz, ^4J = 1.2 Hz, 1 H, H-1), 3.54 (d, $^2J_{1\text{-}1'}$ = 14.3 Hz, 1 H, H-1') 3.95–4.04 (dq, $^3J_{9\text{-}7}$ = 9.6 Hz, $^3J_{6\text{-}7}$ = 10.2 Hz, 1 H, H-7), 6.89 (s, 1 H, H-10), 7.56–7.66 (m, 3 H, H-14, H-15), 7.83–7.87 (m, 2 H, H-13).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0 (d, C-9), 22.8 (u, C-4), 27.1 (u, C-5), 29.7 (d, C-11), 38.5 (u, C-3), 49.4 (d, C-6), 63.3 (u, C-2), 65.7 (u, C-1), 75.0 (d, C-7), 128.5 (d, C-13), 129.6 (d, C-14), 133.0 (d, C-15), 139.6 (u, C-12), 154.2 (u, C-8).

IR (KBr): ν = 3684 (w), 3651 (w), 3402 (m), 3351 (s), 3061 (w), 2967 (m), 2939 (m), 2890 (m), 2796 (w), 2345 (w), 1712 (s), 1582 (w), 1450 (m), 1390 (m), 1364 (m), 1316 (m), 1236 (s), 1176 (w), 1133 (m), 1093 (m), 1061 (m), 1013 (m), 974 (w), 892 (m), 862 (m), 772 (m), 747 (m), 692 (w), 653 (m), 619 (w) cm^{-1}.

MS (EI): *m/z* (%) = 323 [M^++1] (21), 294 (13), 170 (11), 169 (21), 168 (100), 154 (13), 140 (56), 125 (55), 124 (55), 114 (13), 108 (26), 107 (34), 106 (16), 95 (11), 94 (15), 91 (18), 82 (11), 81 (43).

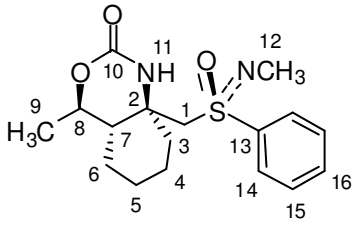
Elemental Analysis:

$C_{16}H_{22}N_2O_3S$ (322.4)	C	H	N
Calculated	59.60	6.88	8.69
Found	59.90	6.96	8.74

Melting point: 148 °C (decomposition).

Optical rotation: $[\alpha]_D$ = –103.3 ° (*c* 1.09, CH_2Cl_2).

2.4.2 (4*R*,4a*S*,8a*R*)-4-Methyl-8a-(((*R*)-N-methylphenylsulfonimidoyl)methyl)hexahydro-1*H*-benzo[*d*][1,3]oxazin-2(4*H*)-one (29b)



To a solution of alcohol **28b** (1.94 g, 6.62 mmol) in CH_2Cl_2 (60 mL) at room temperature was added trichloroacetyl isocyanate (1.18 mL, 8.61 mmol). The solution was stirred until TLC showed complete conversion (5 h). Then MeOH (30 mL) and $(NH_4)_2CO_3$ (3.18 g, 33.0 mmol) were added and the mixture was stirred at room temperature for 12 h. H_2O (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried with $MgSO_4$ and the solvents were removed in vacuum. The crude carbamate **40b** was taken in THF (50 mL), the solution was cooled to –78 °C and *n*-BuLi (5.4 mL of 1.6 M solution in *n*-hexane, 8.60 mmol) was added. Then the mixture was allowed to warm to room temperature within 12 h. Saturated aqueous NH_4Cl (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed in vacuum, the ^{1}H NMR spectrum of the crude mixture gave no indication of the presence any other diastereomer. Washing of the solid residue with Et_2O (3 × 20 mL) gave sulfoximine **29b** as a colorless solid. Purification of the mother liquor by column chromatography (EtOAc/*i*-PrOH, 95:5) afforded additional **29b** (1.72 g, 77%, combined yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04–1.21 (m, 2 H, CH_2), 1.32 (d, $^3J_{8–9}$ = 6.3 Hz, 3 H, H-9), 1.43–1.59 (m, 4 H, CH_2), 1.65–1.81 (m, 2 H, CH_2), 2.54–2.62 (m, 1 H, CH_2), 2.71 (s, 3 H, H-12), 3.06 (dd, $^3J_{1´-1}$ = 14.3 Hz, ^4J = 1.4 Hz, 1 H, H-1), 3.93 (d, $^3J_{1´-1}$ = 14.6 Hz, 1 H, H-1´), 4.58 (dq, $^3J_{9–8}$ = 6.3 Hz, $^3J_{7–8}$ = 10.4 Hz, 1 H, H-8), 7.56–7.68 (m, 4 H, H-11, H-15, H-16), 7.85–7.90 (m, 2 H, H-14).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9 (d, C-9), 19.7 (u, CH_2), 22.2 (u, CH_2), 22.8 (u, CH_2), 29.6 (d, C-12), 33.5 (u, CH_2), 43.2 (d, C-7), 55.8 (u, C-2), 62.4 (u, C-1), 71.7 (d, C-8), 128.6 (d, C-14), 129.5 (d, C-15), 133.1 (d, C-16), 139.7 (u, C-13), 152.2 (u, C-10).

IR (KBr): ν = 3356 (s), 3256 (m), 3059 (w), 2934 (m), 2876 (m), 2795 (w), 1707 (s), 1618 (m), 1449 (m), 1390 (m), 1324 (m), 1237 (s), 1178 (w), 1141 (m), 1102 (m), 1075 (m), 1046 (w), 1010 (m), 929 (w), 904 (w), 875 (w), 832 (m), 749 (m), 695 (m), 636 (m), 606 (m) cm^{-1}.

MS (CI, methane): *m/z* (%) = 337 [M^++1] (100), 210 (14), 182 (12), 170 (27), 156 (10).

Elemental Analysis:

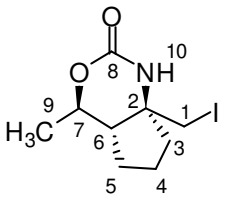
$C_{17}H_{24}N_2O_3S$ (336.5)	C	H	N
Calculated	60.69	7.19	8.33
Found	61.00	7.13	8.41

Melting point: 152 °C (decomposition).

Optical rotation: $[\alpha]_D$ = –77.1 ° (*c* 1.08, CH_2Cl_2).

3. The Ring-closing metathesis route

3.1 (4*R*,4a*S*,7a*R*)-7a-(Iodomethyl)-4-methylhexahydrocyclopenta[*d*][1,3]oxazin-2(1*H*)-one (**50**)



1-Chloroethyl chloroformate **54** (338 µL, 3.10 mmol) was added at room temperature to a mixture of sulfoximine **29a** (500 mg, 1.55 mmol) and NaI (1.16 g, 7.75 mmol) in CH_3CN (7 mL). The mixture was stirred at room temperature until TLC indicated almost a complete conversion of the sulfoximine (3 h). Concentration in vacuum and purification of the residue by column chromatography on silica gel (EtOAc/cyclohexane, 4:1) afforded the desired iodide **50** (348 mg, 76%) as a brown solid.
R_f(iodide **50**) = 0.45 and R_f(sulfinamide **55**) = 0.9 in EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, $^3J_{7\text{-}9}$ = 6.3 Hz, 3 H, H-9), 1.49–1.58 (m, 1 H, CH_2), 1.59–1.70 (m, 1 H, CH_2), 1.75–1.87 (m, 2 H, CH_2), 1.94–2.08 (m, 3 H, H-6, CH_2), 3.35 (d, $^2J_{1'\text{-}1}$ = 10.4 Hz, 1 H, H-1), 3.41 (d, $^2J_{1\text{-}1'}$ = 10.4 Hz, 1 H, H-1´), 4.02 (dq, $^3J_{9\text{-}7}$ = 6.3 Hz, $^3J_{6\text{-}7}$ = 10.2 Hz, 1 H, H-7), 5.92 (bs, 1 H, H-10).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1 (u, C-9), 20.7 (u, C-1), 23.0 (u, CH_2), 28.1 (u, CH_2), 40.1 (u, CH_2), 47.4 (d, C-6), 63.5 (u, C-2), 76.2 (d, C-7), 155.3 (u, C-8).

IR ($CHCl_3$): ν = 3250 (m), 3123 (m), 2956 (s), 2879 (m), 1712 (s), 1455 (m), 1393 (s), 1323 (s), 1205 (m), 1092 (m), 1059 (m), 1007 (m), 968 (w), 918 (w), 873 (w), 765 (m), 637 (w), 612 (w) cm^{-1}.

MS (EI): *m/z* (%) = 295 [M^+] (1), 154 (100), 110 (45), 81 (11).

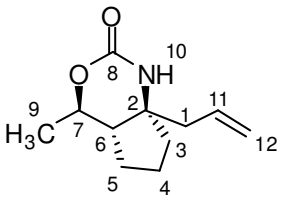
Elemental Analysis:

$C_9H_{14}INO_2$ (295.1)	C	H	N
Calculated	36.63	4.78	4.75
Found	36.53	4.85	4.61

Melting point: 85 °C.

Optical rotation: $[\alpha]_D$ = +2.03 ° (*c* 0.935, CH_2Cl_2).

3.2 (4*R*,4a*S*,7a*S*)-7a-Allyl-4-methylhexahydrocyclopenta[*d*][1,3]oxazin-2(1*H*)-one (60)

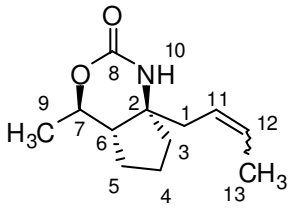


To a suspension of CuI (210 mg, 1 mmol) in THF (2 mL) was added vinylmagnesium bromide (2 mL of 1 M solution in THF, 2 mmol) at –30 °C. The turbid solution was stirred 30 min at this temperature whereby it turned black. The cuprate solution was added to a solution of **50** in THF (2 mL) at –30 °C, which turned black. After 2 h at –30 °C the mixture was allowed to warm to room temperature within 12 h. TLC showed complete conversion. Saturated aqueous $(NH_4)_2CO_3$ (30 mL) and 10 mL concentrated aqueous NH_3 were added and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed in vacuum. The residue was purified by flash chormatography on silica gel (EtOAc/cyclohexane, 1:1) to give the desired alkene **60** as (16 mg, 40%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, $^3J_{7\text{-}9}$ = 6.2 Hz, 3 H, H-9), 1.40–2.02 (m, 7 H, H-3, H-4, H-5, H-6), 2.15–2.37 (m, 2 H, H-1), 3.92–4.06 (dq, $^3J_{6\text{-}7}$ = 9.9 Hz, $^3J_{9\text{-}7}$ = 6.2 Hz, 1 H, H-7), 5.12–5.27 (m, 2 H, H-12), 5.72–5.90 (m, 2 H, H-10, H-11).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (d, C-9), 22.5 (u, CH_2), 27.6 (u, CH_2), 39.2 (u, CH_2), 45.9 (u, C-1), 46.9 (u, C-6), 63.6 (u, C-2), 75.9 (d, C-7), 120.6 (u, C-12), 132.0 (d, C-11), 156.1 (u, C-8).

3.3 (4*R*,4a*S*,7a*S*)-7a-(But-2-enyl)-4-methylhexahydrocyclopenta[*d*][1,3]oxazin-2(1*H*)-one (62)



To a suspension of CuI (1.16 g, 6.07 mmol) in THF (3 mL) was added 1-propenylmagnesium bromide (24.3 mL of 0.5 M solution in THF, 12.1 mmol) at –30 °C. The turbid solution was stirred 30 min at this temperature whereby it turned yellow–brown. The cuprate solution was added to a solution of **50** in THF (3 mL) at –30 °C, which turned red, then orange and then yellow–brown color. After 2 h at –30 °C the mixture was allowed to warm to room temperature within 12 h. During this time it turned black. TLC showed complete conversion. Saturated aqueous $(NH_4)_2CO_3$ (30 mL) and 10 mL concentrated aqueous NH_3 were added and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried with $MgSO_4$ and solvent was removed in vacuum. The residue was purified by flash chormatography on silica gel (EtOAc/cyclohexane, 1:1) to give the desired alkene **62** as a *Z*/*E* mixture in ratio 2:1 (208 mg, 82%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) *Z*-62: δ = 1.33 (d, $^{3}J_{7\text{-}9}$ = 6.2 Hz, 3 H, H-9), 1.41–1.52 (m, >1 H, CH_2), 1.60–2.00 (m, >9 H, H-3, H-4, H-5, H-6, H-13), 2.05–2.38 (m, >2 H, H-1), 3.97 (dq, $^{3}J_{6\text{-}7}$ = 10.1 Hz, $^{3}J_{9\text{-}7}$ = 6.0 Hz, >1 H, H-7), 5.35–5.50 (m, >1 H, H-11), 5.66–5.80 (tdq, $^{3}J_{11\text{-}12}$ = 10.9 Hz, $^{3}J_{13\text{–}12}$ = 6.7 Hz, $^{4}J_{1\text{-}12}$ = 1.2 Hz, 1 H, H-12), 6.10 (bs, 1 H, H-10).

^{13}C NMR (75 MHz, $CDCl_3$) *Z*-62: δ = 13.1 (d, C-13), 19.2 (d, C-9), 22.6 (u, CH_2), 27.7 (u, CH_2), 38.5 (u, CH_2), 39.3 (u, C-1), 47.0 (d, C-6), 64.2 (u, C-2), 76.0 (d, C-7), 123.7 (d, C-11), 129.0 (d, C-12), 156.3 (u, C-8).

^{1}H NMR (300 MHz, $CDCl_3$) *E*-62: (Only distinct signals are given) δ = 1.32 (d, $^3J_{7\text{-}9}$ = 6.2 Hz, 3 H, H-9), 5.51–5.66 (m, 1 H, H-12) 6.04 (bs, 1 H, H-10).

^{13}C NMR (75 MHz, $CDCl_3$) *E*-62: δ = 18.1 (d, C-13), 19.2 (d, C-9), 22.5 (u, CH_2), 27.5 (u, CH_2), 39.0 (u, CH_2), 44.5 (u, C-1), 46.7 (d, C-6), 63.8 (u, C-2), 75.9 (d, C-7), 124.4 (d, C-11), 131.3 (d, C-12), 156.3 (u, C-8).

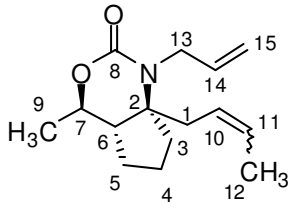
IR (capillary): ν = 3851 (m), 3743 (m), 3251 (m), 3121 (w), 2949 (m), 2353 (s), 1710 (s), 1549 (m), 1461 (w), 1394 (m), 1318 (m), 1083 (m), 790 (w) cm^{-1}.

MS (EI): *m/z* (%) = 210 [M^++1] (19), 209 [M^+] (0.3), 154 (63), 110 (100), 93 (13).

Elemental Analysis:

$C_{12}H_{19}NO_2$ (209.1)	C	H	N
Calculated	68.87	9.15	6.69
Found	69.25	9.08	7.05

3.4 (4*R*,4a*S*,7a*S*)-1-Allyl-7a-(but-2-enyl)-4-methylhexahydrocyclopenta[*d*][1,3]oxazin-2(1*H*)-one (52)



To a solution of alkene **62** (208 mg, 0.99 mmol) in DMF (5 mL) at room temperature was added NaH (63 mg of 50% in mineral oil, 1.31 mmol), the mixture was stirred for 30 min and allyl bromide (113 µL, 1.31 mmol, 1.3 eq) was added. It was stirred for further 12 h. Then DMF was removed in vacuum and the residue was purified by column chromatography on silca gel (EtOAc/cyclohexane, 1:2) to give diene **52** as a *Z*/*E* mixture in ratio 2:1 (211 mg, 85%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) *Z*-52: Only distinct signals are given. δ = 1.30 (d, $^3J_{7\text{-}9}$ = 6.2 Hz, >3 H, H-9), 1.38–1.51 (m, >1 H, CH_2), 1.61 (bd, $^3J_{11\text{-}12}$ = 6.9 Hz, 3 H, H-12), 1.70–2.13 (m, >6 H, H-6, CH_2), 2.21-2.44 (m, >2 H, H-1), 3.50–3.64 (m, >1 H, H-13), 3.82-3.93 (m, >1 H, H-7), 4.15–4.27 (m, >1 H, H-13´), 5.07–5.22 (m, >2 H, H-15), 5.23–5.36 (m, >1 H, H-10), 5.60–5.73 (m, 1 H, H-11), 5.86–6.01 (m, >1 H, H-14).

^{13}C NMR (75 MHz, $CDCl_3$) *Z*-52: Only distinct signals are given. δ = 13.3 (d, C-12), 18.8 (d, C-9), 23.1 (u, CH_2), 28.2 (u, CH_2), 35.6 (u, C-1), 39.5 (u, CH_2), 47.2 (u, C-13), 47.9 (d, C-6), 69.4 (u, C-2), 74.6 (d, C-7), 115.9 (u, C-15), 123.6 (d, C-10), 128.2 (d, C-11), 134.8 (d, C-14), 156.5 (u, C-8).

^{1}H NMR (300 MHz, $CDCl_3$) *E*-52: Only distinct signals are given. δ = 1.63 (bd, $^3J_{11\text{-}12}$ = 5.2 Hz, 3 H, H-12), 5.46-5.58 (m, 1 H, H-11).

^{13}C NMR (75 MHz, $CDCl_3$) *E*-52: Only distinct signals are given. δ = 18.1 (d, C-9), 28.3 (u, CH_2), 39.4 (u, CH_2), 41.8 (u, C-1), 47.1 (u, C-13), 47.6 (d, C-6), 74.7 (d, C-7), 124.4 (d, C-11), 130.7 (d, C-14).

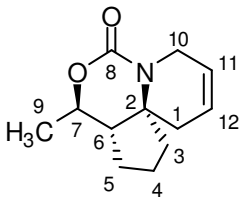
IR (capillary): ν = 3080 (w), 3018 (w), 2956 (m), 2880 (m), 1701 (s), 1538 (w), 1438 (m); 1397 (m), 1309 (m), 1237 (m), 1106 (m), 1067 (m), 970 (m), 920 (m), 772 (m), 716 (w), 643 (w) cm^{-1}.

MS (EI): *m/z* (%) = 250 [M^++1] (4), 195 (13), 194 (100), 150 (67).

HRMS:

$C_{15}H_{23}NO_2$ (249.3)	[M^++1]
Calculated	250.18053
Found	250.18070

3.5 (3a*S*,4*R*,11[1]*S*)-4-Methyl-2,3,3a,4,8,11-hexahydrocyclopenta[*d*]pyrido[1,2-*c*][1,3]oxazin-6(1*H*)-one (53)



To a solution of diene **52** (211 mg, 0.85 mmol) in CH_2Cl_2 (85 mL, 0.01 M) at room temperature was added Grubbs II catalyst **68** (37 mg, 0.042 mmol, 5 mol%). The mixture was stirred at room temperature. After 1h TLC showed a complete conversion. Then DMSO (0.2 mL) was added and the mixture was stirred at room temperature for 1 h. Solvent was removed in vacuum and the residue was purified by column chromatography on silica gel (Et_2O) to give the desired tricycle **53** (166 mg, 95%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, $^3J_{7\text{-}9}$ = 6.3 Hz, 3 H, H-9), 1.43–1.92 (m, 5 H, H-6, CH_2), 1.95–2.19 (m, 4 H, H-1, CH_2), 3.51–3.60 (m, 1 H, H-10), 3.99 (dq, $^3J_{9\text{-}7}$ = 6.3 Hz, $^3J_{6\text{-}7}$ = 9.9 Hz, 1 H, H-7), 4.65–4.75 (m, 1 H, H-10), 6.65–6.79 (m, 2 H, H-11, H-12).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9 (d, C-9), 22.4 (u, CH_2), 27.8 (u, CH_2), 36.3 (u, CH_2), 37.3 (u, C-1), 41.9 (u, C-10), 50.3 (d, C-6), 63.1 (u, C-2), 74.3 (d, C-7), 122.9 (d, CH), 124.2 (d, CH), 154.6 (u, C-8).

IR (capillary): ν = 3859 (w), 3364 (m), 2964 (s), 1693 (s), 1609 (m), 1413 (s), 1308 (m), 1265 (m), 1198 (w), 1128 (m), 1067 (m), 751 (m), 662 (w), 621 (w) cm^{-1}.

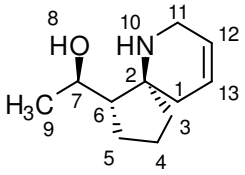
MS (EI): *m/z* (%) = 207 [M^+] (100), 192 (18), 164 (11), 163 (12), 162 (62), 150 (17), 148 (17), 146 (13), 134 (23), 124 (12), 120 (37), 107 (13), 106 (21), 95 (11), 94 (13), 93 (11), 81 (12), 80 (17).

HRMS:

$C_{15}H_{27}NO_2$ (207.3)	[M^+]
Calculated	207.12593
Found	207.12606

Optical rotation: $[\alpha]_D = -72.2$ ° (*c* 1.58, CH_2Cl_2)

3.6 (*R*)-1-((1*S*,5*S*)-6-Azaspiro[4.5]dec-8-en-1-yl)ethanol (49)



A mixture of tricycle **53** (113 mg, 0.546 mmol), CsOH (0.705 g, 8.18 mmol), MeOH (3 mL) and H_2O (3 mL) was stirred at reflux temperature for 3 d. The solution was carrefully neutralized to pH = 7 by using concentrated aqueous HCl (3N). Then methanol was removed in vacuum and water was removed by lyophilization to give colorless salts. The salts were triturated in a mixture of $CHCl_3$/MeOH (1:1) to extract the organic compounds. After repeating this process (3 × 10 mL), the organic layers were combined and dried with $MgSO_4$. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/NEt_3, 90:10:1) to give the desired amino alcohol **49** (71 mg, 72%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (d, $^3J_{7\text{-}9}$ = 8.9 Hz, 3 H, H-9), 1.27–1.60 (m, 2 H, CH_2), 1.64–1.85 (m, 5 H, H-6, CH_2), 1.86–1.98 (m, 1 H, H-11), 2.61 (bd, $^2J_{11\text{-}11'}$ = 17.8 Hz, 1 H, H-11´), 3.52 (bs, 2 H, H-1), 3.90 (dq, $^3J_{6\text{-}7}$ = 9.9 Hz, $^3J_{9\text{-}7}$ = 6.2 Hz, 1 H, H-7), 5.30 (bs, 2 H, H-8, H-10), 5.64–5.80 (m, 2 H, H-12, H-13).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0 (d, C-9), 23.5 (u, CH_2), 29.5 (u, CH_2), 36.1 (u, CH_2), 37.9 (u, C-11), 40.6 (u, C-1), 56.7 (d, C-6), 62.3 (u, C-2), 68.7 (d, C-7), 122.9 (d, CH), 125.4 (d, CH).

IR (capillary): ν = 3950 (w), 3902 (w), 3813 (w), 3729 (w), 3664 (w), 3369 (s), 3024 (m), 2958 (s), 2801 (m), 2726 (w), 2676 (w), 2560 (w), 2470 (w), 2401 (w), 1629 (s), 1569 (s), 1452 (s), 1330 (m), 1260 (w), 1219 (m), 1175 (w), 1137 (s), 1109 (m), 1062 (s), 1010 (m), 958 (m), 931 (m), 881 (m), 812 (m), 713 (w), 658 (s), 606 (w) cm^{-1}.

MS (EI): *m/z* (%) = 181 [M^+] (40), 180 (100), 162 (61), 120 (13), 108 (37), 106 (11), 95 (11), 94 (10).

HRMS:

$C_{11}H_{19}NO$ (181.3)	[M^+]
Calculated	181.14666
Found	181.14664

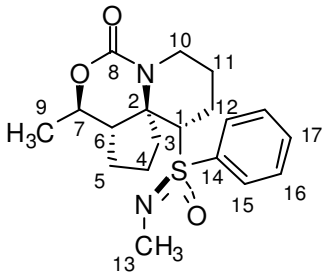
Optical rotation: $[\alpha]_D = -33.0$ ° (*c* 1.62, CH_2Cl_2).

4. Cycloalkylation and removal of the sulfoximine

4.1 General procedure for the cycloalkylation (GP_1)

n-BuLi (1.38 mL of 1.6 M solution in *n*-hexane, 2.2 mmol) was added to a solution of the oxazinone (1.0 mmol) in THF (40 mL). The mixture was allowed to warm slowly to –10 °C within 1 h, cooled to –50 °C, and then treated with the ditosylate (1.1 mmol). The mixture was then allowed to warm to room temperature over 12 h. Then saturated aqueous NH_4Cl (40 mL) was added and the mixture was extracted with CH_2Cl_2 (3×40 mL). The combined organic phases were dried with $MgSO_4$. The solvents were removed in vacuum and the residue was purified by column chromatography on silica gel.

4.2 (3a*S*,4*R*,11*S*,11[1]*R*)-4-Methyl-11-((*R*)-*N*-methylphenylsulfonimidoyl)octahydrocyclopenta[*d*]pyrido[1,2-*c*][1,3]oxazin-6(1*H*)-one (71)



According to GP_1, sulfoximine **29a** (505 mg, 1.57 mmol) was treated with *n*-BuLi (2.16 mL of 1.6 M solution in *n*-hexane, 3.46 mmol) and 1,3-propanediol di-*p*-tosylate (665 mg, 1.73 mmol) to give after work up and column chromatography (EtOAc/cyclohexane, 2:1) the diastereomerically pure tricycle **71** (426 mg, 75%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (d, $^3J_{7\text{-}9}$ = 6.1 Hz, 3 H, H-9), 1.46–1.79 (m, 5 H, H-4, H-5, H-11, H-12), 1.88–2.22 (m, 3 H, H-4´, H-3, H-11´), 2.28–2.39 (m, 1 H, H-5´), 2.55 (s, 3 H, H-13), 2.62–2.73 (m, 1 H, H-3´), 2.86–2.97 (m, 1 H, H-10), 3.20–3.28 (dd, $^3J_{12\text{-}}$

$_1$ = 13.2 Hz, $^3J_{12'\text{-}1}$ = 3.3 Hz, 1 H, H-1), 3.76–3.85 (m, 1 H, H-1), 3.91–4.07 (m, 2 H, H-10´, H-7), 7.53–7.64 (m, 3 H, H-16, H-17), 7.74–7.80 (m, 2 H, H-15).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6 (d, C-9), 23.4 (u, CH_2), 23.6 (u, CH_2), 23.9 (u, CH_2), 29.9 (d, C-13), 30.3 (u, C-5), 34.4 (u, C-3), 42.1 (u, C-10), 49.2 (d, C-6), 67.8 (d, C-1), 71.0 (u, C-2), 75.3 (d, C-7), 129.3 (d, C-15), 129.6 (d, C-16), 132.7 (d, C-17), 137.7 (u, C-14), 156.2 (u, C-8).

IR (KBr): ν = 3854 (w), 3062 (w), 2958 (m), 2874 (m), 2801 (w), 1700 (s), 1447 (m), 1392 (s), 1336 (w), 1302 (m), 1272 (s), 1233 (s), 1144 (s), 1108 (m), 1075 (m), 1036 (m), 955 (w), 855 (m), 777 (m), 751 (m), 695 (m), 608 (m) cm^{-1}.

MS (EI): *m/z* (%) = 362 [M^+] (13), 208 (14), 182 (10), 164 (100), 163 (41), 148 (18), 125 (10).

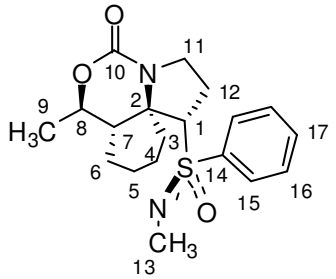
Elemental Analysis:

$C_{19}H_{26}N_2O_3S$ (362.5)	C	H	N
Calculated	62.96	7.23	7.73
Found	63.18	7.43	7.63

Melting point: 135–137 °C.

Optical rotation: $[\alpha]_D$ = –60.3 ° (*c* 0.970, CH_2Cl_2).

4.3 (1*S*,7*R*,7a*S*,11^1*R*)-7-Methyl-1-((*R*)-*N*-methylphenylsulfonimidoyl)octahydrobenzo[*d*]pyrrolo[1,2-*c*][1,3]oxazin-5(1*H*)-one (72)



According to GP_1, sulfoximine **29b** (100 mg, 0.30 mmol) was treated with *n*-BuLi (0.41 mL of 1.6 M solution in *n*-hexane, 0.66 mmol) and ethylene glycol di-*p*-tosylate (122 mg, 0.33 mmol) to give after work up and column chromatography (EtOAc/cyclohexane, 2:1) the diastereomerically pure tricycle **72** (64 mg, 57%) as a colorless solid and remaining starting material **29b** (22 mg, 22%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.36 (m, 1 H, CH_2), 1.40 (d, $^3J_{8\text{-}9}$ = 6.3 Hz, 3 H, H-9), 1.51–1.78 (m, 5 H, CH_2), 1.80–1.95 (m, 1 H, H-7), 2.23–2.47 (m, 3 H, CH_2), 2.64 (s, 3 H, H-13), 3.24–3.52 (m, 3 H, H-1, H-12, CH_2), 3.82–3.92 (m, 1 H, H-11´), 4.58–4.68 (dq, $^3J_{7\text{-}8}$ = 10.4 Hz, $^3J_{9\text{-}8}$ = 6.3 Hz, 1 H, H-8), 7.53–7.66 (m, 3 H, H-16, H-17), 7.76–7.81 (m, 2 H, H-15).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9 (d, C-9), 19.3 (u, CH_2), 21.6 (u, CH_2), 22.5 (u, CH_2), 25.2 (u, CH_2), 29.3 (d, C-13), 29.8 (u, CH_2), 40.8 (u, C-11), 44.0 (d, C-7), 67.5 (u, C-2), 71.8 (d, C-1), 73.0 (d, C-8), 128.9 (d, C-15), 129.4 (d, C-16), 132.8 (d, C-17), 139.0 (u, C-14), 152.5 (u, C-10).

IR (KBr): ν = 3055 (w), 2933 (s), 2864 (m), 2800 (w), 1688 (s), 1422 (s), 1378 (w), 1332 (m), 1267 (w), 1217 (m), 1143 (m), 1105 (m), 1075 (m), 994 (w), 957 (w), 881 (w), 855 (m), 754 (m), 692 (m), 612 (m) cm^{-1}.

MS (EI): *m/z* (%) = 362 [M^+], 285 (24), 284 (41), 241 (18), 240 (60), 208 (17), 207 (97), 206 (10), 183 (13), 182 (100), 164 (34), 163 (28), 162 (24), 153 (11), 148 (22), 138 (25), 136 (11), 135 (28), 134 (22), 125 (26), 122 (15), 120 (15), 109 (11), 108 (12), 107 (18), 106 (12), 95 (15), 91 (11), 81 (11), 80 (12).

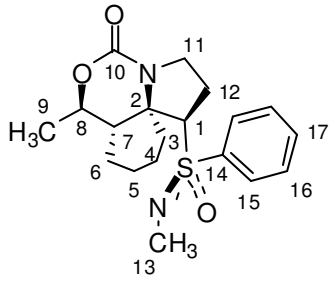
Elemental Analysis:

$C_{19}H_{26}N_2O_3S$ (362.5)	C	H	N
Calculated	62.96	7.23	7.73
Found	62.80	7.37	7.70

Melting point: 193 °C (decomposition).

Optical rotation: $[\alpha]_D$ = +11.2 ° (*c* 1.00, CH_2Cl_2).

4.4 (1*R*,7*R*,7a*S*,11[1]*R*)-7-Methyl-1-((*R*)-*N*-methylphenylsulfonimidoyl)octahydrobenzo[*d*]pyrrolo[1,2-*c*][1,3]oxazin-5(1*H*)-one (*epi*-72)



Preparation by spirocyclization of **29b**

n-BuLi (0.56 mL of 1.6 M solution in *n*-hexane, 0.90 mmol) was added to a solution of the oxazinone **29b** (100 mg, 0.30 mmol) in THF (5 mL). The mixture was allowed to warm to –10 °C within 1 h, cooled to –50 °C, and then treated with ethylene glycol di-*p*-tosylate (244 mg, 0.67 mmol). The mixture was then allowed to warm to room temperature within 12 h. Then saturated aqueous NH_4Cl (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with $MgSO_4$. The solvents were removed in vacuum and the residue was purified by column chromatography (EtOAc) to give the diastereomerically pure tricycle *epi*-**72** (73 mg, 67%) as a colorless solid.

Preparation by epimerization of **72**

To a solution of tricycle **72** (68 mg, 0.19 mmol) in dry THF (4 mL) at –50 °C was added *n*-BuLi (0.14 mL of 1.6 M solution in *n*-hexane, 0.23 mmol). The mixture was allowed to warm up to room temperature within 12 h. Then saturated aqueous NH_4Cl (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with $MgSO_4$. The solvents were removed in vacuum and the residue was purified by column chromatography (EtOAc) to give the diastereomerically pure tricycle *epi*-**72** (58 mg, 85%) as a colorless solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16–1.40 (m, 3 H, CH_2), 1.45 (s, 3 H, H-9), 1.48–1.62 (m, 1 H, CH_2), 1.63–1.81 (m, 2 H, CH_2), 1.82–1.93 (m, 1 H, CH_2), 2.05–2.32 (m, 3 H, CH_2), 2.70 (s, 3 H, H-13), 2.99–3.09 (bd, $^3J_{8\text{-}7}$ = 10.6 Hz, 1 H, H-7), 3.29–3.40 (dt, J = 9.7 Hz, J = 2.2 Hz, 1 H, H-11), 3.50 (d, $^3J_{12\text{-}1}$ = 7.2 Hz, 1 H, H-1), 4.04 (q, J = 9.4 Hz, 1 H, H-11´),

4.68 (dq, $^3J_{7\text{-}8}$ = 10.6 Hz, $^3J_{9\text{-}8}$ = 6.2 Hz, 1 H, H-8), 7.55–7.66 (m, 3 H, H-16, H-17), 7.79–7.87 (m, 2 H, H-15).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7 (d, C-9), 19.9 (u, CH_2), 23.8 (u, CH_2), 24.4 (u, CH_2), 25.5 (u, CH_2), 29.2 (d, C-13), 35.9 (u, CH_2), 28.2 (d, C-7), 44.0 (u, C-11), 66.7 (u, C-2), 68.1 (d, C-1), 73.1 (d, C-8), 129.5 (d, CH), 129.7 (d, CH), 133.0 (d, C-17), 138.3 (u, C-14), 152.9 (u, C-10).

IR (KBr): ν = 3371 (w), 2943 (m), 2807 (w), 2243 (w), 1688 (s), 1419 (s), 1330 (w), 1250 (m), 1197 (w), 1140 (m), 1074 (m), 914 (m), 867 (w), 731 (s), 644 (w) cm^{-1}.

MS (EI): *m/z* (%) = 362 [M^+] (9), 183 (11), 182 (100), 164 (14), 163 (11).

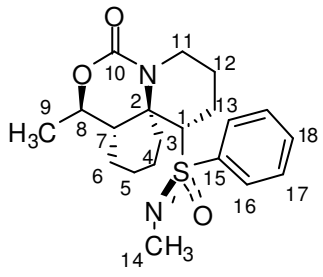
Elemental Analysis:

$C_{19}H_{26}N_2O_3S$ (362.5)	C	H	N
Calculated	62.96	7.23	7.73
Found	62.90	7.11	7.62

Melting point: 184–186 °C

Optical rotation: $[\alpha]_D$ = –88.4 ° (*c* 0.925, CH_2Cl_2).

4.5 (1*S*,8*R*,8a*S*,12^1*R*)-8-Methyl-1-((*R*)-N-methylphenylsulfonimidoyl)octahydro-1H-benzo[*d*]pyrido[1,2-*c*][1,3]oxazin-6(2*H*)-one (73)



According to GP_1, oxazinone **29b** (100 mg, 0.30 mmol) was treated with *n-B*uLi (0.41 mL of 1.6 M solution in *n*-hexane, 0.66 mmol) and 1,3-propanediol di-*p*-tosylate (127 mg, 0.33 mmol) to give after work up and column chromatography (EtOAc/cyclohexane, 2:1) the diastereomerically pure tricycle **73** (66 mg, 59%) as a colorless solid and remaining starting material **29b** (18 mg, 18%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24–1.42 (m, 1 H, H-4), 1.47–1.72 (m, 10 H, H-4´, H-5, H-6, H-9, H-12, H-13), 1.88–1.98 (m, 1 H, H-6´), 2.09–2.22 (m, 2 H, H-3, H-13´), 2.37–2.46 (m, 1 H, H-3´), 2.57 (s, 3 H, H-14), 2.91–3.01 (m, 1 H, H-11), 3.51–3.59 (dd, ^3J = 12.9 Hz, ^3J = 4.1 Hz, 1 H, H-1), 3.70–3.78 (m, 1 H, H-7), 4.11–4.19 (m, 1 H, H-11´), 4.21–4.30 (dq, $^3J_{9\text{-}8}$ = 6.9 Hz, $^3J_{7\text{-}8}$ = 4.4 Hz, 1 H, H-8), 7.53–7.64 (m, 3 H, H-17, H-18), 7.72–7.77 (m, 2 H, H-16).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (u, CH_2), 21.8 (u, CH_2), 22.0 (u, CH_2), 22.1 (d, C-9), 23.6 (u, CH_2), 27.1 (u, CH_2), 27.2 (u, CH_2), 29.8 (d, C-14), 39.06 (u, C-11), 39.12 (u, C-7), 61.9 (u, C-2), 66.8 (d, C-1), 77.5 (d, C-8), 129.3 (d, CH), 129.5 (d, CH), 132.6 (d, C-18), 137.3 (u, C-15), 154.5 (u, C-10).

IR (KBr): ν = 3422 (m), 2932 (m), 2960 (m), 2792 (w), 1673 (s), 1444 (m), 1400 (s), 1261 (m), 1228 (m), 1141 (s), 1100 (m), 1074 (m), 1051 (m), 937 (w), 861 (m), 749 (m), 696 (m), 623 (m) cm^{-1}.

MS (EI): *m/z* (%) = 376 [M^+] (23), 221 (12), 209 (20), 182 (16), 179 (15), 178 (100), 177 (43), 176 (13), 162 (23), 150 (16), 149 (29), 148 (21), 139 (31), 136 (10), 134 (13), 125 (20), 124 (11), 122 (11), 109 (19), 108 (13), 107 (28), 106 (13), 97 (14).

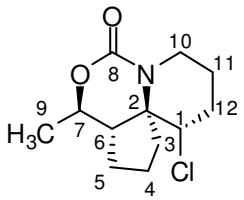
HRMS:

$C_{20}H_{28}N_2O_3S$ (376.2)	[M^+]
Calculated	376.18207
Found	376.18208

Melting point: 157–158 °C (decomposition).

Optical rotation: $[\alpha]_D$ = –48.1 ° (*c* 0.905, CH_2Cl_2).

4.6 (3a*S*,4*R*,11*S*,11[1]*R*)-11-Chloro-4-methyloctahydrocyclopenta[*d*]pyrido[1,2-*c*][1,3]oxazin-6(1*H*)-one (74)



To a solution of sulfoximine **71** (70 mg, 0.193 mmol) in CH_2Cl_2 (2 mL) was added 1-chloroethyl chloroformate (40 µL, 0.386 mmol) and the solution was stirred at rt for 2 d. The solvent was removed in vacuum and the residue was purified by column chromatography (EtOAc/cyclohexane, 1:2) to give chloride **74** (35 mg, 74%) as a colorless oil.
R_f(chloride **74**) = 0.5 and R_f(sulfinamide **55**) = 0.75 in EtOAc/cyclohexane, 1:1.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (d, $^3J_{7\text{-}9}$ = 6.4 Hz, 3 H, H-9), 1.55–1.63 (m, 1 H, H-5), 1.65–2.00 (m, 6 H, H-3, H-4, H-11, H-12), 2.03–2.12 (m, 1 H, H-5´), 2.13–2.19 (m, 1 H, H-12´), 2.24–2.32 (m, 2 H, H-3´, H-6), 2.85–2.94 (m, 1 H, H-10), 3.86–3.92 (dd, $^3J_{12\text{-}1}$ = 11.9 Hz, $^3J_{12'\text{-}1}$ = 4.0 Hz, 1 H, H-1), 3.93–4.01 (dq, $^3J_{6\text{-}7}$ = 10.4 Hz, $^3J_{9\text{-}7}$ = 6.4 Hz, 1 H, H-7), 4.10–4.16 (m, 1 H, H-10´)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5 (d, C-9), 24.4 (u, C-4), 25.0 (u, C-11), 30.3 (u, C-5), 31.7 (u, C-3), 32.5 (u, C-12), 42.0 (u, C-10), 50.9 (d, C-6), 66.2 (d, C-1), 70.7 (u, C-2), 74.0 (d, C-7), 155.7 (u, C-8).

IR (KBr): ν = 2954 (m), 2877 (m), 1704 (s), 1452 (m), 1396 (m), 1333 (w), 1264 (m), 1148 (m), 1038 (w), 949 (w), 913 (w), 634 (w) cm^{-1}.

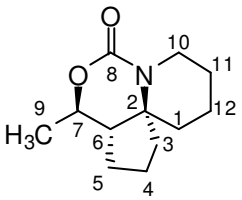
MS (EI): *m/z* (%) = 245 [M^++2] (11), 244 [M^++1] (11), 243 [M^+] (32), 209 (13), 208 (100), 164 (34), 91 (17).

HRMS:

$C_{12}H_{18}ClNO_2$ (243.7)	$[M^+]$
Calculated	243.10261
Found	243.10257

Optical rotation: $[\alpha]_D$ = +38.2 ° (*c* 0.815, CH_2Cl_2).

4.7 (3a*S*,4*R*,11[1]*S*)-4-Methyloctahydrocyclopenta[*d*]pyrido[1,2-*c*][1,3]oxazin-6(1*H*)-one (75)



Nickel aluminium alloy powder (50:50, 1.54 g, 17.9 mmol) was suspended in desalted H_2O (60 mL) and treated with KOH until the evolution of H_2 ceased. Subsequenly, the suspension was heated at 80 °C for 30 min. After the mixture had cooled to room temperature, the aqueous layer was decanted, and the RANEY nickel was washed with desalted H_2O (10 × 50 mL) and suspended in THF/H_2O (4:1, 30 mL). Sulfoximine **71** (162 mg, 0.447 mmol) was added to the RANEY nickel and the mixture was stirred for 24 h at room temperature. The suspension was filtered over celite and saturated aqueous NaCl (15 mL) was added to the filtrate. The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic phases were dried with $MgSO_4$. The solvents were removed in vacuum and the residue was filtered over silica gel (EtOAc) to give the desired tricycle **75** (90 mg, 96%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.38 (m, 4 H, H-9, CH_2), 1.39–1.84 (m, 10 H, H-6 CH_2), 1.91–2.03 (m, 1 H, CH_2), 2.24–2.36 (m, 1 H, CH_2), 2.75–2.85 (m, 1 H, H-10), 3.86–3.96 (dq, $^3J_{6\text{-}7}$ = 10.7 Hz, $^3J_{9\text{-}7}$ = 6.3 Hz, 1 H, H-7), 4.21–4.30 (m, 1 H, H-10´).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7 (d, C-9), 20.8 (u, CH_2), 22.3 (u, CH_2), 24.4 (u, CH_2), 26.9 (u, CH_2), 34.2 (u, CH_2), 36.8 (u, CH_2), 42.8 (u, C-10), 51.4 (d, C-6), 65.4 (u, C-2), 74.0 (d, C-7), 154.9 (u, C-8).

IR (KBr): ν = 2929 (s), 2877 (m), 1679 (s), 1517 (w), 1449 (m), 1415 (s), 1374 (w), 1332 (m), 1266 (s), 1178 (m), 1147 (w), 119 (m), 1071 (m), 1042 (m), 977 (m), 893 (w), 760 (m), 668 (w), 640 (w) cm^{-1}.

MS (EI): *m/z* (%) = 209 [M^+] (41), 168 (10), 167 (100), 166 (17), 152 (74), 150 (17), 136 (31), 122 (19), 108 (15), 97 (19).

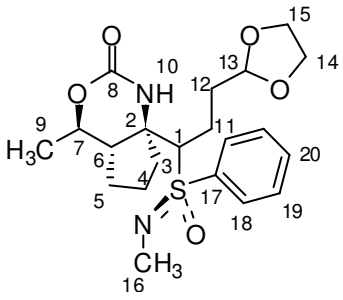
HRMS:

$C_{12}H_{19}NO_2$ (209.3)	[M^+]
Calculated	209.14158
Found	209.14167

Optical rotation: $[\alpha]_D$ = +18.5 ° (*c* 1.04, CH_2Cl_2).

5. N-Acyl iminium ion route

5.1 (4*R*,4a*S*,7a*R*)-7a-((*R*)-3-(1,3-Dioxolan-2-yl)-1-((*R*)-N-methylphenylsulfonimidoyl)propyl)-4-methylhexahydrocyclopenta[*d*][1,3]oxazin-2(1*H*)-one (80)



n-BuLi (6.4 mL of 1.6 M solution in *n*-hexane, 10.2 mmol) was added to a solution of the oxazinone **29a** (1.50 g, 4.64 mmol) in THF (150 mL). The mixture was allowed to warm to –10 °C within 1 h, cooled to –50 °C, and then treated with 2-(2-bromoethyl)-1,3-dioxolane (0.60 mL, 5.12 mmol). The mixture was allowed to warm to room temperature within 12 h. Then saturated aqueous NH_4Cl (150 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried with $MgSO_4$. The solvents were removed in vacuum and the residue was purified by column chromatography (EtOAc to EtOAc/*i*-PrOH, 9:1) to give the diastereomerically pure sulfoximine **80** (1.28 g, 65%) as a colorless oil and remaining starting material **29b** (152 mg, 10%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.45 (m, 1 H, CH_2), 1.32 (d, $^3J_{7\text{-}9}$ = 6.0 Hz, 3 H, H-9), 1.53–1.67 (m, 3 H, H-12, CH_2), 1.75–1.90 (m, 3 H, CH_2), 1.97–2.12 (m, 3 H, H-6, H-11), 2.72–2.87 (m, 1 H, CH_2), 2.76 (s, 3 H, H-16), 3.34 (bd, $^3J_{11\text{-}1}$ = 7.7 Hz, 1 H, H-1), 3.74–3.99 (m, 5 H, H-7, H-14, H-15), 4.66 (t, $^3J_{12\text{-}13}$ = 4.1 Hz, 1 H, H-13), 7.24 (bs, 1 H, H-10), 7.54–7.66 (m, 3 H, H-19, H-20), 7.82–7.88 (m, 2 H, H-18).

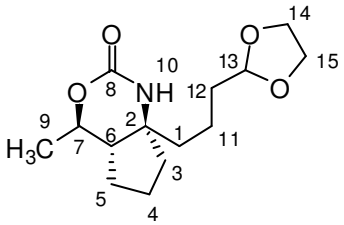
^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 (d, C-9), 20.5 (u, C-11), 22.2 (u, CH_2), 26.7 (u, CH_2), 29.7 (d, C-16), 32.8 (u, C-12), 39.1 (u, CH_2), 46.6 (d, C-6), 64.7 (u, CH_2), 65.0 (u, CH_2), 68.2 (u, C-2), 70.4 (d, C-1), 74.8 (d, C-7), 103.5 (d, C-13), 129.4 (d, CH), 129.6 (d, CH), 133.1 (d, C-20), 139.7 (u, C-17), 155.2 (u, C-8).

IR ($CHCl_3$): ν = 3377 (w), 3275 (w), 2957 (m), 2883 (m), 1710 (s), 1446 (m), 1392 (m), 1322 (m), 1235 (s), 1138 (s), 1078 (m), 861 (w), 760 (m), 713 (m) cm^{-1}.

MS (CI, isobutane): *m/z* (%) = 423 [M^++1] (3), 269 (14), 268 (84), 224 (15), 206 (24), 181 (10), 156 (100).

Optical rotation: $[\alpha]_D$ = –80.6 ° (*c* 1.16, CH_2Cl_2).

5.2 Synthesis of (4*R*,4a*S*,7a*S*)-7a-(3-(1,3-Dioxolan-2-yl)propyl)-4-methylhexahydrocyclopenta[*d*][1,3]oxazin-2(1*H*)-one (79)



Preparation by cuprate substitution of iodide **50**

To a solution of 2-(2-bromoethyl)-1,3-dioxolane (0.32 mL, 2.72 mmol) in dry THF (20 mL) at –78 °C was added *t*-BuLi (3.63 mL of 1.6 M solution in *n*-pentane, 5.44 mmol). The mixture was stirred at this temperature for 2 h. Then it was added to a mixture of CuI (259 mg, 1.36 mmol) in THF (5 mL) and Me_2S (1 mL) at –30 °C. The mixture was stirred at this temperature for 30 min. During this time it turned black. Then it was added to a solution of iodide **50** (100 mg, 0.34 mmol) in THF (2 mL) at –30 °C. The mixture was allowed to warm to room temperature within 2 h. TLC showed a complete conversion. Saturated aqueous $(NH_4)_2CO_3$ (10 mL) and concentrated NH_3 (10 mL) were added and the mixture was extracted with EtOAc (3 × 20 mL). The organic layer was dried with $MgSO_4$ and the solvents were removed in vacuum. The residue was purified by column chromatography on silica gel (EtOAc) to give the desired acetal **79** (66 mg, 72%) as a colorless oil.

Remark: Increasing the scale, the yield droped dramatically.

Preparation by reduction of sulfoximine **80**

Nickel aluminium alloy powder (50:50, 10.0 g, 0.114 mol) was suspended in desalted H_2O (500 mL) and treated with KOH until the evolution of H_2 ceased. Subsequently, the suspension was heated at 80 °C for 30 min. After the mixture had cooled to room temperature, the aqueous layer was decanted, and the RANEY nickel was washed with desalted H_2O (10×100 mL) and suspended in THF/H_2O (4:1, 150 mL). Sulfoximine **80** (1.21 g, 2.86 mmol) was added to the RANEY nickel and the mixture was stirred for 24 h at room temperature. The suspension was filtered over celite and NaCl was added to the filtrate. The aqueous layer was extracted with EtOAc (2×50 mL) and the combined organic phases were dried with $MgSO_4$. The solvents were removed in vacuum and the residue was filtered over silica gel (EtOAc) to give the desired acetal **79** (692 mg, 90%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, $^3J_{7\text{-}9}$ = 6.0 Hz, 3 H, H-9), 1.40–1.97 (m, 13 H, H-1, H-3, H-4, H-5, H-6, H-11, H-12), 3.82–3.87 (m, 2 H, H-15), 3.93–4.01 (m, 3 H, H-7, H-14), 4.84 (t, ^3J = 4.7 Hz, 1 H, H-13), 5.83 (bs, 1 H, H-10).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1 (u, CH_2), 19.2 (d, C-9), 22.6 (u, CH_2), 27.7 (u, CH_2), 33.7 (u, CH_2), 39.9 (u, CH_2), 41.6 (u, CH_2), 46.7 (d, C-6), 64.1 (u, C-2), 64.8 (u, C-14, C-15), 75.9 (d, C-7), 104.0 (d, C-13), 156.1 (u, C-8).

IR ($CHCl_3$): ν = 3247 (m), 3115 (w), 2954 (s), 2882 (m), 1706 (s), 1458 (m), 1404 (m), 1317 (m), 1220 (m), 1137 (m), 1048 (m), 941 (w), 756 (s), 666 (w) cm^{-1}.

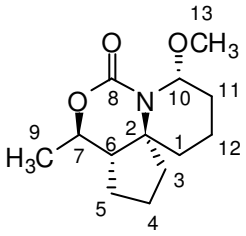
MS (EI): *m/z* (%) = 269 [M^+] (5), 226 (17), 154 (82), 153 (20), 136 (20), 127 (10), 110 (100), 99 (12), 93 (11).

HRMS:

$C_{14}H_{23}NO_4$ (269.3)	[M^+]
Calculated	269.16271
Found	269.16283

Optical rotation: $[\alpha]_D$ = +11.8 ° (*c* 1.80, CH_2Cl_2).

5.3 Synthesis of (3a*S*,4*R*,8*R*,11[1]*S*)-8-Methoxy-4-methyloctahydrocyclopenta[*d*]pyrido[1,2-*c*][1,3]oxazin-6(1*H*)-one (76)



To a solution of acetal **79** (100 mg, 0.37 mmol) in dry MeOH (4 mL) was added concentrated H_2SO_4 (3 drops). The mixture was stirred at room temperature until TLC showed a complete conversion (3 d). Then saturatued aqueous $NaHCO_3$ (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried with $MgSO_4$ and the solvents were removed in vacuum. The residue was purified by column chromatography on silica gel (EtOAc/cyclohexane, 1:2) to give diastereomerically pure (N,O)-acetal **76** (61 mg, 69%) as a colorless oil.

^{1}H NMR (500 MHz, C_6D_6): δ = 0.71–0.79 (ddt, J = 15.3 Hz, J = 4.0 Hz, J = 2.1 Hz, 1 H, H-1), 0.79–0.88 (m, 1 H, CH_2), 1.01 (d, $^3J_{7\text{-}9}$ = 6.1 Hz, 3 H, H-9), 1.03–1.14 (m, 2 H, H-12), 1.18–1.36 (m, 5 H, H-1´, H-3, H-6), 1.36–1.46 (m, 1 H, H-11), 1.72–1.82 (m, 2 H, H-11´, H-12´), 2.20–2.27 (ddd, J = 12.8 Hz, J = 8.2 Hz, J = 0.9 Hz, 1 H, H-3´), 3.19 (s, 3 H, H-13), 3.49–3.57 (dq, $^3J_{6\text{-}7}$= 10.4 Hz, $^3J_{9\text{-}7}$= 6.1 Hz, 1 H, H-7), 5.98 (dd, $^3J_{11\text{-}10}$= 4.0 Hz, $^3J_{11´\text{-}10}$= 1.8 Hz, 1 H, H-10).

^{13}C NMR (75 MHz, C_6D_6): δ = 15.2 (u, CH_2), 18.5 (d, C-9), 20.9 (u, CH_2), 23.6 (u, CH_2), 29.8 (u, C-11), 34.4 (u, C-1), 34.9 (u, C-3), 50.9 (d, C-6), 55.0 (d, C-13), 63.4 (u, C-2), 72.3 (d, C-7), 83.0 (d, C-10), 153.3 (u, C-8).

IR ($CHCl_3$): ν = 2944 (s), 1691 (s), 1453 (m), 1403 (s), 1369 (m), 1308 (m), 1279 (w), 1244 (w), 1211 (w), 1192 (w), 1161 (w), 1123 (m), 1070 (s), 973 (w), 952 (w), 913 (m), 843 (w), 759 (m), 698 (w), 617 (w) cm^{-1}.

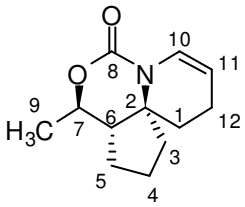
MS (EI): *m/z* (%) = 239 [M^+] (8), 225 (14), 224 (100), 209 (16), 208 (35), 197 (35), 182 (25), 180 (22), 164 (22), 163 (10), 162 (24), 154 (11), 122 (11), 121 (17), 110 (10), 93 (13).

HRMS:

$C_{13}H_{21}NO_3$ (239.3)	$[M^+]$
Calculated	239.15214
Found	239.15205

Optical rotation: $[\alpha]_D$ = +39.5 ° (*c* 0.965, EtOAc).

5.4 (3a*S*,4*R*,11[1]*S*)-4-methyl-2,3,3a,4,10,11-hexahydrocyclopenta[*d*]pyrido[1,2-*c*][1,3]oxazin-6(1*H*)-one (78)



To a mixture of acetal **79** (105 mg, 0.390 mmol) in dry toluene (2 mL) was added *p*-toluenesulfonic acid (6.7 mg, 0.039 mmol) and the mixture was stirred at reflux temperature for 1 h. Then saturated aqueous $NaHCO_3$ (5 mL) is added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layer was dried with $MgSO_4$ and the solvents were removed in vacuum. Purification by column chromatography on silica gel (EtOAc/cyclohexane, 1:1) gave the desired enamide **78** (60 mg, 74%) as a colorless solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, $^3J_{7\text{-}9}$ = 6.2 Hz, 3 H, H-9), 1.48–1.90 (m, 7 H, H-6, CH_2) 1.93–2.09 (m, 2 H, CH_2), 2.09–2.14 (m, 2 H, CH_2), 4.12–4.24 (dq, $^3J_{6\text{-}7}$ = 9.6 Hz, $^3J_{9\text{-}7}$ = 6.2 Hz, 1 H, H-7) 5.04–5.13 (m, 1 H, H-11), 6.86–6.93 (dt, $^3J_{11\text{-}10}$ = 8.4 Hz, $^4J_{12\text{-}10}$ = 2.0 Hz, 1 H, H-10).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (d, C-9), 19.3 (u, CH_2), 20.5 (u, CH_2), 25.7 (u, CH_2), 30.9 (u, CH_2), 33.7 (u, CH_2), 48.0 (d, C-6), 63.5 (u, C-2), 74.1 (d, C-7), 108.8 (d, C-11), 125.7 (d, C-10).

IR (KBr): ν = 3061 (w), 2965 (m), 2903 (m), 1673 (s), 1516 (w), 1459 (w), 1406 (s), 1373 (m), 1315 (s), 1205 (w), 1168 (w), 1124 (m), 1054 (m), 977 (w), 945 (w), 912 (w), 809 (w), 757 (m), 728 (m), 624 (w) cm^{-1}.

MS (EI): *m/z* (%) = 207 [M^+] (100), 163 (12), 162 (47), 148 (85), 135 (20), 134 (98), 120 (26), 108 (21), 95 (43), 94 (28), 91 (12), 82 (16), 80 (15).

Elemental Analysis:

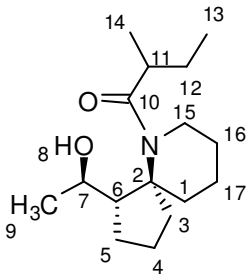
$C_{12}H_{17}NO_2$ (207.1)	C	H	N
Calculated	69.54	8.27	6.76
Found	69.63	7.88	6.61

Melting point: 99–102 °C

Optical rotation: $[\alpha]_D$ = +67.3 ° (*c* 1.15, CH_2Cl_2).

6. Efforts toward the formal total synthesis of halichlorine and pinnaic acid

6.1 1-((1*S*,5*S*)-1-((*R*)-1-hydroxyethyl)-6-azaspiro[4.5]decan-6-yl)-2-methylbutan-1-one (93)



To a solution of tricycle **75** (100 mg, 0.478 mmol), TMEDA (72 µL, 0.478 mmol) and THF (7 mL) at 0 °C was added *sec*-BuLi (0.51 mL of 1.4 M solution in cyclohexane, 0.717 mmol). After the solution was stirred at this temperature for 40 min, allyl bromide (62 µL, 0.717 mmol) was added and the solution had been stirred for 2 h at 0 °C. Then saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried with $MgSO_4$. The solvents were removed in vacuum and the residue was purified by column chromatography (EtOAc/cyclohexane, 1:2) to give amides **93** and *epi*-**93** (31 mg, 24%) and starting material **75** (62 mg, 62%) could be isolated by washing the column with EtOAc. Small amounts of amides **93** and *epi*-**93** could be obtained in a pure form.

R_f(amide **93**) = 0.75, R_f(amide *epi*-**93**) = 0.63 and R_f(tricycle **75**) = 0.33 in Et_2O.

• Analytical data of 93

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, $^3J_{12\text{-}13}$ = 7.4 Hz, 3 H, H-13), 1.07 (d, $^3J_{11\text{-}14}$ = 6.7 Hz, 3 H, H-14), 1.14 (d, $^3J_{7\text{-}9}$ = 6.2 Hz, 3 H, H-9), 1.26–1.48 (m, 3 H, CH_2), 1.50–1.76 (m, 9 H, H-6, CH_2), 1.78–1.90 (m, 1 H, CH_2), 1.97–2.16 (m, 2 H, CH_2), 2.39–2.53 (m, 1 H, CH_2), 2.50–2.63 (m, 1 H, H-11), 3.54–3.70 (m, 2 H, H-15), 3.72–3.85 (m, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (d, C-13), 17.1 (u, CH_2), 17.2 (d, C-14), 22.8 (u, CH_2), 23.9 (d, C-9), 24.3 (u, CH_2), 27.1 (u, CH_2), 30.4 (u, CH_2), 34.2 (u, CH_2), 37.4 (u, CH_2), 39.3 (d, C-11), 41.9 (u, C-15), 60.4 (d, C-6), 68.6 (u, C-2), 69.6 (d, C-7), 176.7 (u, C-10).

IR ($CHCl_3$): ν = 3423 (m), 2943 (s), 2869 (s), 1723 (w), 1618 (s), 1463 (s), 1427 (s), 1371 (w), 1321 (w), 1228 (m), 1148 (m), 1116 (m), 1062 (m), 971 (w), 924 (w), 869 (w), 754 (m) cm^{-1}.

MS (EI): *m/z* (%) = 267 [M^+] (15), 249 (31), 210 (30), 184 (14), 182 (34), 181 (33), 180 (44), 169 (10), 168 (62), 166 (45), 138 (24), 110 (60), 98 (42), 97 (100), 84 (31).

• **Analytical data of *epi*-93**

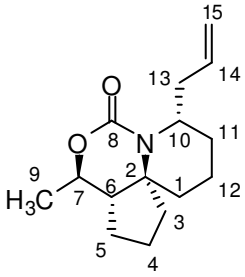
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, $^3J_{12\text{-}13}$ = 7.7 Hz, 3 H, H-13), 1.09 (d, $^3J_{11\text{-}14}$ = 6.9 Hz, 3 H, H-14), 1.15 (d, $^3J_{7\text{-}9}$ = 6.2 Hz, 3 H, H-9), 1.28–1.46 (m, 4 H, CH_2), 1.48–1.74 (m, 8 H, H-6, CH_2), 1.77–1.90 (m, 1 H, CH_2), 1.99–2.17 (m, 2 H, CH_2), 2.46–2.63 (m, 2 H, H-11, CH_2), 3.50–3.82 (m, 3 H, H-7, H-15).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (d, C-13), 17.0 (u, CH_2), 17.7 (d, C-14), 22.6 (u, CH_2), 24.1 (d, C-9), 24.4 (u, CH_2), 27.3 (u, CH_2), 30.7 (u, CH_2), 34.2 (u, CH_2), 37.6 (u, CH_2), 39.4 (d, C-11), 41.5 (u, C-15), 60.6 (d, C-6), 68.6 (u, C-2), 69.5 (d, C-7), 176.5 (u, C-10).

IR ($CHCl_3$): ν = 3409 (m), 2943 (s), 2869 (s), 1618 (s), 1463 (s), 1430 (s), 1372 (m), 1320 (m), 1147 (m), 1117 (m), 1059 (m), 974 (w), 924 (w), 868 (w), 756 (m), 664 (w) cm^{-1}.

MS (EI): *m/z* (%) = 267 [M^+] (18), 249 (28), 210 (34), 184 (14), 182 (34), 181 (34), 180 (44), 169 (10), 168 (67), 166 (45), 138 (22), 110 (60), 98 (41), 97 (100), 84 (31).

6.2 (3a*S*,4*R*,8*S*,11[1]*S*)-8-allyl-4-methyloctahydrocyclopenta[*d*]pyrido[1,2-*c*][1,3]oxazin-6(1*H*)-one (87)



To a solution of acetal **76** (31 mg, 0.129 mmol) in CH_2Cl_2 (4 mL) at –78 °C was added $BF_3.OEt_2$ (98 µL, 0.774 mmol) and allyltrimethylsilane (123 µL, 0.774 mmol). The mixture was allowed to warm to room temperature within 5 h. Then saturated aqueous $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and the solvents were removed in vacuum. ^{1}H NMR spectroscopy of the crude mixture showed a mixture of alkene **87** (≥ 98% de) and enamide **78** in a ratio of 3:1. Column chromatography of the crude mixture (*n*-pentane/*i*-PrOH, 16:1) gave **87** (23 mg, 71%, R_f = 0.5) as a colorless oil and **78** (6 mg, 22%, R_f = 0.4) as a colorless solid.

Analytical data of alkene 87

^{1}H NMR (500 MHz, C_6D_6): δ = 0.69-0.78 (ddt, *J* = 13.1 Hz, *J* = 4.0 Hz, *J* = 1.5 Hz, 1 H, H-1), 0.84-0.94 (m, 1 H, H-5), 0.99 (d, $^3J_{7\text{-}9}$ = 6.1 Hz, 3 H, H-9), 1.00-1.14 (m, 3 H, H-1´, H-4, H-12), 1.15-1.48 (m, 7 H, H-3, H-4´, H-5´, H-6, H-11, H-12), 1.67-1.75 (m, 1 H, H-3´), 2.04-2.13 (m, 1 H, H-13), 2.28-2.36 (m, 1 H, H-13´), 3.47-3.55 (dq, $^3J_{6\text{-}7}$ = 9.8 Hz, $^3J_{9\text{-}7}$ = 6.4 Hz, 1 H, H-7), 5.00-5.07 (m, 2 H, H-15), 5.07-5.12 (m, 1 H, H-10), 5.80-5.90 (m, 1 H, H-14).

^{13}C NMR (125 MHz, C_6D_6): δ = 15.5 (u, C-12), 18.6 (d, C-9), 20.7 (u, C-4), 23.9 (u, C-5), 26.7 (u, C-11), 35.3 (u, C-3), 35.6 (u, C-1), 38.3 (u, C-13), 50.1 (d, C-6), 51.4 (d, C-10), 63.4 (u, C-2), 71.5 (d, C-7), 116.3 (u, C-15), 136.7 (d, C-14), 153.1 (u, C-8).

IR (KBr): ν = 3074 (w), 2938 (s), 1680 (s), 1452 (w), 1405 (s), 1369 (m), 1308 (m), 1276 (m), 1128 (m), 1089 (m), 997 (w), 916 (m), 759 (m), 658 (w) cm^{-1}.

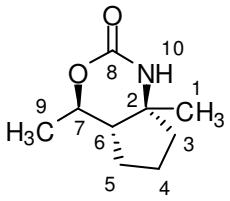
MS (EI): *m/z* (%) = 250 [M^++1] (37), 249 [M^+] (1), 209 (13), 208 (100), 165 (12), 164 (93), 147 (23), 121 (37), 108 (11), 105 (14), 93 (19), 82 (10).

HRMS:

$C_{15}H_{23}NO_2$ (249.4)	[M^+]
Calculated	249.17288
Found	249.17276

Optical rotation: $[\alpha]_D$ = –7.08 ° (*c* 0.565, CH_2Cl_2).

6.2 (4*R*,4a*S*,7a*R*)-4,7a-dimethylhexahydrocyclopenta[*d*][1,3]oxazin-2(1*H*)-one (105)



Preparation by reduction of iodide **50** *by the undesired formation of copper hydride species*

To a solution of 4-bromobut-1-ene (0.42 mL, 4.07 mmol) in dry THF (5 mL) at –78 °C was added *t*-BuLi (5.40 mL of 1.6 M solution in *n*-pentane, 8.16 mmol). The mixture was stirred at this temperature for 2 h. Then it was added to a solution of CuI (388 mg, 2.04 mmol) in THF (5 mL) and Me_2S (1 mL) at –30 °C. The mixture was stirred at this temperature for 30 min. During this time it turned black. Then it was added to a solution of iodide **50** (150 mg, 0.51 mmol) in THF (2 mL) at –30 °C. The mixture was allowed to warm to room temperature within 2 h. TLC showed a complete conversion. Saturated aqueous $(NH_4)_2CO_3$ (10 mL) and concentrated NH_3 (10 mL) were added and the mixture was extracted with EtOAc. The organic layer was dried with $MgSO_4$ and the solvents were removed in vacuum. The residue was purified by column chromatography on silica gel (EtOAc) to give a colorless oil (54 mg) which contained oxazinone **105** as the major compound according to NMR.

Preparation by reduction of sulfoximine **29a**

Nickel aluminium alloy powder (50:50, 3.30 g, 38.4 mmol) was suspended in desalted H_2O (100 mL) and treated with KOH until the evolution of hydrogen ceased. Subsequenly, the suspension was heated at 80 °C for 30 min. After the mixture had cooled to room temperature, the aqueous layer was decanted, and the RANEY nickel was washed with desalted H_2O (10×80 mL) and suspended in THF/H_2O (4:1, 50 mL). Sulfoximine **29a** (310 mg, 0.961 mmol) was added to the RANEY nickel and the mixture was stirred for 24 h at room temperature. The suspension was filtered over celite and saturated aqueous NaCl was added to the filtrate. The aqueous layer was extrated with EtOAc (2×50 mL) and the combined organic phases were dried with $MgSO_4$. Solvent was removed in vacuum and the residue was filtered over silica gel (EtOAc) to give the desired tricycle **105** (120 mg, 74%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.22 (s, 3 H, H-1), 1.27 (d, $^3J_{7\text{-}9}$ = 6.3 Hz, 3 H, H-9), 1.34-1.44 (m, 1 H, CH_2), 1.50-1.73 (m, 5 H, H-6, CH_2), 1.85-1.96 (m, 1 H, CH_2), 3.88-3.97 (dq, $^3J_{6\text{-}7}$ = 10.2 Hz, $^3J_{9\text{-}7}$ = 6.3 Hz, 1 H, H-7), 6.76 (bs, 1 H, H-10).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.2 (d, C-9), 22.5 (u, CH_2), 27.3 (u, CH_2), 29.5 (d, C-1), 41.0 (u, CH_2), 48.5 (d, C-6), 61.1 (u, C-2), 76.0 (d, C-7), 156.1 (u, C-8).

IR (KBr): ν = 3247 (m), 3112 (m), 2963 (m), 2878 (m), 1705 (s), 1412 (m), 1324 (m), 1223 (w), 1174 (w), 1084 (m), 1058 (m), 979 (w), 777 (w), 623 (w) cm^{-1}.

MS (EI): *m/z* (%) = 169 [M^+] (22), 154 (33), 127 (100), 126 (19), 112 (45), 110 (56), 97 (11), 96 (63), 83 (16), 82 (30), 81 (13).

HRMS:

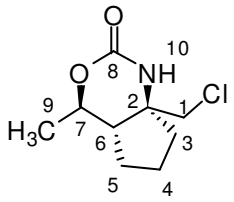
$C_9H_{15}NO_2$ (169.22)	[M^+]
Calculated	169.11028
Found	169.11033

Melting point: 76–78°C.

Optical rotation: $[\alpha]_D$ = +31.2 ° (*c* 1.20, CH_2Cl_2).

7. Synthesis of protected β-amino acids

7.1 (4*R*,4a*S*,7a*R*)-7a-(Chloromethyl)-4-methylhexahydrocyclopenta[*d*][1,3]oxazin-2(1*H*)-one (115)



1-Chlorethyl chloroformate (304 µL, 2.82 mmol) was added at room temperature to a solution of oxazinone **29a** (700 mg, 2.17 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature until TLC indicated almost a complete conversion of the sulfoximine (4 h). Concentration in vacuum and purification of the residue by column chromatography (EtOAc/cyclohexane, 2:1) afforded the desired chloride **115** (356 mg, 81%) as a colorless solid.

R_f(chloride **115**) = 0.55 and R_f(sulfinamide **55**) = 0.9 in EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, $^3J_{7\text{-}9}$ = 6.2 Hz, 3 H, H-9), 1.48–2.12 (m, 7 H, H-3, H-4, H-5, H-6), 3.49 (d, $^2J_{1'\text{-}1}$ = 11.4 Hz, 1 H, H-1), 3.56 (d, $^3J_{1\text{-}1'}$ = 11.1 Hz, 1 H, H-1´), 4.02 (dq, $^3J_{9\text{-}7}$ = 6.2 Hz, $^3J_{6\text{-}7}$ = 9.6 Hz, 1 H, H-7), 6.19 (bs, 1 H, H-10).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1 (d, C-9), 23.0 (u, CH_2), 28.3 (u, CH_2), 37.9 (u, CH_2), 46.2 (d, C-6), 52.7 (u, C-1), 65.0 (u, C-2), 75.9 (d, C-7), 156.2 (u, C-8).

IR (KBr): ν = 3337 (m), 3248 (m), 3132 (m), 2976 (s), 2940 (m), 2889 (m), 1704 (s), 1457 (m), 1431 (m), 1391 (s), 1321 (s), 1281 (m), 1213 (w), 1162 (w), 1119 (w), 1086 (m), 1054 (m), 1014 (m), 975 (w), 938 (w), 865 (w), 752 (m), 707 (m), 623 (m) cm^{-1}.

MS (CI, methane): *m/z* (%) = 204 [M^++1] (100).

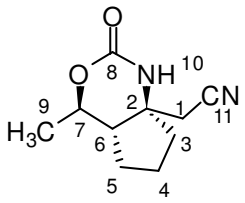
Elemental Analysis:

$C_9H_{14}ClNO_2$ (203.1)	C	H	N
Calculated	53.08	6.93	6.88
Found	53.16	6.95	6.75

Melting point: 118–120°C.

Optical rotation: $[\alpha]_D$ = +1.07 ° (*c* 1.02, CH_2Cl_2).

7.2 2-((4*R*,4a*S*,7a*S*)-4-methyl-2-oxooctahydrocyclopenta[*d*][1,3]oxazin-7a-yl)acetonitrile (116)



KCN (234 mg, 3.56 mmol) was added at room temperature to a solution of chloride **115** (365 mg, 1.80 mmol) in DMF (9 mL). The resulting mixture was heated with stirring at 100 °C for 2 h. After the mixture had been cooled to room temperature, the solvent was removed in vacuum. The remaining solid was purified by column chromatography (EtOAc) to afford the desired nitrile **116** (329 mg, 94%) as a colorless solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (d, $^3J_{7\text{-}9}$ = 6.4 Hz, 3 H, H-9), 1.52–2.15 (m, 7 H, H-3, H-4, H-5, H-6), 2.63 (d, $^2J_{1'\text{-}1}$ = 16.8 Hz, 1 H, H-1), 2.71 (d, $^2J_{1\text{-}1'}$ = 16.6 Hz, 1 H, H-1´), 3.97–4.09 (m, 1 H, H-7), 7.12 (bs, 1 H, H-10)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 (d, C-9), 23.0 (u, CH_2), 28.3 (u, CH_2), 31.1 (u, C-1), 40.0 (u, CH_2), 47.4 (d, C-6), 62.2 (u, C-2), 76.2 (d, C-7), 116.8 (u, C-11), 156.2 (u, C-8).

IR (KBr): *v* = 3294 (s), 3116 (w), 2961 (m), 2934 (m), 2254 (w), 1671 (s), 1471 (m), 1416 (s), 1317 (s), 1215 (w), 1168 (m), 1126 (w), 1081 (m), 1052 (m), 1026 (m), 943 (w), 865 (w), 772 (m), 636 (w) cm^{-1}.

MS (EI): *m/z* (%) = 194 [M^+] (0.5), 154 (72), 121 (14), 110 (100), 107 (11), 93 (11), 82 (15).

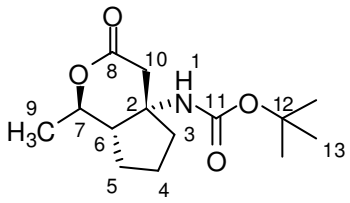
Elemental Analysis:

$C_{10}H_{14}N_2O_2$ (194.2)	C	H	N
Calculated	61.84	7.27	14.42
Found	61.69	7.22	14.33

Melting point: 120 °C.

Optical rotation: $[\alpha]_D$ = +27.6 ° (*c* 1.03, CH_2Cl_2).

7.3 *Tert*-butyl (1*R*,4a*S*,7a*S*)-1-methyl-3-oxooctahydrocyclopenta[*c*]pyran-4a-ylcarbamate (118)



A mixture of nitrile **116** (150 mg, 0.77 mmol), CsOH (1.74 g, 11.6 mmol), MeOH (3 mL) and H_2O (3 mL) was stirred at reflux temperature for 3 d. The solution was carrefully acidified to pH = 5 with concentrated aqueous HCl (3N). Then MeOH was removed in vacuum and H_2O was removed by lyophilization to give a mixture of colorless salts. The salts were stirred in a solution of $CHCl_3$/MeOH (1:1) to extract the organic compounds. After repeating this process (3 × 15 mL), the organic layers were combined and dried with $MgSO_4$. The solvent was removed in vacuum to give the crude amino acid **117** which was directly used for the next step. To a solution of the crude amino acid **117** in CH_2Cl_2 (5 mL) was added triethylamine (0.54 mL, 3.85 mmol) and Boc-anhydride (840 mg, 3.85 mmol). The mixture was stirred at room temperature for 3 d. Then saturated aqueous NH_4Cl was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried with $MgSO_4$ and the solvents were removed in vacuum. Purification by column chromatography (EtOAc/cyclohexane, 1:2) gave lactone **118** (114 mg, 55%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, $^{3}J_{7\text{-}9}$ = 6.3 Hz, 3 H, H-9), 1.41–1.51 (m, 3 H, CH_2), 1.44 (s, 9 H, H-13), 1.69–1.80 (m, 1 H, H-6), 1.81–1.96 (m, 2 H, CH_2), 2.37 (d, $^{2}J_{1'\text{-}1}$ = 17.9 Hz, 1 H, H-1), 2.40–2.47 (m, 1 H, CH_2), 3.70 (bd, $^{2}J_{1\text{-}1'}$ = 17.6 Hz, 1 H, H-1´), 4.37–4.49 (m, 2 H, H-1, H-7).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.0 (u, CH_2), 21.1 (d, C-9), 23.5 (u, CH_2), 28.4 (d, C-13), 36.5 (u, C-10), 41.6 (u, C-12), 51.2 (d, C-6), 60.4 (u, C-2), 76.2 (d, C-7), 169.9 (u, C-8).

IR (KBr): *v* = 3360 (m), 2978 (s), 1708 (s), 1515 (s), 1382 (m), 1248 (m), 1166 (s), 1056 (m), 1022 (m), 976 (m), 853 (w), 783 (m) cm^{-1}.

MS (CI, isobutane): *m/z* (%) = 270 [M^++1] (43), 215 (13), 214 (100).

HRMS:

$C_{14}H_{23}NO_4$ (269.3)	[$M^+ - C_4H_8$]
Calculated	213.10011
Found	213.10035

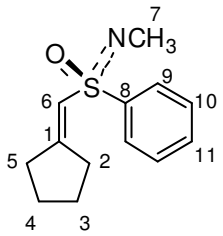
Melting point: 40–42 °C

Optical rotation: $[\alpha]_D$ = –31.4 ° (*c* 1.93, $CDCl_3$).

8. Synthesis of cycloalkenyl oxiranes starting from vinylic sulfoximines

8.1 Preparation of the cyclic vinyl sulfoximines

8.1.1 (+)-(*R*)-(S-Cyclopentylidenmethyl)-N-methyl-S-phenylsulfoximine (31a)



Vinyl sulfoximine **31a** was prepared according to the literature procedure. The analytical data were in agreement with those reported.[33]

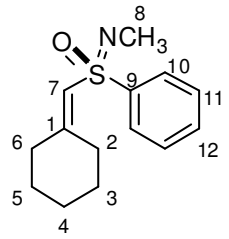
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46–1.76 (m, 4 H, CH_2), 2.18–2.48 (m, 3 H, CH_2), 2.66 (s, 3 H, H-7), 2.79–2.93 (m, 1 H, CH_2), 6.33 (qui, $^4J_{2\text{-}6} = {}^4J_{5\text{-}6} = 2.3$ Hz, 1 H, H-6), 7.46–7.59 (m, 3 H, H-10, H-11), 7.84–7.93 (m, 2 H, H-9).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2 (u, CH_2), 26.4 (u, CH_2), 29.2 (d, C-7), 30.3 (u, CH_2), 36.1 (u, CH_2), 121.7 (d, C-6), 128.7 (d, CH), 129.0 (d, CH), 132.2 (C-11), 140.4 (u, C-8), 164.4 (d, C-1).

Optical rotation for (*S*)-31a, literature: $[\alpha]_D$ = –53.7 ° (*c* 1.21, acetone).

Optical rotation for (*R*)-31a, found: $[\alpha]_D$ = +52.9 ° (*c* 1.18, acetone).

8.1.2 (+)-(*R*)-(S-Cyclohexylidenmethyl)-N-methyl-S-phenylsulfoximine (31b)



Vinyl sulfoximine **31b** was prepared according to the literature procedure. The analytical data were in agreement with those reported.[33]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26–1.37 (m, 1 H, CH_2), 1.45–1.68 (m, 5 H, CH_2), 2.12–2.19 (m, 2 H, CH_2), 2.45–2.54 (m, 1 H, CH_2), 2.61–2.72 (m, 1 H, CH_2), 2.66 (s, 3 H, H-8), 6.21–6.23 (m, 1 H, H-7), 7.48–7.56 (m, 3 H, H-11, H-12), 7.87–7.93 (m, 2 H, H-10).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7 (u, CH_2), 27.0 (u, CH_2), 28.3 (u, CH_2), 29.1 (u, CH_2), 29.2 (d, C-8), 37.4 (u, CH_2), 123.7 (d, C-7), 128.5 (d, CH), 129.0 (d, CH), 132.1 (C-12), 141.2 (u, C-9), 164.4 (d, C-1).

Optical rotation for (*S*)-31b, literature: $[\alpha]_D$ = –180.8 ° (*c* 1.21, acetone).

Optical rotation for (*R*)-31b, found: $[\alpha]_D$ = +176.9 ° (*c* 1.18, acetone).

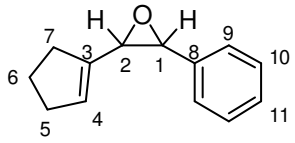
8.2 General procedure for the synthesis of vinyl epoxides (GP_2)

Me_3OBF_4 reagent (1.3 mmol) was added at 10 °C to a solution of the vinylic sulfoximine (1 mmol) in CH_2Cl_2 (20 mL). The progress of the reaction was monitored by TLC (EtOAc). After the mixture had been stirred at 10 °C for 3 h, it was cooled to –78 °C and the aldehyde (1.4 mmol) and DBU (1.7 mmol) were added. The mixture was allowed to warm up slowly to room temperature over 12 h and was stirred for further 2 h. Saturated aqueous $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ and carefully concentrated in vacuum using a vacuum

controller because of the high volatility of the compounds. Purification by flash chromatography (Et_2O/*n*-pentane) gave a mixture of *trans*- and *cis*-oxiranes.
The diastereoselectivities were determined by ^{1}H NMR spectroscopy, the enantioselectivities were determined by HPLC. The *trans*- and *cis* oxiranes were not separated, so that for the minor one (*cis*) only separated signals are given.

8.3 Preparation of the cyclic alkenyloxiranes

8.3.1 2-Cyclopentenyl-3-phenyloxirane (131a)



According to GP_2, from sulfoximine **31a** (450 mg, 1.91 mmol), Me_3OBF_4 (369 mg, 2.45 mmol), DBU (486 µL, 3.25 mmol) and benzaldehyde (273 µL, 2.68 mmol), a mixture of oxiranes *trans*-**131a** and *cis*-**131a** (149 mg, 42%) was isolated as a colorless oil.

de	88%	The *trans* isomer is the major one.
ee_{trans}	32%	Column: Chiralpack-AD, L = 250 mm, ∅ = 4.6 mm Solvents: *n*-heptane (99%), *i*-PrOH (1%) Conditions: 1 mL.min^{-1}, 29 bar Detector: UV (230 nm) Retention times: t_1(major) = 5.2 min, t_2(minor) = 9.3 min

^{1}H NMR (300 MHz, $CDCl_3$) *trans*-131a: δ = 1.82–2.04 (m, >2 H, CH_2), 2.16–2.46 (m, >4 H, CH_2), 3.56 (bd, $^3J_{1\text{-}2}$ = 2.2 Hz, 1 H, H-2), 3.89 (d, $^3J_{2\text{-}1}$ = 2.2 Hz, 1 H, H-1), 5.92 (m, 1 H, H-4), 7.24–7.39 (m, >5 H, H-9, H-10, H-11).

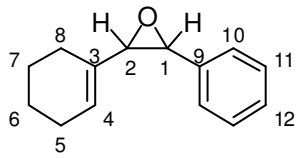
^{13}C NMR (75 MHz, $CDCl_3$) *trans*-131a: δ = 23.1 (u, CH_2), 30.5 (u, CH_2), 32.8 (u, CH_2), 58.5 (d, C-1), 61.3 (d, C-2), 125.5 (d, CH), 128.1 (d, CH), 128.5 (d, CH), 131.3 (d, C-4), 137.6 (u, C), 140.6 (u, C).

^{1}H NMR (300 MHz, $CDCl_3$) *cis*-131a: δ = 3.80 (m, 1 H, H-2), 4.18 (d, $^3J_{2\text{-}1}$ = 4.2 Hz, 1 H, H-1), 5.68 (m, 1 H, H-4).

IR ($CHCl_3$): *v* = 3853 (m), 3744 (s), 3675 (m), 3620 (w), 3440 (m), 3036 (m), 2950 (s), 2356 (s), 1704 (s), 1550 (m), 1456 (m), 1171 (w), 1037 (m), 841 (m), 759 (s), 700 (s) cm^{-1}.

MS (EI): *m/z* (%) = 186 [M^+] (33), 185 (82), 168 (12), 167 (16), 158 (30), 157 (70), 142 (14), 141 (14), 130 (17), 129 (100), 115 (31), 108 (11), 105 (25), 91 (39), 90 (17), 89 (21).

8.3.2 2-Cyclohexenyl-3-phenyloxirane (131b)



According to GP_2, from sulfoximine **31b** (477 mg, 1.91 mmol), Me_3OBF_4 (369 mg, 2.45 mmol), DBU (486 µL, 3.25 mmol) and benzaldehyde (273 µL, 2.68 mmol), a mixture of oxiranes *trans*-**131b** and *cis*-**131b** (168 mg, 44%) was isolated as a colorless oil.

de	82%	The trans isomer is the major one.
ee_{trans}	20%	Column: Chiralpack-AD, L = 250 mm, ∅ = 4.6 mm Solvents: *n*-heptane (99%), *i*-PrOH (1%) Conditions: 1 $mL.min^{-1}$, 32 bar Detector: UV (230 nm) Retention times: t_1(major) = 6.2 min, t_2(minor) = 19.0 min

The spectroscopic data of *trans*-**131b** and *cis*-**131b** are in accordance with those described in the literature.[42,92]

^{1}H NMR (300 MHz, $CDCl_3$) *trans*-131b: δ = 1.49–1.76 (m, >4 H, CH_2), 1.81–1.93 (m, >1 H, CH_2), 1.97–2–10 (m, >3 H, CH_2), 3.28 (bd, $^3J_{1\text{-}2}$ = 1.9 Hz, 1 H, H-2), 3.84 (d, $^3J_{2\text{-}1}$ = 1.9 Hz, 1 H, H-1), 5.90 (m, 1 H, H-4), 7.21–7.36 (m, >5 H, H-10, H-11, H-12).

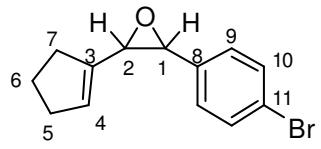
^{13}C NMR (75 MHz, $CDCl_3$) *trans*-131b: δ = 22.2 (u, CH_2), 22.4 (u, CH_2), 22.8 (u, CH_2), 25.2 (u, CH_2), 57.3 (d, C-1), 65.7 (d, C-2), 125.3 (d, CH), 127.3 (d, C-4), 127.7 (d, CH), 128.2 (d, CH), 133.3 (u, C), 137.6 (u, C).

^{1}H NMR (300 MHz, $CDCl_3$) *cis*-131b: δ = 3.60 (m, 1 H, H-2), 4.10 (d, $^3J_{2\text{-}1}$ = 4.4 Hz, 1 H, H-1), 5.70 (m, 1 H, H-4).

IR ($CHCl_3$): ν = 3403 (m), 2930 (s), 1716 (m), 1600 (w), 1495 (m), 1448 (m), 1172 (w), 1068 (m), 921 (w), 881 (m), 841 (m), 755 (s), 700 (m), 619 (m) cm^{-1}.

MS (EI): *m/z* (%) = 200 [M^+] (41), 199 (74), 172 (10), 171 (41), 158 (24), 157 (40), 143 (25), 141 (27), 129 (100), 122 (11), 117 (22), 115 (28), 109 (32), 105 (58), 91 (86), 90 (16), 89 (35), 81 (23).

8.3.3 2-(4-Bromophenyl)-3-cyclopentenyloxirane (131c)



According to GP_2, from sulfoximine **31a** (150 mg, 0.64 mmol), Me_3OBF_4 (123 mg, 0.83 mmol), DBU (162 µL, 1.08 mmol) and *p*-bromobenzaldehyde (165 mg, 0.89 mmol), a mixture of oxiranes *trans*-**131c** and *cis*-**131c** (46 mg, 27%) was isolated as a colorless solide.

de	86%	The trans isomer is the major one.
ee_{trans}	26%	Column: Chiralpack-AD, L = 250 mm, ∅ = 4.6 mm Solvents: *n*-heptane (99.5%), *i*-PrOH (0.5%) Conditions: 0.75 mL.min^{-1}, 21 bar Detector: UV (230 nm) Retention times: t_1(major) = 21.8 min, t_2(minor) = 39.5 min

^{1}H NMR (400 MHz, $CDCl_3$) *trans*-131c: δ = 1.85–2.02 (m, >2 H, CH_2), 2.19–2.32 (m, >1 H, CH_2), 2.33–2.47 (m, >3 H, CH_2), 3.51 (bd, $^3J_{1\text{-}2}$ = 1.7 Hz, 1 H, H-2), 3.85 (bd, $^3J_{2\text{-}1}$ = 1.9 Hz, 1 H, H-1), 5.94 (bs, 1 H, H-4), 7.13–7.19 (bd, 2 H, CH), 7.45–7.50 (bd, 2 H, CH).

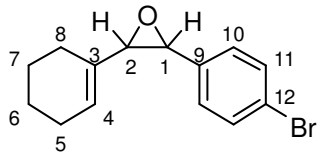
^{13}C NMR (100 MHz, $CDCl_3$) *trans*-131c: δ = 23.0 (u, CH_2), 30.3 (u, CH_2), 32.7 (u, CH_2), 57.8 (d, C-1), 61.2 (d, C-2), 121.7 (u, CH), 126.9 (d, CH), 131.4 (d, CH), 131.6 (d, C-4), 136.5 (u, C), 140.0 (u, C).

^{1}H NMR (400 MHz, $CDCl_3$) *cis*-131c: δ = 3.80 (m, 1 H, H-2), 4.12 (d, $^{3}J_{2\text{-}1}$ = 4.4 Hz, 1 H, H-1), 5.94 (bs, 1 H, H-4).

IR (KBr): ν = 3728 (w), 3637 (w), 3576 (w), 3227 (w), 2928 (s), 2852 (m), 1912 (w), 1724 (w), 1659 (w), 1589 (w), 1486 (m), 1392 (w), 1262 (m), 1071 (s), 1018 (s), 953 (w), 872 (m), 810 (s) cm^{-1}.

MS (EI): *m/z* (%) = 266 (18), 265 (8), 264 [M^+] (18), 263 (8), 237 (29), 235 (29), 186 (13), 185 (100), 184 (23), 183 (26), 171 (10), 168 (12), 167 (14), 157 (35), 156 (79), 155 (22), 129 (13), 128 (19), 108 (12), 89 (14).

8.3.4 2-(4-Bromophenyl)-3–cyclohexenyloxirane (131d)



According to GP_2, from sulfoximine **31b** (159 mg, 0.64 mmol), Me_3OBF_4 (123 mg, 0.83 mmol), DBU (162 µL, 1.08 mmol) and *p*-bromobenzaldehyde (165 mg, 0.89 mmol), a mixture of oxiranes *trans*-**131d** and *cis*-**131d** (59 mg, 33%) was isolated as a colorless solide.

de	86%	The trans isomer is the major one.
ee_{trans}	14%	Column: Chiralpack-AD, L = 250 mm, ∅ = 4.6 mm Solvents: *n*-heptane (98%), *i*-PrOH (2%) Conditions: 0.75 $mL.min^{-1}$, 22 bar Detector: UV (230 nm) Retention times: t_1(major) = 8.2 min, t_2(minor) = 22.0 min

^{1}H NMR (300 MHz, $CDCl_3$) *trans*-131d: δ = 1.49–2.12 (m, >8 H, H-5, H-6, H-7, H-8), 3.24 (bd, ^3J = 1.7 Hz, 1 H, CH), 3.82 (bd, ^3J = 2.0 Hz, 1 H, CH), 5.91 (m, 1 H, H-4), 7.12–7.19 (m, 2 H, CH), 7.42–7.50 (m, 2 H, CH).

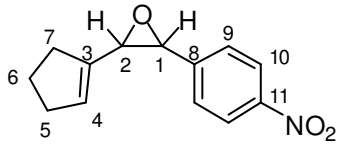
^{13}C NMR (75 MHz, $CDCl_3$) *trans*-131d: δ = 22.2 (u, CH_2), 22.4 (u, CH_2), 22.8 (u, CH_2), 25.2 (u, CH_2), 56.8 (d, CH), 65.9 (d, CH), 121.8 (u, C-12), 127.1 (d, CH), 128.4 (d, C-4), 131.6 (d, CH), 133.2 (u, C), 137.0 (u, C).

^{1}H NMR (300 MHz, $CDCl_3$) *cis*-131d: δ = 3.58–3.64 (m, 1 H, CH), 4.05 (d, ^3J = 4.5 Hz, 1 H, CH), 5.70 (m, 1 H, H-4).

IR (KBr): ν = 3645 (w), 2926 (s), 2857 (s), 2371 (w), 2358 (w), 2343 (w), 1912 (w), 1662 (w), 1586 (w), 1486 (m), 1440 (m), 1390 (w), 1342 (w), 1262 (w), 1107 (w), 1069 (m), 1008 (m), 924 (w), 878 (m), 813 (s) cm^{-1}.

MS (EI): *m/z* (%) = 280 (36), 279 (18), 278 [M^+] (36), 277 (14), 251 (16), 249 (15), 200 (11), 199 (74), 198 (25), 185 (42), 183 (23), 182 (30), 171 (29), 170 (100), 169 (30), 157 (40), 155 (14), 142 (19), 141 (17), 129 (14), 128 (11), 122 (15), 109 (27), 91 (10), 89 (16).

8.3.5 2-Cyclopentenyl-3-(4–nitrophenyl)oxirane (131e)



According to GP_2, from sulfoximine **31a** (150 mg, 0.64 mmol), Me_3OBF_4 (123 mg, 0.83 mmol), DBU (162 µL, 1.08 mmol) and *p*-nitrobenzaldehyde (135 mg, 0.89 mmol), a mixture of oxiranes *trans*-**131e** and *cis*-**131e** (50 mg, 34%) was isolated as a yellow oil.

de	88%	The trans isomer is the major one.
ee_{trans}	22%	Column: Chiralpack-AD, L = 250 mm, ∅ = 4.6 mm Solvents: *n*-heptane (98%), *i*-PrOH (2%) Conditions: 0.75 mL.min^{-1}, 22 bar Detector: UV (230 nm) Retention times: t_1(major) = 15.8 min, t_2(minor) = 24.4 min

^{1}H NMR (400 MHz, $CDCl_3$) *trans*-131e: δ = 1.87–2.03 (m, >2 H, CH_2), 2.21–2.32 (m, >1 H, CH_2), 2.34–2.48 (m, >3 H, CH_2), 3.55 (bd, ^3J = 1.7 Hz, 1H, CH), 4.00 (bd, ^3J = 1.9 Hz, 1 H, CH), 5.98 (m, 1 H, H-4), 7.43–7.48 (m, 2 H, CH), 8.18–8.24 (m, 2 H, CH).

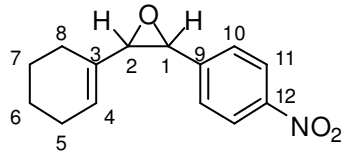
^{13}C NMR (100 MHz, $CDCl_3$) *trans*-131e: δ = 23.0 (u, CH_2), 30.3 (u, CH_2), 32.8 (u, CH_2), 57.3 (d, CH), 61.8 (d, CH), 123.6 (d, CH), 126.0 (d, CH), 132.5 (d, C-4), 139.5 (u, C), 145.0 (u, C), 147.5 (u, C).

^{1}H NMR (400 MHz, $CDCl_3$) *cis*-131e: δ = 3.87 (m, 1 H, CH), 4.25 (bd, ^3J = 4.5 Hz, 1 H, CH), 5.69 (m, 1 H, H-4).

IR ($CHCl_3$): ν = 2948 (m), 2851 (m), 1603 (m), 1522 (s), 1439 (w), 1346 (s), 1217 (m), 1107 (m), 1034 (w), 838 (s), 757 (s), 708 (m), 671 (w) cm^{-1}.

MS (EI): *m/z* (%) = 231 [M^+] (25), 215 (15), 214 (100), 202 (31), 185 (21), 184 (74), 183 (15), 157 (13), 156 (65), 155 (15), 150 (11), 141 (12), 129 (10), 128 (24), 108 (14).

8.3.6 2-Cyclohexenyl-3-(4-nitrophenyl)oxirane (131f)



According to GP_2, from sulfoximine **31b** (159 mg, 0.64 mmol), Me_3OBF_4 (123 mg, 0.83 mmol), DBU (162 µL, 1.08 mmol) and *p*-nitrobenzaldehyde (135 mg, 0.89 mmol), a mixture of oxiranes *trans*-**131f** and *cis*-**131f** (60 mg, 38%) was isolated as a yellow solid.

de	88%	The trans isomer is the major one.
ee_{trans}	10%	Column: Chiralpack-AD, L = 250 mm, ∅ = 4.6 mm Solvents: *n*-heptane (99%), *i*-PrOH (1%) Conditions: 0.75 mL.min^{-1}, 22 bar Detector: UV (230 nm) Retention times: t_1(major) = 24.1 min, t_2(minor) = 52.8 min

^{1}H NMR (400 MHz, $CDCl_3$) *trans*-131f: δ = 1.52–1.78 (m, >4 H, CH_2), 1.82–1.93 (m, >1 H, CH_2), 1.97–2.13 (m, >3 H, CH_2), 3.28 (bd, ^3J = 1.9 Hz, 1 H, CH), 3.97 (bd, ^3J = 1.9 Hz, 1 H, CH), 5.96 (m, 1 H, H-4), 7.43–7.48 (m, 2 H, CH), 8.17–8.23 (m, 2 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$) *trans*-131f: δ = 22.1 (u, CH_2), 22.3 (u, CH_2), 22.6 (u, CH_2), 25.2 (u, CH_2), 56.3 (d, CH), 66.4 (d, CH), 123.6 (d, CH), 126.0 (d, CH), 128.8 (d, C-4), 132.6 (u, C), 145.3 (u, C), 147.4 (u, C).

^{1}H NMR (400 MHz, $CDCl_3$) *cis*-131f: δ = 3.71 (m, 1 H, CH), 4.20 (bd, ^3J = 4.4 Hz, 1 H, CH), 5.73 (m, 1 H, H-4).

IR (KBr): ν = 3961 (w), 2993 (m), 2926 (s), 2863 (m), 1931 (w), 1728 (w), 1659 (w), 1600 (s), 1516 (s), 1447 (m), 1345 (s), 1171 (w), 1104 (m), 1013 (w), 964 (w), 926 (m), 893 (m), 851 (s), 790 (m), 741 (m), 695 (m) cm^{-1}.

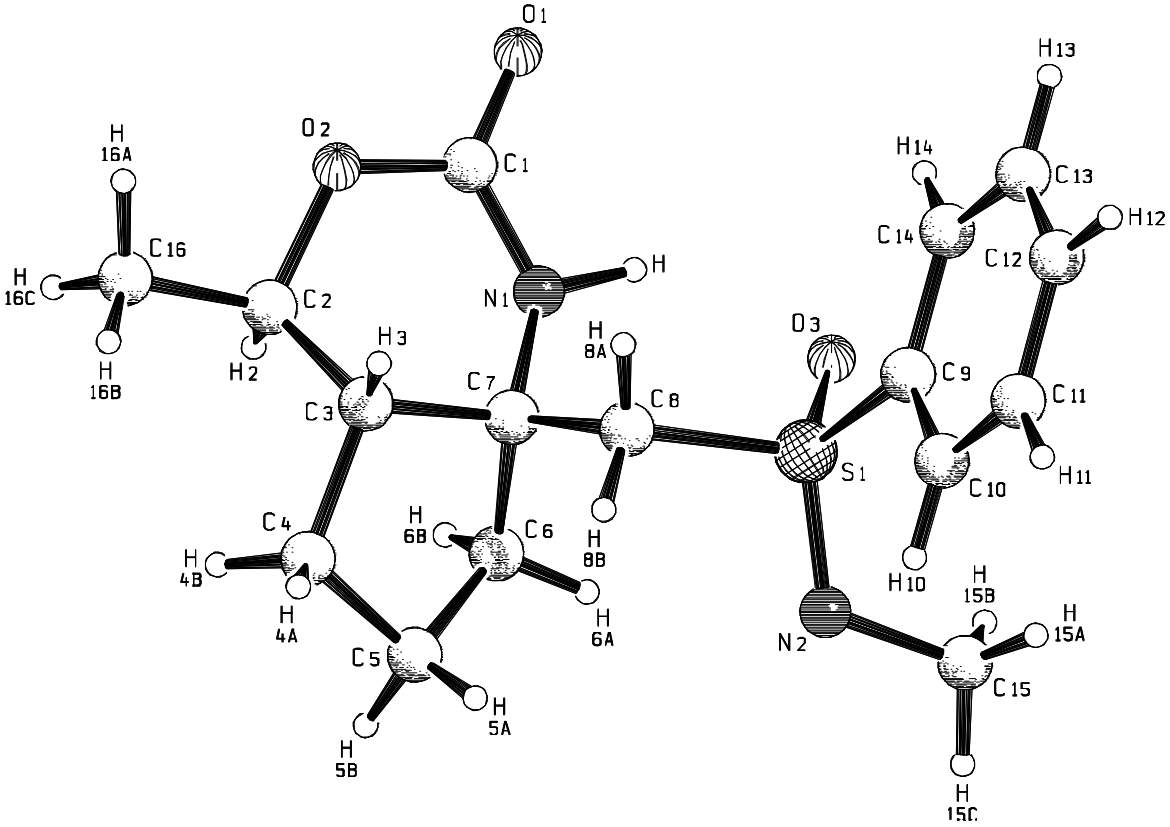
MS (EI): *m/z* (%) = 245 [M^+] (100), 244 (14), 229 (10), 228 (65), 216 (48), 202 (11), 201 (38), 199 (27), 198 (63), 171 (14), 170 (98), 151 (20), 150 (42), 142 (24), 141 (23), 129 (12), 128 (16), 122 (17), 109 (15), 91 (19), 81 (11).

9. X-ray crystal structure analyses

9.1 Structure of sulfoximine 29a

Experimental Details

Crystal data:



Chemical formula	:	$C_{16}H_{22}N_2O_3S$
Formula weight	:	322.43
Crystal system	:	orthorhombic
Space group (No.)	:	$P2_12_12_1$ (19)
Z	:	4
a (Å)	:	10.080(2)
b (Å)	:	11.737(2)
c (Å)	:	13.645(3)
α (°)	:	90.0
β (°)	:	90.0
γ (°)	:	90.0

cell volume	:	1614.3(6)Å^3
Density calculation	:	1.327g/cm^3
Radiation	:	CuKα (1.54179Å)
Range for lattice parameters	:	E<Θ <E
Absorption coefficient	:	1.903 mm^{-1}
Temperature	:	150 K
Crystal source	:	recrystallized from CH_2Cl_2 and Et_2O
Crystal colour	:	colourless
Crystal shape	:	irregular
Crystal size	:	ca.0.3 x 0.3 x 0.3 mm

Data Collection

Diffractometer type	:	Enraf Nonius CAD4
collection method	:	ω/2Θ scans
Absorption correction	:	none
No. of reflections measured	:	2608
No. of independent reflections	:	1855
No. of observed reflections	:	1794
Θ max (E)	:	72.79
hmin 6 hmax	:	-12 6 12
kmin 6 kmax	:	- 4 6 14
lmin 6 lmax	:	-14 6 16
Criterion for observed	:	$I > 2\sigma(I)$
R_{int}	:	0.097(88)
Standard reflections	:	2 2 3; -2 2 3; -2 -2 3
Variation	:	6126(191) 6383(194) 6410(198)
Refinement:		
On	:	F

Treatment of hydrogens	:	Calculated in idealized positions. Us fixed at 1.5×U of the corresponding heavy atom. No refinement of hydrogen parameters
R	:	0.075
Rw	:	0.075
Weighting scheme	:	$w=1/\sigma^2(F)$
No. of parameters refined	:	199
No. of reflections in refmnt.	:	1784
Residual electron density	:	-1.23/0.44e/Å^3
r*[1]	:	not refined
XABS[2]	:	-0.006(97)[a)]
Goodness of fit	:	2.551
Solution	:	XTAL3.7[3]
Remarks	:	[a)]From separate calculation

Definitions

$$U_{eq} = 1/3\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \boldsymbol{a_i}\,\boldsymbol{a_j}$$

The anisotropic displacement factor in the structure factor expression is:

$$t = \exp[-2\pi^2(\Sigma_i\Sigma_j U_{ij} h_i h_j a_i^* a_j^*)]$$

Literature [97,98,99,100]

Atomic Positional and Isotropic Displacement Parameters

Atom	x/a	y/b	z/c	U_{eq}/Å^2
S1	0.61298(9)	0.19263(6)	0.54748(6)	* 0.0300(4)
O1	0.5312(6)	0.1398(3)	0.1968(3)	* 0.088(3)
O2	0.3903(4)	0.0076(2)	0.2426(2)	* 0.053(2)
O3	0.7043(3)	0.2121(2)	0.4648(2)	* 0.038(1)
N1	0.5602(5)	0.0587(3)	0.3462(3)	* 0.050(2)
N2	0.6602(4)	0.1320(3)	0.6391(3)	* 0.043(2)
C1	0.4975(7)	0.0731(3)	0.2595(4)	* 0.053(3)
C2	0.3707(5)	−0.0897(3)	0.3082(3)	* 0.038(2)
C3	0.3700(4)	−0.0480(3)	0.4130(3)	* 0.034(2)
C4	0.3611(6)	−0.1471(4)	0.4881(4)	* 0.056(3)
C5	0.4894(6)	−0.1457(4)	0.5468(5)	* 0.064(4)
C6	0.5868(5)	−0.0806(3)	0.4819(4)	* 0.048(3)
C7	0.5024(4)	0.0130(3)	0.4358(3)	* 0.033(2)
C8	0.4716(4)	0.1118(3)	0.5076(3)	* 0.031(2)
C9	0.5416(4)	0.3286(3)	0.5733(3)	* 0.031(2)
C10	0.4856(5)	0.3457(3)	0.6648(3)	* 0.038(2)
C11	0.4252(5)	0.4509(3)	0.6854(4)	* 0.046(2)
C12	0.4242(6)	0.5341(3)	0.6127(4)	* 0.051(3)
C13	0.4801(6)	0.5164(3)	0.5230(4)	* 0.049(3)
C14	0.5408(5)	0.4124(3)	0.5006(3)	* 0.039(2)
C15	0.7751(5)	0.1811(4)	0.6895(4)	* 0.055(3)
C16	0.2438(5)	−0.1461(4)	0.2742(4)	* 0.055(3)
H	0.6334(−)	0.1145(−)	0.3471(−)	0.075(−)
H10	0.4881(−)	0.2878(−)	0.7125(−)	0.058(−)
H11	0.3849(−)	0.4649(−)	0.7473(−)	0.068(−)
H12	0.3841(−)	0.6061(−)	0.6272(−)	0.078(−)
H13	0.4755(−)	0.5747(−)	0.4750(−)	0.075(−)
H14	0.5807(−)	0.4005(−)	0.4383(−)	0.057(−)
H8a	0.4116(−)	0.1624(−)	0.4762(−)	0.048(−)
H8b	0.4301(−)	0.0800(−)	0.5641(−)	0.048(−)
H6a	0.6568(−)	−0.0490(−)	0.5198(−)	0.072(−)
H6b	0.6239(−)	−0.1286(−)	0.4324(−)	0.072(−)
H5a	0.4760(−)	−0.1082(−)	0.6067(−)	0.095(−)
H5b	0.5190(−)	−0.2215(−)	0.5575(−)	0.095(−)
H4a	0.2875(−)	−0.1369(−)	0.5301(−)	0.082(−)
H4b	0.3523(−)	−0.2179(−)	0.4541(−)	0.082(−)
H3	0.2980(−)	0.0042(−)	0.4217(−)	0.051(−)
H2	0.4395(−)	−0.1429(−)	0.2991(−)	0.057(−)
H16a	0.1967(−)	−0.0945(−)	0.2305(−)	0.082(−)
H16b	0.1875(−)	−0.1609(−)	0.3285(−)	0.082(−)
H16c	0.2621(−)	−0.2136(−)	0.2400(−)	0.082(−)
H15a	0.7559(−)	0.2547(−)	0.7117(−)	0.081(−)
H15b	0.8482(−)	0.1838(−)	0.6443(−)	0.081(−)
H15c	0.7994(−)	0.1332(−)	0.7429(−)	0.081(−)

Atomic Displacement Parameters

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S	0.0320(4)	0.0365(4)	0.0280(4)	0.0049(4)	−0.0003(4)	−0.0037(3)
O1	0.071(2)	0.093(3)	0.045(2)	0.011(2)	0.025(2)	−0.002(2)
O2	0.048(2)	0.054(2)	0.041(1)	0.006(1)	0.003(1)	−0.004(1)
O3	0.028(1)	0.055(2)	0.054(2)	0.013(1)	−0.002(1)	−0.005(1)
N1	0.048(2)	0.050(2)	0.023(1)	0.001(2)	−0.003(1)	−0.005(1)
N2	0.048(2)	0.042(2)	0.026(1)	0.005(1)	0.002(1)	−0.004(1)
C1	0.059(3)	0.055(2)	0.031(2)	−0.001(2)	0.005(2)	−0.010(2)
C2	0.053(2)	0.038(2)	0.039(2)	−0.007(2)	0.002(2)	−0.009(2)
C3	0.049(2)	0.035(2)	0.029(2)	−0.001(2)	0.003(2)	−0.002(1)
C5	0.067(3)	0.051(3)	0.061(3)	−0.011(2)	0.022(2)	0.001(2)
C6	0.037(2)	0.078(3)	0.062(3)	−0.017(2)	0.008(2)	−0.007(2)
C7	0.033(2)	0.073(3)	0.046(2)	−0.006(2)	−0.010(2)	−0.010(2)
C8	0.035(2)	0.044(2)	0.026(2)	−0.005(2)	−0.001(2)	−0.004(1)
C9	0.036(2)	0.040(2)	0.022(1)	−0.001(2)	0.001(1)	0.000(1)
C10	0.073(3)	0.041(2)	0.032(2)	0.005(2)	−0.000(2)	0.007(2)
C11	0.090(3)	0.058(2)	0.029(2)	−0.001(3)	0.004(2)	0.010(2)
C12	0.074(3)	0.064(3)	0.024(2)	0.006(3)	−0.005(2)	0.003(2)
C13	0.041(2)	0.038(2)	0.032(2)	−0.001(2)	0.001(2)	−0.004(2)
C14	0.057(3)	0.040(2)	0.068(3)	0.003(2)	0.009(2)	−0.009(2)
C15	0.078(4)	0.047(3)	0.102(4)	−0.011(3)	0.026(3)	−0.019(3)
C16	0.084(4)	0.084(4)	0.064(3)	−0.039(3)	0.029(3)	−0.030(3)
C17	0.050(3)	0.095(4)	0.046(2)	−0.023(3)	0.001(2)	−0.012(3)
C18	0.043(2)	0.059(3)	0.045(2)	−0.002(2)	−0.001(2)	−0.002(2)
C19	0.067(3)	0.062(2)	0.030(2)	0.004(3)	0.011(2)	−0.004(2)
C20	0.078(3)	0.041(2)	0.054(2)	0.006(2)	−0.002(3)	−0.004(2)
H6a	0.090(−)					
H19a	0.075(−)					
H5a	0.090(−)					
H10b	0.075(−)					
H12a	0.081(−)					
H7a	0.076(−)					
H7b	0.076(−)					
H90	0.050(−)					
H11a	0.090(−)					
H3	0.057(−)					
H19b	0.075(−)					
H18	0.075(−)					
H10a	0.075(−)					
H16	0.116(−)					
H6b	0.090(−)					
H20a	0.087(−)					
H19c	0.075(−)					
H14	0.083(−)					
H20b	0.087(−)					
H5b	0.090(−)					
H2	0.065(−)					
H15	0.114(−)					
H12b	0.081(−)					
H11b	0.090(−)					
H20c	0.087(−)					
H17	0.095(−)					

Bond distances, bond angles and dihedral angles

Bond Distances	(Angstroms)
S1-O3	1.474(3)
S1-N2	1.516(4)
S1-C9	1.786(3)
S1-C8	1.796(4)
O2-C1	1.346(7)
O2-C2	1.465(5)
O1-C1	1.208(6)
N1-H	.987(4)
N1-C1	1.351(7)
N1-C7	1.457(6)
N2-C15	1.465(7)
C7-C6	1.525(6)
C7-C3	1.546(6)
C7-C8	1.550(5)
C14-H14	.951(4)
C14-C9	1.397(5)
C14-C13	1.399(6)
C10-H10	.941(4)
C10-C9	1.385(6)
C10-C11	1.405(6)
C8-H8a	.950(4)
C8-H8b	.953(4)
C2-H2	.942(4)
C2-C3	1.510(6)
C2-C16	1.514(7)
C3-H3	.957(4)
C3-C4	1.552(6)
C12-H12	.957(4)
C12-C13	1.364(8)
C12-C11	1.392(7)
C6-H6a	.950(5)
C6-H6b	.957(5)
C6-C5	1.526(8)
C15-H15a	.935(5)
C15-H15c	.953(5)
C15-H15b	.962(5)
C4-H4a	.945(6)
C4-H4b	.956(5)
C4-C5	1.521(9)
C13-H13	.948(5)
C5-H5a	.939(6)
C5-H5b	.950(4)
C11-H11	.953(5)
C16-H16c	.937(5)
C16-H16b	.950(6)
C16-H16a	.974(5)

Bond Angles	(degrees)
O3-S1-N2	120.6(2)
O3-S1-C9	105.3(2)
O3-S1-C8	110.2(2)
N2-S1-C9	112.6(2)
N2-S1-C8	104.5(2)
C9-S1-C8	102.3(2)
C1-O2-C2	116.6(4)

H-N1-C1	106.1(4)
H-N1-C7	122.2(4)
C1-N1-C7	126.4(5)
C15-N2-S1	116.7(3)
N1-C7-C6	112.9(4)
N1-C7-C3	110.3(3)
N1-C7-C8	109.6(3)
C6-C7-C3	103.4(3)
C6-C7-C8	112.9(3)
C3-C7-C8	107.5(3)
H14-C14-C9	121.9(4)
H14-C14-C13	120.6(4)
C9-C14-C13	117.5(4)
H10-C10-C9	120.6(4)
H10-C10-C11	120.5(4)
C9-C10-C11	118.9(4)
H8a-C8-H8b	109.2(4)
H8a-C8-C7	108.0(4)
H8a-C8-S1	108.2(2)
H8b-C8-C7	107.8(3)
H8b-C8-S1	108.1(3)
C7-C8-S1	115.3(3)
H2-C2-O2	109.7(4)
H2-C2-C3	110.1(4)
H2-C2-C16	106.9(3)
O2-C2-C3	109.1(3)
O2-C2-C16	105.5(4)
C3-C2-C16	115.4(4)
H3-C3-C2	109.2(4)
H3-C3-C7	109.5(3)
H3-C3-C4	110.7(4)
C2-C3-C7	109.6(3)
C2-C3-C4	112.5(3)
C7-C3-C4	105.3(4)
H12-C12-C13	119.7(5)
H12-C12-C11	118.3(5)
C13-C12-C11	122.0(4)
C10-C9-C14	122.5(3)
C10-C9-S1	118.1(3)
C14-C9-S1	119.4(3)
H6a-C6-H6b	108.9(5)
H6a-C6-C7	110.9(3)
H6a-C6-C5	111.0(5)
H6b-C6-C7	110.5(5)
H6b-C6-C5	111.5(4)
C7-C6-C5	103.9(4)
H15a-C15-H15c	110.5(5)
H15a-C15-H15b	109.7(5)
H15a-C15-N2	110.6(5)
H15c-C15-H15b	108.2(5)
H15c-C15-N2	109.3(4)
H15b-C15-N2	108.6(5)
H4a-C4-H4b	109.3(5)
H4a-C4-C5	110.3(5)
H4a-C4-C3	110.5(4)
H4b-C4-C5	110.1(5)
H4b-C4-C3	109.7(4)
C5-C4-C3	106.9(4)
O1-C1-O2	118.3(5)
O1-C1-N1	124.7(6)
O2-C1-N1	117.0(4)
H13-C13-C12	119.3(4)
H13-C13-C14	120.0(5)

C12-C13-C14	120.7(4)
H5a-C5-H5b	110.4(6)
H5a-C5-C4	110.0(6)
H5a-C5-C6	111.3(4)
H5b-C5-C4	109.7(5)
H5b-C5-C6	110.9(5)
C4-C5-C6	104.3(4)
H11-C11-C12	120.5(4)
H11-C11-C10	120.9(4)
C12-C11-C10	118.5(4)
H16c-C16-H16b	110.6(5)
H16c-C16-H16a	108.5(6)
H16c-C16-C2	110.9(5)
H16b-C16-H16a	107.5(5)
H16b-C16-C2	110.2(5)
H16a-C16-C2	109.1(4)

Dihedral Angles	**(degrees)**
O3-S1-N2-C15	56.5(4)
C8-S1-N2-C15	-178.9(3)
C9-S1-N2-C15	-68.8(4)
O3-S1-C8-C7	40.9(3)
O3-S1-C8-H8a	-80.2(3)
O3-S1-C8-H8b	161.6(2)
N2-S1-C8-C7	-90.0(3)
N2-S1-C8-H8a	148.9(3)
N2-S1-C8-H8b	30.7(3)
C9-S1-C8-C7	152.5(3)
C9-S1-C8-H8a	31.4(4)
C9-S1-C8-H8b	-86.8(3)
O3-S1-C9-C14	22.0(4)
O3-S1-C9-C10	-159.7(3)
N2-S1-C9-C14	155.2(3)
N2-S1-C9-C10	-26.5(4)
C8-S1-C9-C14	-93.2(4)
C8-S1-C9-C10	85.1(4)
C1-O2-C2-C3	54.6(5)
C1-O2-C2-C16	179.1(4)
C1-O2-C2-H2	-66.1(5)
C2-O2-C1-O1	166.0(4)
C2-O2-C1-N1	-13.9(6)
C1-N1-C7-C8	-102.7(5)
C1-N1-C7-C3	15.4(5)
C1-N1-C7-C6	130.5(4)
H-N1-C7-C8	48.0(6)
H-N1-C7-C3	166.2(4)
H-N1-C7-C6	-78.8(5)
C7-N1-C1-O2	-23.6(7)
C7-N1-C1-O1	156.6(5)
H-N1-C1-O2	-178.1(4)
H-N1-C1-O1	2.0(7)
S1-N2-C15-H15a	62.3(6)
S1-N2-C15-H15b	-58.1(5)
S1-N2-C15-H15c	-175.9(4)
N1-C7-C8-S1	-61.9(4)
N1-C7-C8-H8a	59.3(4)
N1-C7-C8-H8b	177.2(4)
C3-C7-C8-S1	178.2(3)
C3-C7-C8-H8a	-60.6(4)
C3-C7-C8-H8b	57.3(4)
C6-C7-C8-S1	64.8(4)

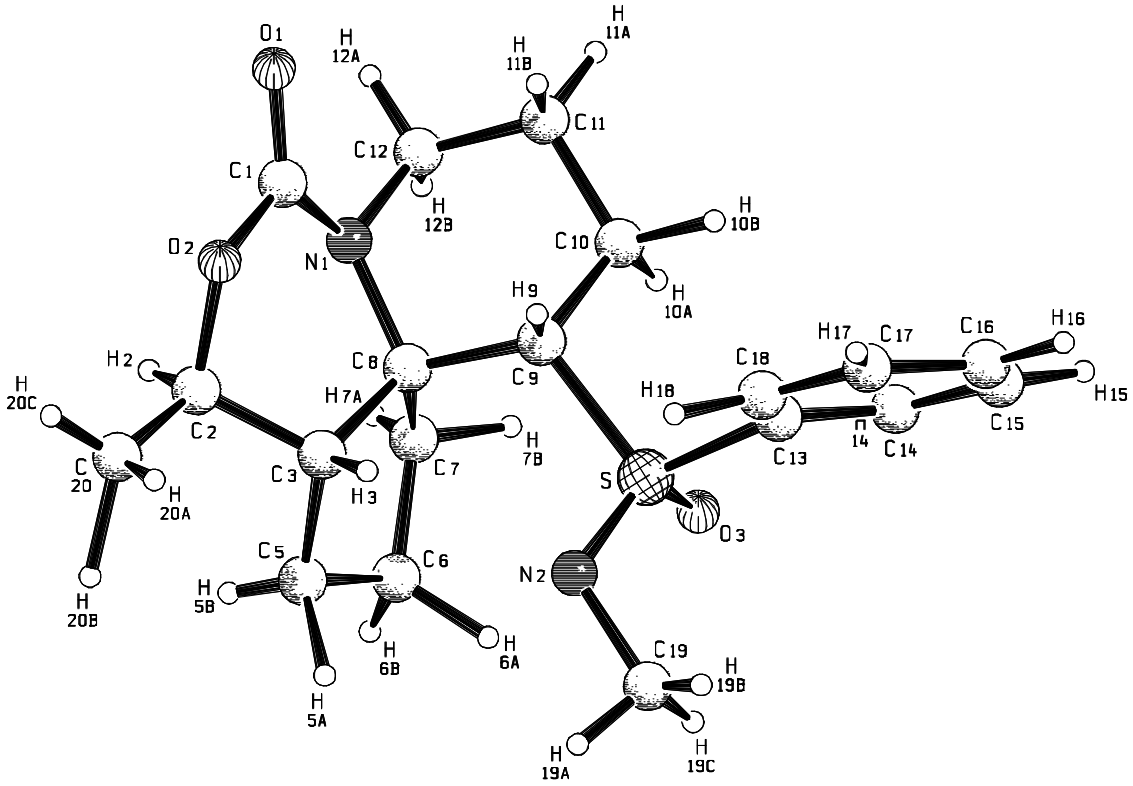
C6-C7-C8-H8a	-174.0(3)
C6-C7-C8-H8b	-56.1(5)
N1-C7-C3-C2	26.1(4)
N1-C7-C3-C4	147.3(3)
N1-C7-C3-H3	-93.7(4)
C8-C7-C3-C2	145.5(3)
C8-C7-C3-C4	-93.3(4)
C8-C7-C3-H3	25.7(5)
C6-C7-C3-C2	-94.8(4)
C6-C7-C3-C4	26.4(4)
C6-C7-C3-H3	145.4(4)
N1-C7-C6-C5	-158.9(4)
N1-C7-C6-H6a	81.8(5)
N1-C7-C6-H6b	-39.2(5)
C8-C7-C6-C5	76.1(4)
C8-C7-C6-H6a	-43.2(6)
C8-C7-C6-H6b	-164.2(4)
C3-C7-C6-C5	-39.8(4)
C3-C7-C6-H6a	-159.1(4)
C3-C7-C6-H6b	79.9(5)
C13-C14-C9-S1	178.0(4)
C13-C14-C9-C10	-.2(7)
H14-C14-C9-S1	-2.8(6)
H14-C14-C9-C10	179.0(4)
C9-C14-C13-C12	-.1(7)
C9-C14-C13-H13	-178.4(5)
H14-C14-C13-C12	-179.3(5)
H14-C14-C13-H13	2.4(8)
C11-C10-C9-S1	-178.0(4)
C11-C10-C9-C14	.3(7)
H10-C10-C9-S1	2.1(6)
H10-C10-C9-C14	-179.6(4)
C9-C10-C11-C12	-.0(7)
C9-C10-C11-H11	179.2(5)
H10-C10-C11-C12	179.8(5)
H10-C10-C11-H11	-.9(8)
O2-C2-C3-C7	-58.6(4)
O2-C2-C3-C4	-175.4(4)
O2-C2-C3-H3	61.3(5)
C16-C2-C3-C7	-177.1(3)
C16-C2-C3-C4	66.2(5)
C16-C2-C3-H3	-57.2(4)
H2-C2-C3-C7	61.8(4)
H2-C2-C3-C4	-54.9(5)
H2-C2-C3-H3	-178.2(3)
O2-C2-C16-H16a	-14.5(6)
O2-C2-C16-H16b	-132.3(4)
O2-C2-C16-H16c	105.0(5)
C3-C2-C16-H16a	106.0(5)
C3-C2-C16-H16b	-11.8(6)
C3-C2-C16-H16c	-134.6(4)
H2-C2-C16-H16a	-131.2(5)
H2-C2-C16-H16b	111.0(5)
H2-C2-C16-H16c	-11.7(6)
C7-C3-C4-C5	-3.4(5)
C7-C3-C4-H4a	116.6(5)
C7-C3-C4-H4b	-122.8(5)
C2-C3-C4-C5	115.9(4)
C2-C3-C4-H4a	-124.0(5)
C2-C3-C4-H4b	-3.4(6)
H3-C3-C4-C5	-121.6(4)
H3-C3-C4-H4a	-1.6(6)
H3-C3-C4-H4b	119.1(5)

C11-C12-C13-C14	.3(8)
C11-C12-C13-H13	178.6(5)
H12-C12-C13-C14	179.1(5)
H12-C12-C13-H13	-2.6(9)
C13-C12-C11-C10	-.3(8)
C13-C12-C11-H11	-179.5(5)
H12-C12-C11-C10	-179.1(5)
H12-C12-C11-H11	1.7(9)
C7-C6-C5-C4	37.8(4)
C7-C6-C5-H5a	-80.8(6)
C7-C6-C5-H5b	155.8(5)
H6a-C6-C5-C4	157.1(4)
H6a-C6-C5-H5a	38.6(7)
H6a-C6-C5-H5b	-84.9(6)
H6b-C6-C5-C4	-81.2(5)
H6b-C6-C5-H5a	160.2(5)
H6b-C6-C5-H5b	36.8(7)
C3-C4-C5-C6	-20.9(5)
C3-C4-C5-H5a	98.6(5)
C3-C4-C5-H5b	-139.8(5)
H4a-C4-C5-C6	-141.1(4)
H4a-C4-C5-H5a	-21.6(6)
H4a-C4-C5-H5b	100.0(6)
H4b-C4-C5-C6	98.1(5)
H4b-C4-C5-H5a	-142.4(5)
H4b-C4-C5-H5b	-20.7(7)

9.2 Structure of sulfoximine 71

Experimental Details

Structure:



Chemical formula	:	$C_{19}H_{26}N_2O_3S$
formula weight	:	362.49
Crystal system	:	orthorhombic
Space group (No.)	:	$P\ 2_12_12_1$ (19)
Z	:	4
a (Å)	:	6.800(1)
b (Å)	:	13.202(8)
c (Å)	:	20.524(8)
α (°)	:	90.0
β (°)	:	90.0
γ (°)	:	90.0
cell volume	:	1842.5(14)Å^3
Density calc.	:	1.307g/cm^3
Radiation	:	CuKα (1.54179Å)

Range for lattice parameters	:	14.89E<Θ <21.18E
Absorption coefficient	:	1.727mm^{-1}
Temperature	:	298K
Crystal source	:	recrystallized from CH_2Cl_2 and Et_2O
Crystal colour	:	colourless
Crystal shape	:	irregular
Crystal size	:	ca. 0.3x0.3.x0.3mm

Data Collection

Diffractometer type	:	Enraf-Nonius CAD4
collection method	:	$\omega/2\vartheta$ scans
Absorption correction	:	none
No. of reflections measured	:	3923
No. of independent reflections	:	3339
No. of observed reflections	:	3168
Θ_{max} (E)	:	67.78
h_{min} 6 h_{max}	:	- 8 6 8
k_{min} 6 k_{max}	:	- 15 6 15
l_{min} 6 l_{max}	:	- 24 6 24

Criterion for observed	:	$I > 2\sigma(I)$
R_{int}	:	0.020(31)
Standard reflections	:	2 2 2, -2 -2 2, 1 -3 4
Variation	:	1930(48) 2103(69) 11100(238)
Refinement:		
On	:	*F*
Treatment of hydrogens	:	Calculated in idealized positions. Us fixed at 1.5xU of the relevant heavy atom prior to final refinement. No refinement of hydrogen parameters.

R	:	0.053
R_w	:	0.076
Weighting scheme	:	$w=1/\sigma^2(F)$
No. of parameters refined	:	226
No. of reflections in refmnt.	:	3157
Residual electron density	:	-0.63/0.32/Å^3
r*[1]	:	not refined
XABS[2][a)]	:	-0.007(043)
Goodness of fit	:	3.357
Solution	:	XTAL3.7[3]
Remarks	:	

Definitions

$$U_{eq} = 1/3\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i\, a_j$$

The anisotropic displacement factor in the structure factor expression is:

$$t = \exp[-2\pi^2(\Sigma_i\Sigma_j U_{ij} h_i h_j a_i^* a_j^*)]$$

Literature [97,98,99,100]

Atomic Positional and Isotropic Displacement Parameters

Atom	x/a	y/b	z/c	U_{eq}/Å^2
S	0.3807(1)	0.36648(6)	0.34072(4)	* 0.0322(4)
O1	0.0183(5)	0.5709(3)	0.5612(1)	* 0.070(2)
O2	0.0721(4)	0.6559(2)	0.4703(1)	* 0.048(2)
O3	0.5786(4)	0.3249(2)	0.3499(1)	* 0.046(2)
N1	0.3040(5)	0.5409(2)	0.5052(1)	* 0.040(2)
N2	0.3389(5)	0.4459(2)	0.2895(1)	* 0.039(2)
C1	0.1262(7)	0.5865(3)	0.5150(2)	* 0.048(2)
C2	0.2333(6)	0.6971(3)	0.4306(2)	* 0.043(2)
C3	0.3276(6)	0.6117(3)	0.3926(2)	* 0.038(2)
C5	0.5192(8)	0.6475(3)	0.3596(2)	* 0.060(3)
C7	0.6140(6)	0.5239(4)	0.4405(2)	* 0.051(2)
C8	0.3841(6)	0.5227(3)	0.4391(2)	* 0.035(2)
C9	0.2952(5)	0.4180(3)	0.4177(2)	* 0.033(2)
C10	0.3306(7)	0.3332(3)	0.4679(2)	* 0.049(2)
C11	0.2637(8)	0.3640(4)	0.5367(2)	* 0.059(3)
C12	0.3564(8)	0.4643(3)	0.5544(2)	* 0.054(3)
C13	0.2283(6)	0.2578(3)	0.3268(2)	* 0.037(2)
C14	0.3087(7)	0.1623(3)	0.3284(2)	* 0.055(3)
C15	0.197(1)	0.0814(4)	0.3070(3)	* 0.076(4)
C16	0.007(1)	0.0965(5)	0.2847(3)	* 0.077(4)
C17	-0.0744(7)	0.1919(5)	0.2855(2)	* 0.063(3)
C18	0.0360(7)	0.2741(4)	0.3062(2)	* 0.049(2)
C19	0.3786(8)	0.4149(3)	0.2220(2)	* 0.053(2)
C20	0.1423(8)	0.7779(3)	0.3880(2)	* 0.057(3)
C6	0.6772(7)	0.5678(4)	0.3761(2)	* 0.059(3)
H6a	0.7040(-)	0.5101(-)	0.3335(-)	0.090(-)
H19a	0.3701(-)	0.4827(-)	0.1980(-)	0.075(-)
H5a	0.4913(-)	0.6544(-)	0.2975(-)	0.090(-)
H10b	0.2399(-)	0.2594(-)	0.4496(-)	0.075(-)
H12a	0.3241(-)	0.4845(-)	0.5989(-)	0.081(-)
H7a	0.6583(-)	0.5472(-)	0.4682(-)	0.076(-)
H7b	0.6956(-)	0.4429(-)	0.4478(-)	0.076(-)
H90	0.1619(-)	0.4211(-)	0.4089(-)	0.050(-)
H11a	0.2806(-)	0.3081(-)	0.5703(-)	0.090(-)
H3	0.2311(-)	0.5856(-)	0.3588(-)	0.057(-)
H19b	0.3132(-)	0.3768(-)	0.2025(-)	0.075(-)
H18	-0.0282(-)	0.3485(-)	0.2970(-)	0.075(-)
H10a	0.4792(-)	0.3063(-)	0.4688(-)	0.075(-)
H16	-0.0927(-)	0.0365(-)	0.2668(-)	0.116(-)
H6b	0.8008(-)	0.5948(-)	0.3725(-)	0.090(-)
H20a	0.0627(-)	0.7587(-)	0.3549(-)	0.087(-)
H19c	0.4993(-)	0.3830(-)	0.2171(-)	0.075(-)
H14	0.4696(-)	0.1634(-)	0.3629(-)	0.083(-)
H20b	0.2361(-)	0.8228(-)	0.3419(-)	0.087(-)
H5b	0.5425(-)	0.7058(-)	0.3679(-)	0.090(-)
H2	0.2966(-)	0.7255(-)	0.4606(-)	0.065(-)
H15	0.2676(-)	0.0109(-)	0.3136(-)	0.114(-)
H12b	0.4929(-)	0.4632(-)	0.5601(-)	0.081(-)
H11b	0.1201(-)	0.3681(-)	0.5314(-)	0.090(-)
H20c	0.0434(-)	0.8235(-)	0.4031(-)	0.087(-)
H17	-0.2080(-)	0.2028(-)	0.2711(-)	0.095(-)

Atomic Displacement Parameters

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S	0.0320(4)	0.0365(4)	0.0280(4)	0.0049(4)	−0.0003(4)	−0.0037(3)
O1	0.071(2)	0.093(3)	0.045(2)	0.011(2)	0.025(2)	−0.002(2)
O2	0.048(2)	0.054(2)	0.041(1)	0.006(1)	0.003(1)	−0.004(1)
O3	0.028(1)	0.055(2)	0.054(2)	0.013(1)	−0.002(1)	−0.005(1)
N1	0.048(2)	0.050(2)	0.023(1)	0.001(2)	−0.003(1)	−0.005(1)
N2	0.048(2)	0.042(2)	0.026(1)	0.005(1)	0.002(1)	−0.004(1)
C1	0.059(3)	0.055(2)	0.031(2)	−0.001(2)	0.005(2)	−0.010(2)
C2	0.053(2)	0.038(2)	0.039(2)	−0.007(2)	0.002(2)	−0.009(2)
C3	0.049(2)	0.035(2)	0.029(2)	−0.001(2)	0.003(2)	−0.002(1)
C5	0.067(3)	0.051(3)	0.061(3)	−0.011(2)	0.022(2)	0.001(2)
C6	0.037(2)	0.078(3)	0.062(3)	−0.017(2)	0.008(2)	−0.007(2)
C7	0.033(2)	0.073(3)	0.046(2)	−0.006(2)	−0.010(2)	−0.010(2)
C8	0.035(2)	0.044(2)	0.026(2)	−0.005(2)	−0.001(2)	−0.004(1)
C9	0.036(2)	0.040(2)	0.022(1)	−0.001(2)	0.001(1)	0.000(1)
C10	0.073(3)	0.041(2)	0.032(2)	0.005(2)	−0.000(2)	0.007(2)
C11	0.090(3)	0.058(2)	0.029(2)	−0.001(3)	0.004(2)	0.010(2)
C12	0.074(3)	0.064(3)	0.024(2)	0.006(3)	−0.005(2)	0.003(2)
C13	0.041(2)	0.038(2)	0.032(2)	−0.001(2)	0.001(2)	−0.004(2)
C14	0.057(3)	0.040(2)	0.068(3)	0.003(2)	0.009(2)	−0.009(2)
C15	0.078(4)	0.047(3)	0.102(4)	−0.011(3)	0.026(3)	−0.019(3)
C16	0.084(4)	0.084(4)	0.064(3)	−0.039(3)	0.029(3)	−0.030(3)
C17	0.050(3)	0.095(4)	0.046(2)	−0.023(3)	0.001(2)	−0.012(3)
C18	0.043(2)	0.059(3)	0.045(2)	−0.002(2)	−0.001(2)	−0.002(2)
C19	0.067(3)	0.062(2)	0.030(2)	0.004(3)	0.011(2)	−0.004(2)
C20	0.078(3)	0.041(2)	0.054(2)	0.006(2)	−0.002(3)	−0.004(2)
H6a	0.090(−)					
H19a	0.075(−)					
H5a	0.090(−)					
H10b	0.075(−)					
H12a	0.081(−)					
H7a	0.076(−)					
H7b	0.076(−)					
H90	0.050(−)					
H11a	0.090(−)					
H3	0.057(−)					
H19b	0.075(−)					
H18	0.075(−)					
H10a	0.075(−)					
H16	0.116(−)					
H6b	0.090(−)					
H20a	0.087(−)					
H19c	0.075(−)					
H14	0.083(−)					
H20b	0.087(−)					
H5b	0.090(−)					
H2	0.065(−)					
H15	0.114(−)					
H12b	0.081(−)					
H11b	0.090(−)					
H20c	0.087(−)					
H17	0.095(−)					

Bond distances, bond angles and dihedral angles

Bond Distances	(Angstroms)
S-O3	1.465(3)
S-N2	1.511(3)
S-C13	1.793(4)
S-C9	1.816(3)
O2-C1	1.347(5)
O2-C2	1.470(5)
N1-C1	1.365(6)
N1-C12	1.472(5)
N1-C8	1.482(4)
N2-C19	1.471(5)
C8-C3	1.562(5)
C8-C7	1.563(6)
C8-C9	1.571(5)
C3-H3	1.014(4)
C3-C2	1.514(5)
C3-C5	1.543(6)
C1-O1	1.217(5)
C18-H18	1.092(5)
C18-C17	1.386(7)
C18-C13	1.391(6)
C9-H90	.925(4)
C9-C10	1.540(5)
C13-C14	1.375(6)
C7-H7a	.713(4)
C7-H7b	1.215(5)
C7-C6	1.506(6)
C5-H5b	.805(5)
C5-H5a	1.292(5)
C5-C6	1.541(7)
C10-H10a	1.071(5)
C10-H10b	1.213(4)
C10-C11	1.539(6)
C12-H12b	.936(5)
C12-H12a	.975(4)
C12-C11	1.511(7)
C17-H17	.966(5)
C17-C16	1.376(9)
C11-H11b	.984(5)
C11-H11a	1.017(4)
C19-H19b	.781(5)
C19-H19c	.928(5)
C19-H19a	1.024(4)
C2-H2	.839(4)
C2-C20	1.513(6)
C14-H14	1.304(5)
C14-C15	1.384(7)
C20-H20a	.906(5)
C20-H20c	.954(5)
C20-H20b	1.286(5)
C16-H16	1.105(6)
C16-C15	1.383(9)
C15-H15	1.057(5)
C6-H6b	.916(5)
C6-H6a	1.174(5)

Bond Angles	**(degrees)**
O3-S-N2	121.4(2)
O3-S-C13	104.6(2)
O3-S-C9	108.8(2)
N2-S-C13	109.6(2)
N2-S-C9	106.6(2)
C13-S-C9	104.7(2)
C1-O2-C2	115.1(3)
C1-N1-C12	114.6(3)
C1-N1-C8	122.1(3)
C12-N1-C8	115.4(3)
C19-N2-S	115.3(3)
N1-C8-C3	110.3(3)
N1-C8-C7	110.4(3)
N1-C8-C9	104.9(3)
C3-C8-C7	104.4(3)
C3-C8-C9	113.4(3)
C7-C8-C9	113.5(3)
H3-C3-C2	109.4(3)
H3-C3-C5	110.6(3)
H3-C3-C8	108.7(3)
C2-C3-C5	110.9(3)
C2-C3-C8	110.4(3)
C5-C3-C8	106.9(3)
O1-C1-O2	118.7(4)
O1-C1-N1	125.0(4)
O2-C1-N1	116.2(3)
H18-C18-C17	115.8(4)
H18-C18-C13	124.5(4)
C17-C18-C13	118.8(4)
H90-C9-C10	108.5(3)
H90-C9-C8	113.1(3)
H90-C9-S	99.2(2)
C10-C9-C8	113.1(3)
C10-C9-S	105.0(2)
C8-C9-S	116.7(2)
C14-C13-C18	121.5(4)
C14-C13-S	120.0(3)
C18-C13-S	118.0(3)
H7a-C7-H7b	95.0(4)
H7a-C7-C6	114.4(5)
H7a-C7-C8	116.2(5)
H7b-C7-C6	108.5(4)
H7b-C7-C8	116.7(4)
C6-C7-C8	105.9(3)
H5b-C5-H5a	99.8(4)
H5b-C5-C6	118.0(5)
H5b-C5-C3	111.4(5)
H5a-C5-C6	111.6(4)
H5a-C5-C3	109.3(4)
C6-C5-C3	106.5(4)
H10a-C10-H10b	102.7(3)
H10a-C10-C11	110.5(4)
H10a-C10-C9	113.5(4)
H10b-C10-C11	110.3(4)
H10b-C10-C9	107.3(3)
C11-C10-C9	112.0(3)
H12b-C12-H12a	96.4(4)
H12b-C12-N1	109.7(4)
H12b-C12-C11	115.4(4)
H12a-C12-N1	113.6(4)
H12a-C12-C11	111.7(4)

N1-C12-C11	109.6(3)
H17-C17-C16	120.8(6)
H17-C17-C18	119.1(5)
C16-C17-C18	120.2(5)
H11b-C11-H11a	103.1(4)
H11b-C11-C12	113.1(4)
H11b-C11-C10	101.9(4)
H11a-C11-C12	115.2(4)
H11a-C11-C10	113.5(4)
C12-C11-C10	109.3(4)
H19b-C19-H19c	98.9(5)
H19b-C19-H19a	106.6(4)
H19b-C19-N2	123.8(5)
H19c-C19-H19a	113.3(5)
H19c-C19-N2	113.0(4)
H19a-C19-N2	101.5(3)
H2-C2-O2	98.2(3)
H2-C2-C20	108.5(4)
H2-C2-C3	119.6(4)
O2-C2-C20	106.0(4)
O2-C2-C3	109.0(3)
C20-C2-C3	113.6(3)
H14-C14-C13	109.7(3)
H14-C14-C15	130.0(4)
C13-C14-C15	118.8(5)
H20a-C20-H20c	89.9(5)
H20a-C20-H20b	82.7(3)
H20a-C20-C2	118.8(4)
H20c-C20-H20b	107.3(3)
H20c-C20-C2	123.1(4)
H20b-C20-C2	123.2(4)
H16-C16-C17	114.4(6)
H16-C16-C15	125.3(6)
C17-C16-C15	120.2(5)
H15-C15-C16	126.5(5)
H15-C15-C14	112.8(6)
C16-C15-C14	120.5(5)
H6b-C6-H6a	92.9(4)
H6b-C6-C7	118.9(4)
H6b-C6-C5	110.8(5)
H6a-C6-C7	116.7(4)
H6a-C6-C5	112.8(4)
C7-C6-C5	104.9(4)

Dihedral Angles	**(degrees)**
C2-O2-C1-N1	-19.3(5)
O3-S-N2-C19	60.9(4)
C9-S-N2-C19	-173.9(3)
C13-S-N2-C19	-61.2(4)
O3-S-C9-C8	76.0(3)
O3-S-C9-C10	-50.2(3)
O3-S-C9-H90	-162.3(2)
N2-S-C9-C8	-56.6(3)
N2-S-C9-C10	177.3(3)
N2-S-C9-H90	65.2(3)
C13-S-C9-C8	-172.7(3)
C13-S-C9-C10	61.2(3)
C13-S-C9-H90	-50.9(3)
O3-S-C13-C18	-170.0(3)
O3-S-C13-C14	1.7(4)
N2-S-C13-C18	-38.4(3)

N2-S-C13-C14	133.3(3)
C9-S-C13-C18	75.6(3)
C9-S-C13-C14	-112.7(3)
C2-O2-C1-N1	-19.3(5)
C2-O2-C1-O1	158.8(4)
C1-O2-C2-C3	61.4(4)
C1-O2-C2-C20	-175.9(3)
C1-O2-C2-H2	-63.9(4)
C1-N1-C8-C3	35.8(5)
C1-N1-C8-C9	-86.6(4)
C1-N1-C8-C7	150.7(4)
C12-N1-C8-C3	-177.0(3)
C12-N1-C8-C9	60.6(4)
C12-N1-C8-C7	-62.1(4)
C8-N1-C1-O2	-31.6(5)
C8-N1-C1-O1	150.4(4)
C12-N1-C1-O2	-179.1(3)
C12-N1-C1-O1	3.0(6)
C8-N1-C12-C11	-65.5(5)
C8-N1-C12-H12a	168.7(4)
C8-N1-C12-H12b	62.1(5)
C1-N1-C12-C11	84.2(4)
C1-N1-C12-H12a	-41.5(6)
C1-N1-C12-H12b	-148.2(4)
S-N2-C19-H19a	-168.1(3)
S-N2-C19-H19b	72.8(6)
S-N2-C19-H19c	-46.5(5)
N1-C8-C3-C5	128.8(3)
N1-C8-C3-C2	8.1(4)
N1-C8-C3-H3	-111.9(3)
C9-C8-C3-C5	-114.0(3)
C9-C8-C3-C2	125.4(3)
C9-C8-C3-H3	5.4(4)
C7-C8-C3-C5	10.1(4)
C7-C8-C3-C2	-110.6(3)
C7-C8-C3-H3	129.4(3)
N1-C8-C9-S	-174.8(2)
N1-C8-C9-C10	-52.8(4)
N1-C8-C9-H90	71.1(4)
C3-C8-C9-S	64.8(4)
C3-C8-C9-C10	-173.2(3)
C3-C8-C9-H90	-49.4(4)
C7-C8-C9-S	-54.2(4)
C7-C8-C9-C10	67.9(4)
C7-C8-C9-H90	-168.3(3)
N1-C8-C7-C6	-146.4(3)
N1-C8-C7-H7a	-18.2(6)
N1-C8-C7-H7b	92.7(4)
C3-C8-C7-C6	-27.8(4)
C3-C8-C7-H7a	100.4(5)
C3-C8-C7-H7b	-148.7(3)
C9-C8-C7-C6	96.1(4)
C9-C8-C7-H7a	-135.7(5)
C9-C8-C7-H7b	-24.7(4)
C8-C3-C5-C6	10.7(4)
C8-C3-C5-H5a	131.3(3)
C8-C3-C5-H5b	-119.3(5)
C2-C3-C5-C6	131.1(4)
C2-C3-C5-H5a	-108.3(4)
C2-C3-C5-H5b	1.1(6)
H3-C3-C5-C6	-107.4(4)
H3-C3-C5-H5a	13.2(5)
H3-C3-C5-H5b	122.6(5)

C8-C3-C2-O2	-51.9(4)
C8-C3-C2-C20	-169.9(4)
C8-C3-C2-H2	59.8(5)
C5-C3-C2-O2	-170.1(3)
C5-C3-C2-C20	71.9(5)
C5-C3-C2-H2	-58.4(5)
H3-C3-C2-O2	67.7(4)
H3-C3-C2-C20	-50.3(5)
H3-C3-C2-H2	179.4(4)
C17-C18-C13-S	170.2(3)
C17-C18-C13-C14	-1.4(6)
H18-C18-C13-S	1.1(6)
H18-C18-C13-C14	-170.5(4)
C13-C18-C17-C16	-.9(7)
C13-C18-C17-H17	-180.0(4)
H18-C18-C17-C16	169.1(4)
H18-C18-C17-H17	-10.0(7)
S-C9-C10-C11	-179.5(3)
S-C9-C10-H10b	-58.3(4)
S-C9-C10-H10a	54.4(4)
C8-C9-C10-C11	52.2(5)
C8-C9-C10-H10b	173.4(3)
C8-C9-C10-H10a	-73.9(4)
H90-C9-C10-C11	-74.1(4)
H90-C9-C10-H10b	47.1(4)
H90-C9-C10-H10a	159.8(3)
S-C13-C14-C15	-169.4(4)
S-C13-C14-H14	23.3(5)
C18-C13-C14-C15	2.0(7)
C18-C13-C14-H14	-165.3(3)
C8-C7-C6-C5	34.8(5)
C8-C7-C6-H6a	-90.8(4)
C8-C7-C6-H6b	159.3(5)
H7a-C7-C6-C5	-94.5(6)
H7a-C7-C6-H6a	139.9(5)
H7a-C7-C6-H6b	30.0(8)
H7b-C7-C6-C5	160.8(3)
H7b-C7-C6-H6a	35.2(5)
H7b-C7-C6-H6b	-74.7(6)
C3-C5-C6-C7	-28.2(5)
C3-C5-C6-H6a	99.8(4)
C3-C5-C6-H6b	-157.6(4)
H5a-C5-C6-C7	-147.4(4)
H5a-C5-C6-H6a	-19.4(5)
H5a-C5-C6-H6b	83.2(5)
H5b-C5-C6-C7	97.9(6)
H5b-C5-C6-H6a	-134.2(5)
H5b-C5-C6-H6b	-31.6(7)
C9-C10-C11-C12	-52.4(5)
C9-C10-C11-H11a	177.6(4)
C9-C10-C11-H11b	67.5(5)
H10b-C10-C11-C12	-171.8(4)
H10b-C10-C11-H11a	58.2(6)
H10b-C10-C11-H11b	-51.9(5)
H10a-C10-C11-C12	75.4(5)
H10a-C10-C11-H11a	-54.6(6)
H10a-C10-C11-H11b	-164.7(4)
N1-C12-C11-C10	56.8(5)
N1-C12-C11-H11a	-174.1(4)
N1-C12-C11-H11b	-56.0(5)
H12a-C12-C11-C10	-176.4(4)
H12a-C12-C11-H11a	-47.4(7)
H12a-C12-C11-H11b	70.8(5)

H12b-C12-C11-C10	-67.6(5)
H12b-C12-C11-H11a	61.5(6)
H12b-C12-C11-H11b	179.7(3)
C18-C17-C16-C15	2.6(8)
C18-C17-C16-H16	-179.2(4)
H17-C17-C16-C15	-178.4(5)
H17-C17-C16-H16	-.1(8)
O2-C2-C20-H20a	-71.6(6)
O2-C2-C20-H20b	-172.3(3)
O2-C2-C20-H20c	39.3(6)
C3-C2-C20-H20a	48.2(7)
C3-C2-C20-H20b	-52.5(5)
C3-C2-C20-H20c	159.1(4)
H2-C2-C20-H20a	-176.2(5)
H2-C2-C20-H20b	83.1(5)
H2-C2-C20-H20c	-65.3(7)
C13-C14-C15-C16	-.3(8)
C13-C14-C15-H15	-175.5(5)
H14-C14-C15-C16	164.1(5)
H14-C14-C15-H15	-11.2(9)
C17-C16-C15-C14	-2.0(9)
C17-C16-C15-H15	172.6(6)
H16-C16-C15-C14	180.0(5)
H16-C16-C15-H15	-5(1)

Appendix

List of Abbreviations

$[\alpha]_D$	specific optical rotation
Ac	acetyl
AEI route	addition-elimination-isomerisation route
All*	chiral allyl rest
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
i-Bu	*i*-butyl
n-Bu	*n*-butyl
sec-Bu	*sec*-butyl
t-Bu	*tert*-butyl
Bus	*tert*-butylsulfonyl
Cbz or Z	benzyloxycarbonyl
CI	chemical ionisation
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminium hydride
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
er	enantiomeric ratio
δ	chemical shift
d	day
de	diastereomeric excess
dppe	bis(diphenylphosphino)ethane
dr	diastereomeric ratio
EI	electronic impact
Et	ethyl
eV	electronvolt

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
IR	infrared spectroscopy
J	coupling constant (in NMR spectroscopy)
LDA	lithium diisopropylamine
LDBB	Lithium di-*tert*-butylbiphenyl
LG	leaving group
LTA_4	leukotriene A_4
M	molar
Me	methyl
MEM	2-methoxyethoxymethyl
Mes	2,4,6-trimethylphenyl (mesityl)
mol	mole
m.p.	melting point
MS	mass spectroscopy
ν	wave number
NBS	N-bromosuccinimide
NMO	N-methylmorpholinoxide
NMR	nuclear magnetic resonance
NOE	nuclear OVERHAUSER effect
$cPLA_2$	cytosolic phospholipase A_2
i-Pr	*iso*-propyl
PG	Protecting group
RCM	ring-closing metathesis
rt	room temperature
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
THP	tetrahydropyrane
TMEDA	tetramethylethylendiamine
TMS	trimethylsilyl
TMS-allyl	allyltrimethylsilane
Tol	*p*-toluyl

TOCSY	total correlation spectroscopy
Ts	*p*-toluenesulfonyl (tosyl)
TS	transition state
VCAM-1	Vascular cell adhesion molecule - 1

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