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# Asymmetric Synthesis of Highly Substituted Azapolycyclic Compounds via 2-Alkenyl Sulfoximines: Potential Scaffolds for Peptide Mimetics

Michael Reggelin,* Bernd Junker,[‡] Timo Heinrich,[§] Stefan Slavik, and Philipp Bühle[||]

*Contribution from the Clemens-Schöpf-Institute of Organic Chemistry and Biochemistry, Technical University of Darmstadt, Petersenstrasse 22, 64287 Darmstadt, Germany*

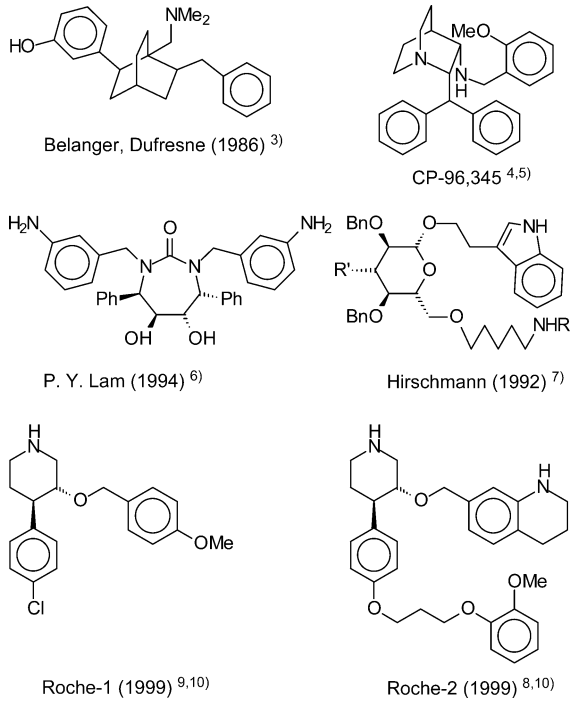
Received October 21, 2005; E-mail: re@punk.oc.chemie.tu-darmstadt.de

***Abstract:*** The application of metalated, enantiomerically pure acyclic and cyclic 2-alkenyl sulfoximines for the synthesis of highly substituted aza(poly)cyclic ring systems is described. The method relies on a *one-pot* combination of a reagent-controlled allyl transfer reaction to α- or β-amino aldehydes, followed by a Michael-type cyclization of the intermediate vinyl sulfoximines generated in the first step. The sulfur-free target compounds are preferentially obtained by samarium iodide treatment of the sulfonimidoyl substituted heterocycles. In addition to this methodological work, initial results on the biological activity of selected examples are reported. Furthermore, a concept for the transformation of peptidic lead structures into non-peptide mimetics is described, and the relevance of the new approach to highly substituted azaheterocycles in this context is discussed.

## Introduction

In a seminal paper published by Farmer more than 20 years ago the author defines peptidomimetics as novel scaffolds designed to replace the entire peptide backbone while retaining the isosteric topography of the enzyme-bound peptide (or assumed receptor-bound) conformation.[1] Since that time the term "peptidomimetic" has been given so many different meanings that there is now a considerable confusion of ideas. In 1998 Rich et al. presented a classification scheme which very much clarified the situation.[2] According to this work three types of peptidomimetics have to be distinguished (type-I to -III). Among them "*type-III mimetics represent the ideal in peptidomimetics in that they possess novel templates which, though appearing unrelated to the original peptides, contain the necessary groups positioned on a novel nonpeptide scaffold to serve as topographical mimetics*".[2] The synthetic methodology to be described in this article aims at the synthesis of this kind of peptidomimetics. In the meantime quite a number of type-III mimetics have been synthesized (Chart 1[3−10]) among which the two piperidines Roche-1 and Roche-2 merit special interest. These two non-peptide peptidomimetic inhibitors of renin were found to stabilize an enzyme conformation not previously observed for this enzyme.[11]

***Chart 1.*** Examples for "Type-III Mimetics"




Although the question whether these non-peptidic leads are really true mimics of the peptide is a matter of debate,[12,13] many

[‡] Current address: Aventis Pharma Deutschland GmbH, Process Development Chemistry, Industriepark Höchst, G 838, 65926 Frankfurt, Germany.

[§] Current address: Merck KGaA, Med Chem DA3, Frankfurter Str. 250, 64293 Darmstadt, Germany.

[||] Current address: Merck KGaA, Pigments R&D Cosmetics, Frankfurter Str. 250, 64293 Darmstadt, Germany.

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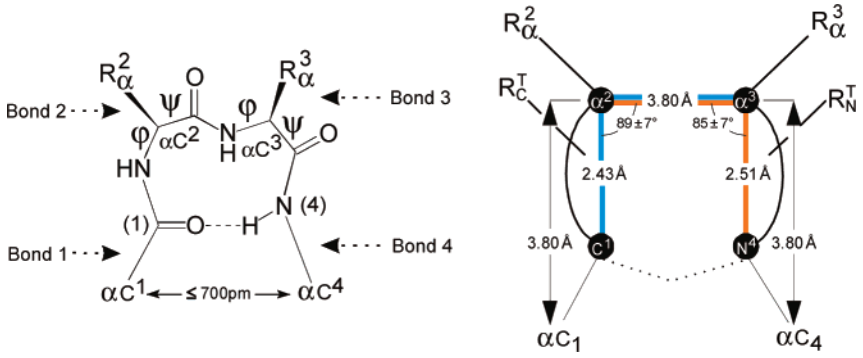


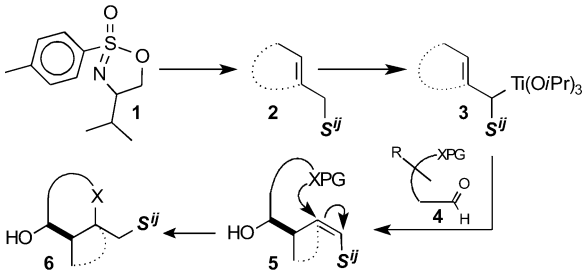

***Figure 1.*** $\beta$-Turn structure and definitions of the torsional angles $\varphi$ and $\psi$ (left). Topographical abstraction and definition of $\underline{\beta}$ as the angle between the planes spanned by the atoms connected in blue with those connected in red (right).

of them display high levels of biological activity. Despite these successes, the structural transition from a bioactive peptide to a nonpeptidic compound is still a very tedious process, involving the identification of the crucial amino acid side chains, the establishment of their spatial relationship, and finally the selection of an organic template suitable for reproducing the geometry of the pharmacophoric model.

To solve the latter problem a structural variable connecting the peptide with the "non-peptide world" would improve the situation considerably. If one assumes, and there is much evidence for the validity of this assumption,[14−16] that $\beta$-turns play a dominant role in the molecular recognition process, one such variable has been proposed by Ball in 1993.[17] Contrasting the common description of $\beta$-turn topography based on the backbone angles $\varphi$ and $\psi$, he proposed a pseudo-dihedral $\underline{\beta}$ as a means to describe and to compare the spatial relationship of potentially pharmacophoric groups in *both* peptides and nonpeptides (Figure 1).

The basis for this approach is the observation that the conformational relationship between bonds 1 and 2 and atom $\alpha C^3$ (as well as bonds 3/4 and $\alpha C^2$) remains approximately constant for any turn containing trans peptide bonds. The pseudo-dihedral $\underline{\beta}$ [TORS ($C^1$, $\alpha^2$, $\alpha^3$, $N^4$) thus describes the relationship between these two conformational subunits. This way $\underline{\beta}$ is a measure of the relative orientation of the exposed side chains at positions 2 and 3 ($R\alpha^2$ and $R\alpha^3$) which are suspected to be of major importance in the ligand/receptor interaction. With these ideas in mind it seems promising to develop a new synthesis of highly functionalized nitrogen heterocycles giving access to a broad range of compounds displaying pharmacophoric groups under a wide range of $\underline{\beta}$. This entails the necessity to find a synthetic protocol flexible enough to generate mono- and polycyclic systems with varying side chains and maximum control of both the relative and absolute configuration at the stereogenic centers. In this article we would like to describe our efforts toward this goal.

***Scheme 1.*** General Outline of the Method; $S^{ij}$ Denotes the Chiral Sulfonimidoyl Unit as Specified in Chart 3




## General Outline of the Method

In 1994 we discovered that titanated open-chain 2-alkenyl sulfoximines **3**, derived from cyclic sulfonimidates **1**, are highly stereoselective allyl transfer reagents (Scheme 1).[18] Shortly after that, Gais et al. introduced *N*-methyl substituted 2-alkenyl sulfoximines which he elaborated into useful synthetic tools for asymmetric synthesis.[19]

In the time to follow we developed this chemistry further by the introduction of cyclic 2-alkenyl sulfoximines **2** and the exploitation of the electron-deficient double bond in the primary products **5** of the allyl transfer reaction.[20−23]

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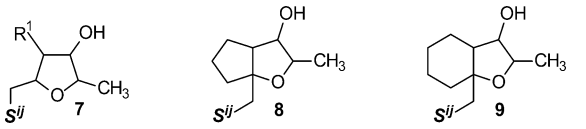
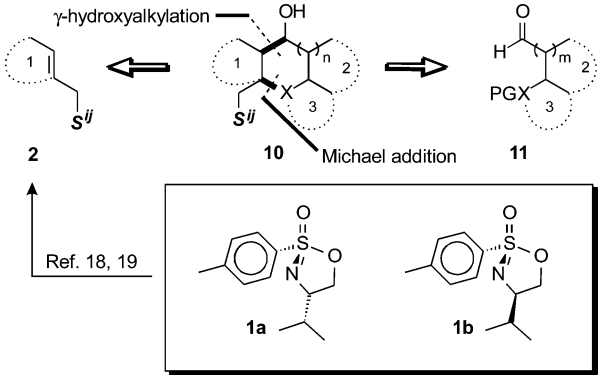
***Chart 2.*** Oxacyclic Compounds Accessible via 2-Alkenyl Sulfoximines and Oxygen Substituted Aldehydes; $S^{ij}$ Denotes the Chiral Sulfonimidoyl Unit as Specified in Chart 3




***Scheme 2***




These efforts led to the synthesis of isomerically pure highly substituted tetrahydrofuranes **7**,[22] 2-oxabicyclo[3.3.0]octanes **8**, and 2-oxabicyclo[4.3.0]nonanes **9**[20] (Chart 2).

As a consequence of this successful elaboration, we began to realize that these syntheses may be just aspects of a widely applicable protocol for the asymmetric synthesis of highly substituted (poly)heterocyclic ring systems (Scheme 2).

The retrosynthetic analysis of the generalized (poly)heterocyclic structure **10** (X = O, N) should lead to allylic sulfoximines **2** and heteroatom-substituted aldehydes **11**. Both fragments may or may not contain rings of variable size and substitution. The sulfoximines **2** can be prepared starting from the cyclic sulfonimidates **1a** or **1b**[24−26] following published procedures.[18,20,23]

A closer look at formula **10** (X = N) reveals that the structure is at least quadricyclic if rings 1−3 are present. The central ring is built up in the course of the reaction sequence, whereas the other three rings are components of the starting materials. This analysis of the target structure leads to an obvious classification: Each ring may be either present (p) or absent (a) entailing the principal accessibility of $2^3 = 8$ structural types. These can be encoded in a binary fashion reaching from type 000 (all rings absent) to 111 (all rings present) (Scheme 3).

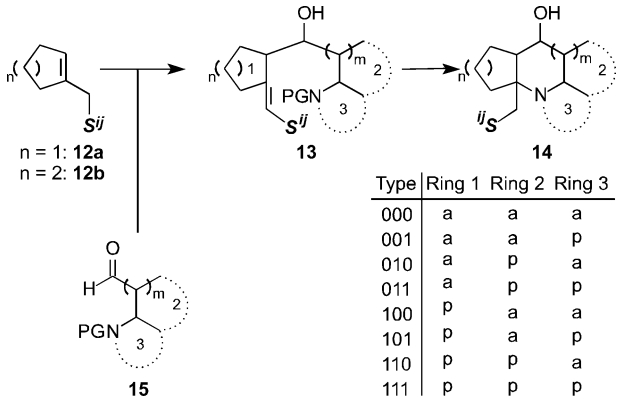
In this article we would like to present our results on the synthesis of the highly substituted aza-(poly)cyclic ring systems of general formula **14** (Scheme 3).

## Synthesis of the Starting Sulfoximines and Aldehydes

The 2-alkenyl sulfoximines used in this study are summarized in Chart 3. Their synthesis has already been described.[18,20,23]

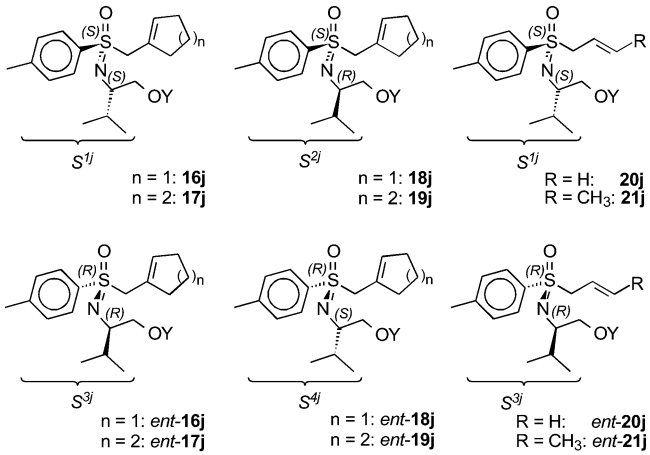
To save journal space, the chiral sulfur moiety has been given the symbol $S^{ij}$ as shown in Chart 3. The first superscript *i* encodes the absolute configuration of the auxiliary and therefore

***Scheme 3.*** Target Structure **14** and Encoding of the Ring Systems (a: absent; p: present)




| Type | Ring 1 | Ring 2 | Ring 3 |
|---|---|---|---|
| 000 | a | a | a |
| 001 | a | a | p |
| 010 | a | p | a |
| 011 | a | p | p |
| 100 | p | a | a |
| 101 | p | a | p |
| 110 | p | p | a |
| 111 | p | p | p |

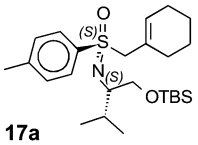
***Chart 3.*** 2-Alkenyl Sulfoximines Used in This Study, Coding of the Absolute Configuration, and the *O*-Substitution in the Sulfur Moiety




Y = TBS: *j* = *a*; Y = TMS: *j* = *b*; Y = H: *j* = *c*

*Example:*

Compound **17a**: Variable *"j"* takes the value of *"a"* entailing TBS as the protecting group *"Y"*. Furthermore, the descriptor for the auxiliary becomes $S^{1a}$ and because n = 2 the compound contains a six-membered ring:




**17a**

can take four different values ($S_S$,$S_C$: $i = 1$; $S_S$,$R_C$: $i = 2$; $R_S$,$R_C$: $i = 3$; $R_S$,$S_C$: $i = 4$). The second superscript *j* can adopt three different values depending on the nature of the protecting group Y (Y = TBS: $j = a$; Y = TMS: $j = b$; Y = H: $j = c$). To facilitate the recognition of the structures, the value of *j* is also used in the compound numbers **16**−**21**. A comprehensive example to clarify the use of this system is also given in Chart 3.

The α-amino aldehydes needed were prepared starting from the corresponding amino acids by the reduction−reoxidation sequences depicted in Schemes 4 and 5. To avoid a symmetrical intermediate, serines **22c** and *ent*-**22c** had to be protected by *t*Bu on both oxygens[27] prior to lithium aluminum hydride (LAH)-reduction. For a successful oxidation of the tryptophane derived alcohol **24f**, Boc-protection of the indole NH was found

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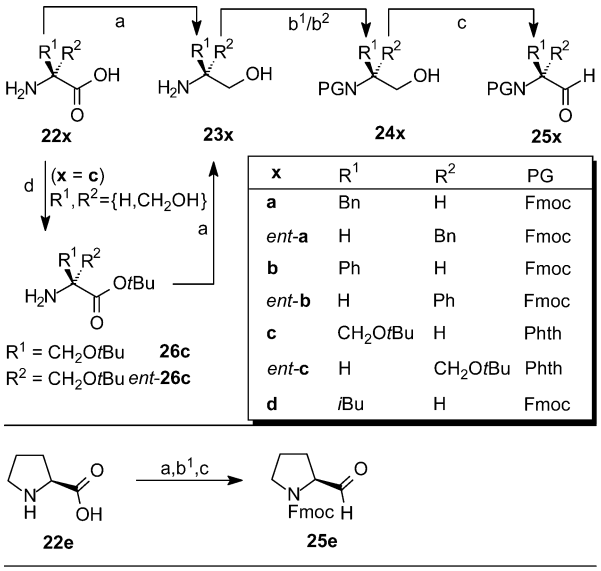
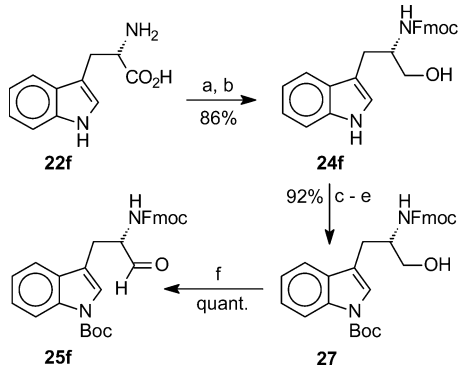
***Scheme 4.*** Synthesis of the α-Aminoaldehydes **25a**−**25e**[a]




| x | $R^1$ | $R^2$ | PG |
|---|---|---|---|
| **a** | Bn | H | Fmoc |
| *ent*-**a** | H | Bn | Fmoc |
| **b** | Ph | H | Fmoc |
| *ent*-**b** | H | Ph | Fmoc |
| **c** | $CH_2OtBu$ | H | Phth |
| *ent*-**c** | H | $CH_2OtBu$ | Phth |
| **d** | *t*Bu | H | Fmoc |

[a] (a) $LiAlH_4$, THF, 65 °C. ($b^1$) Fmoc-Cl, $NaHCO_3$, dioxane, $H_2O$, rt. ($b^2$) Phthalic anhydride, △. (c) DMP, $CH_2Cl_2$, 0 °C to rt. (d) Isobutene, $H_2SO_4$, dioxane.

***Scheme 5.*** Synthesis of the Protected Tryptophanal **25f**[a]

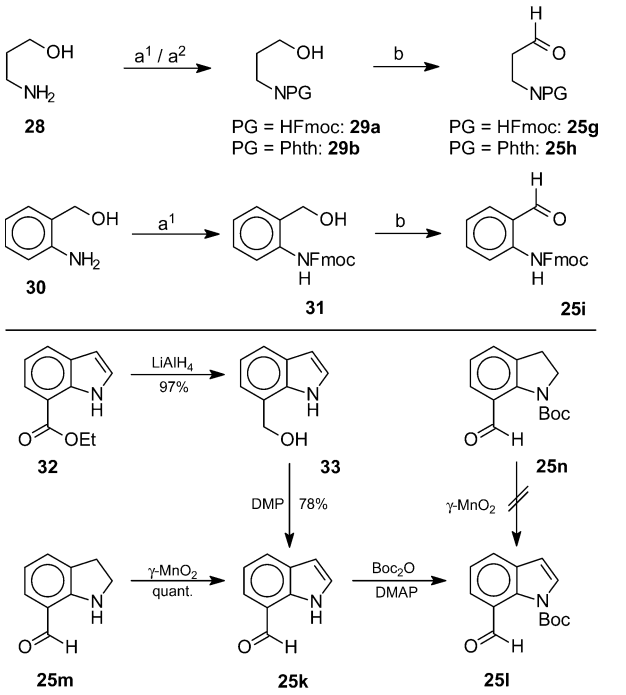



[a] (a) $LiAlH_4$, THF. (b) Fmoc-Cl, $NaHCO_3$, dioxane, $H_2O$, rt. (c) $Me_2NEt$, TMSCl, rt. (d) $Boc_2O$, $CH_3CN$, DMAP. (e) 0.5 N HCl. (f) DMP, $CH_2Cl_2$, 0 °C to rt.

to be advantageous (Scheme 5). The whole sequence including LAH-reduction, protection, and oxidation of the protected amino alcohols **24** by Dess−Martin periodinane (DMP) proceeds without notable racemization[21,28] as checked by NMR-shift experiments using Pr(hfc)3 as a chiral shift reagent. The α-amino aldehydes **25a**−**f** were used without further purification, and the overall yield starting from the amino acids usually exceeded 70%.

The preparation of the β-aminoaldehydes **25g**−**m** is described in Scheme 6. Aldehydes **25g**, **25h**, and **25i** were prepared in a straightforward manner from the commercially available amino alcohols **28** and **30**. For the Boc-protected 7-formyl indole **25l** we started from ester **32**,[29] whereas for the indoline derived aldehydes **25n** and **25m** Boc-indoline[30−32] was used as starting material. LAH-reduction of ester **32** proceeded with 97% yield to alcohol **33** which was oxidized by DMP in 78% yield to

***Scheme 6.*** Synthesis of the β-Amino Aldehydes[a]




[a] ($a^1$) Fmoc-Cl, $NaHCO_3$, dioxane, $H_2O$, rt. ($a^2$) Phthalic anhydride, △. (b) DMP, $CH_2Cl_2$, 0 °C to rt.

aldehyde **25k**. This aldehyde is also accessible via indoline-7-carbaldehyde **25m** by γ-$MnO_2$ oxidation in quantitative yield. This alternative pathway is very interesting, because it avoids the multistep preparation of ester **32** and allows for the preparation of all four aldehydes **25k**−**n** via Boc-indoline as a common precursor.

## Synthesis of the Azaheterocycles: From Acyclic Sulfoximines

As already stated, we would like to organize the material using the binary encoding scheme depicted in Scheme 3. With acyclic sulfoximines as starting material, ring 1 (see Scheme 3) is always absent and therefore only type-0XY systems are covered in this section.

**Type-000 Azacycles: Substituted Pyrrolidines and Piperidines.** From Scheme 3 it is obvious that both the aldehyde and the sulfoximine have to be acyclic. Pyrrolidines are obtained if α-amino aldehydes ($m = 0$) are used (Scheme 7, Table 1), whereas β-amino aldehydes ($m = 1$) give rise to the synthesis of piperidines, as will be discussed later.

After deprotonation of the sulfoximines using *n*BuLi in toluene, followed by transmetalation with chlorotris(isopropoxy)titanium ($ClTi(OiPr)_3$) and addition of the protected aldehydes **25**, the titanated 5-amino-4-hydroxy-vinyl sulfoximines **35a**−**f** and **36a**−**g** were obtained. These intermediates were not isolated but treated with 10 equiv of piperidine typically after 1 h of reaction time at −78 °C. This treatment releases the *N*-nucleophile, which attacks intramolecularly the acceptor-substituted double bond of the vinyl sulfoximines (Figure 2).

After removal of the dibenzofulven−piperidine adduct by crystallization from methanol and a short column filtration, the side chain of the auxiliary was desilylated and the ring nitrogen Boc-protected. The removal of the sulfonimidoyl moiety in the

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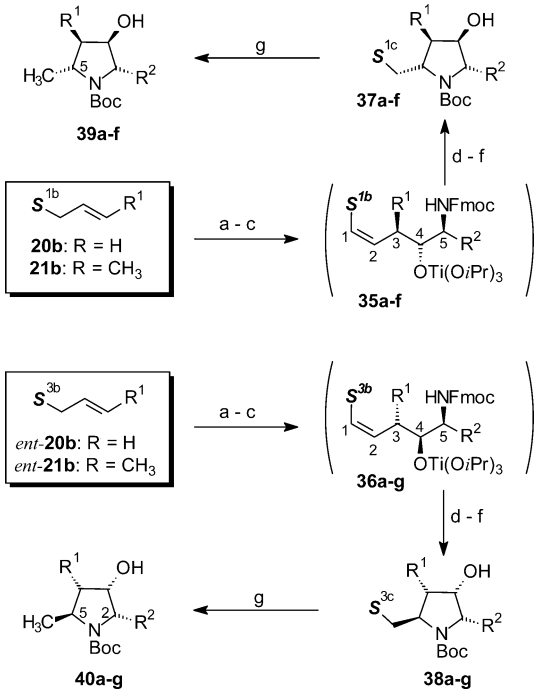
(32) Iwao, M.; Kuraishi, T. *Heterocycles* **1992**, *34*, 1031.

***Scheme 7.*** Highly Substituted Pyrrolidines from Acyclic 2-Alkenyl Sulfoximines[a]




[a] (a) *n*BuLi, −78 °C. (b) ClTi(O*i*Pr)$_3$, 0 °C. (c) Aldehyde **25**, −78 °C. (d) Piperidine, 0 °C, $(NH_4)_2CO_3$. (e) $K_2CO_3$, MeOH. (f) $Boc_2O$, $NaHCO_3$. (g) $SmI_2$.

***Table 1.*** Highly Substituted Pyrrolidines from Metalated Acyclic 2-Alkenyl Sulfoximines[a]

| # | $R^1$ | $R^2$ | Overall Yield [%] | *ds* [%][b] | $[\alpha]_D^{20}$ [c] | mp. [°C] |
|---|---|---|---|---|---|---|
| **39a** | H | Bn | 27 | 67 | -37.71(0.4) | 108.5 |
| **39b** | H | *i*Bu | 23 | 65 | +28.17(0.6) | oil |
| **39c** | H | *t*BuOCH$_2$ | 21 | 68 | +24.46(0.8) | 115.7 |
| **39d** | $CH_3$ | Bn | 63 | ≥96 | -37.29(1.0) | 127.8 |
| **39e** | $CH_3$ | *i*Bu | 42 | ≥96 | -19.99(0.9) | 96.9 |
| **39f** | $CH_3$ | *t*BuOCH$_2$ | 44 | ≥96 | +14.80(0.3) | oil |
| **40a** | H | Bn | 33 | 59 | +6.52(1.4) | 107.7 |
| **40b** | H | *i*Bu | 36 | 67 | -37.29(1.0) | oil |
| **40c** | H | *t*BuOCH$_2$ | 31 | 54 | +1.80(0.3) | 93.1 |
| **40d** | $CH_3$ | Bn | 43 | ≥96 | +26.70(1.0) | 91.0 |
| **40e** | $CH_3$ | *i*Bu | 34 | ≥96 | +66.20(1.0) | 97.3 |
| **40f**[d] | $CH_3$ | *t*BuOCH$_2$ | 30 | ≥96 | -20.80(0.3) | 187.2 |
| **40g** | $CH_3$ | Ph(*S*) | 50 | ≥96 | +83.43(0.5) | 145.4 |
| 2-*epi*-**40g** | $CH_3$ | Ph(*R*) | 49 | ≥96 | -9.00(0.5) | 138.6 |

[a] Compounds in shaded rows have been characterized by X-ray structural analysis. For **39a** and **40a** the structures of their respective minor diastereomers (5-*epi*) have been studied. The .cif files can be found in the Supporting Information (#.cif). [b] Determined by $^1$H NMR spectroscopic analysis of the crude reaction mixture. The *ds*-value corresponds to the selectivity of the cyclization. Therefore the minor diastereomer has the inverted absolute configuration at C-5. [c] (*c* in dichloromethane). [d] *N*-Deprotected and isolated as *p*-toluenesulfonate; value of optical rotation determined in methanol.

thus obtained pyrrolidine derivatives **37a**−**f** and **38a**−**g** was accomplished by $SmI_2$ in methanol/THF as described before.[21]

The relative and absolute configurations of the newly created stereogenic centers in the allyl transfer step (at C-3 and C-4, Scheme 7) are a consequence of the uniform relative topicity (*like*) of attack of the reactive partners onto each other governed by the prochirality of the double bond geometry in the 2-alkenyl sulfoximine and the sense of chirality at sulfur in the auxiliary, respectively.[18,20,21,23]

All pyrrolidines derived from **21b** (*S*-configuration at sulfur) have absolute configurations at C-3 and C-4 being in accordance with a mutual Re-face attack of the aldehyde and the allylic reaction partner. The opposite is true for the products derived from the $R_S$ configured sulfoximines *ent*-**21b**.

It is worth mentioning that even in the cases of *anti*-Cram combinations ($R_S$-configured sulfoximines−*S*-configured amino aldehydes) the configurational preferences of the aldehydes are completely overcompensated (reagent control). This means that the induced absolute configuration at C-3/C-4 is correlated to the absolute configuration of the auxiliary in a predictable manner. The stereochemical outcome at C-5 (pyrrolidine numbering), the stereogenic center being created during the cyclization event, is governed by conformational preferences of the cyclization precursors, the vinylic sulfoximines. The experimental results are in accordance with the assumption that the absolute topicity of attack of the *N*-nucleophile onto C-5 (pyrrolidine numbering) of **35** and **36** is dominated by the minimization of allylic strain and 1,5-repulsion (Figure 2).

For the terminally substituted allylic sulfoximines **21b**/*ent*-**21b** this is fulfilled best in conformation **A**. In contrast, for sulfoximines **20b**/*ent*-**20b** lacking the terminal substituent, conformation **B** is a reasonable alternative leading to an inversion of the absolute topicity of attack onto the double bond. However, due to 1,5-repulsion **B** is still energetically disfavored compared to **A**, so that even in the 4-unsubstituted (pyrrolidine numbering) cases the 3,5-trans pyrrolidines should be obtained in excess, which is indeed the case (Table 1, **39a**−**c**; **40a**−**c**).

The relative and absolute configuration of the pyrrolidines and those of the minor diastereomers epimeric at C-5 have been proven by X-ray crystallographic analysis of **39d**,[33] 2-*epi*-**40g**,[34] **40d**,[34] 5-*epi*-**39a**,[35] and 5-*epi*-**40a**,[36] respectively.

From the above analysis of the stereochemical outcome of the cyclization the expectation follows that cyclic 2-alkenyl sulfoximines with the C-4-substituent (pyrrolidine numbering) being incorporated into the ring (Scheme 2, formula 2) should react with a comparable stereoselectivity as **21**/*ent*-**21** (Chart 3). This expectation is fulfilled perfectly as will be discussed later.

Furthermore, the mode of stereocontrol entails the logical consequence that all enantiomeric pyrrolidines can be prepared simply by switching both the absolute configuration of the aldehyde *and* the sulfoximine.

Following the general outline depicted in Scheme 3 we next increased *m* in **14** from 0 to 1 within the subgroup of 000-type heterocycles, which should lead to substituted piperidines (Scheme 8).

Indeed, reacting the $\beta$-amino aldehyde **25h** with the titanated sulfoximine derived from *ent*-**21b** followed by hydrazine-induced cyclization (the motivation for the development of this alternative cyclization protocol will be discussed in a later

(33) Bats, J. W.; Heinrich, T.; Reggelin, M. *Acta Crystallogr.* **1998**, *C54*, IUC9800033.
(34) Bolte, M. *Acta Crystallogr.* **1997**, *C53*, IUC9700028.
(35) Bats, J. W.; Heinrich, T.; Reggelin, M. *Acta Crystallogr.* **1998**, *C54*, IUC9800039.
(36) Bats, J. W.; Heinrich, T.; Reggelin, M. *Acta Crystallogr.* **1998**, *C54*, IUC9800038.

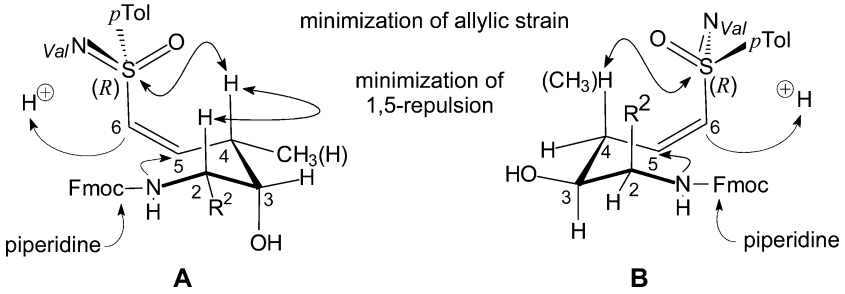
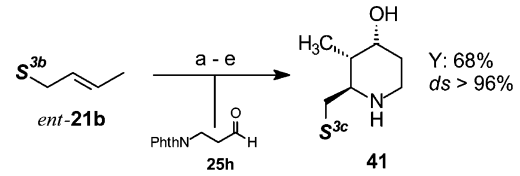


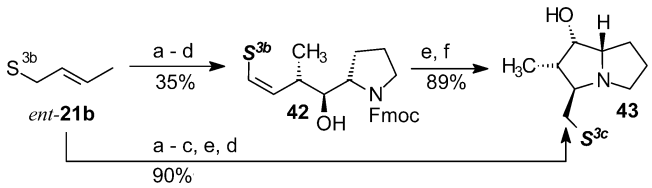

***Figure 2.*** Putative transition state model of the cyclization reaction. *Val* is used as an abbreviation for the trimethylsilylated side chain of the sulfoximine moiety.

***Scheme 8*** [a]




[a] (a) *n*BuLi, −78 °C. (b) ClTi(O*i*Pr)$_3$, −78 °C to 0 °C. (c) −78 °C, **25h**. (d) Hydrazine (80% in $H_2O$), EtOH. (e) $K_2CO_3$, MeOH.

***Scheme 9*** [a]




[a] (a) *n*BuLi, −78 °C. (b) ClTi(O*i*Pr)$_3$, −78 °C to 0 °C. (c) **25e**, −78 °C. (d) $(NH_4)_2CO_3$. (e) Piperidine, 0 °C. (f) $K_2CO_3$, MeOH. (g) Amount of **43** in the crude reaction mixture of the one-pot sequence as judged from $^1$H NMR.

section) led to piperidine **41** with 68% yield under complete stereocontrol.

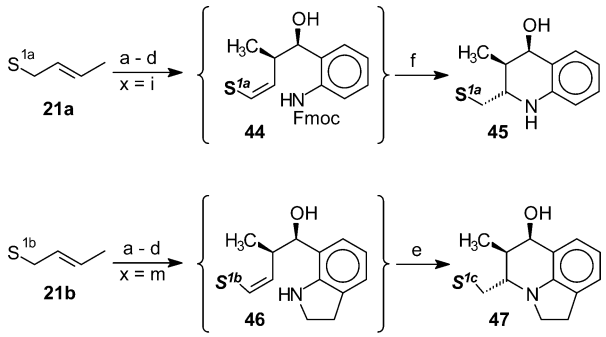
**Type-001, -010, and -011 Heterocycles.** Type-001 heterocycles should be accessible using an open chain sulfoximine and a heteromonocyclic amino aldehyde. To verify that expectation we used sulfoximine *ent*-**21b** and Fmoc-protected prolinal **25e** as starting materials (Scheme 9).

In the first experiment we tried to apply the one-pot protocol to access **43** without isolating the intermediate vinyl sulfoximine **42** which, in analogous cases, proved to be detrimental in terms of overall reaction yield. The pyrrolizidine was formed indeed with a yield around 90% as judged from the $^1$H NMR of the crude reaction mixture, but unfortunately we had difficulties in purifying the highly polar material. To get **43** in a pure state the experiment was repeated, this time isolating **42** albeit with a rather low yield of 35%. To our delight this material underwent smooth cyclization after the addition of piperidine, and analytically pure pyrrolizidine **43** could be isolated as a single isomer. A crystal structural analysis revealed the absolute configuration of the stereogenic centers as drawn.[37]

As examples for type-010 and -011 systems, the bicyclic and tricyclic compounds **45** and **47** were prepared, respectively (Scheme 10).

To make sure that the $\gamma$-hydroxyalkylation of **21a** with aldehyde **25i** (see Scheme 6) proceeded with complete stereocontrol as expected, we isolated the intermediate vinyl sulfoximine **44**. Although the yield was quite disappointing (29%) the compound was obtained as a single diastereomer. The subsequent piperidine-induced cyclization delivered the desired benzopiperidine derivative **45** with moderate 40% yield, again as a single isomer. The overall yield of **45** could be increased to 27% if the one-pot protocol was applied. With crotyl sulfoximine **21b** and the indoline derived aldehyde **25m** (see Scheme 6) the tricyclic system **47** (type 011) was obtained by spontaneous cyclization of the primary addition product **46** with 33% overall yield. It is worth mentioning that it is not necessary to *N*-protect the aldehyde **25m** due to the very low basicity of the titanium reagent produced in step (b) of the sequence.

***Scheme 10.*** Type-010 and -011 Heterocycles[a]




[a] (a) *n*BuLi, −78 °C. (b) ClTi(O*i*Pr)$_3$, −78 °C to 0 °C. (c) **25x**, −78 °C. (d) $(NH_4)_2CO_3$. (e) $K_2CO_3$, MeOH. (f) Piperidine, THF, rt.

## Synthesis of Azaheterocycles: From Cyclic Sulfoximines

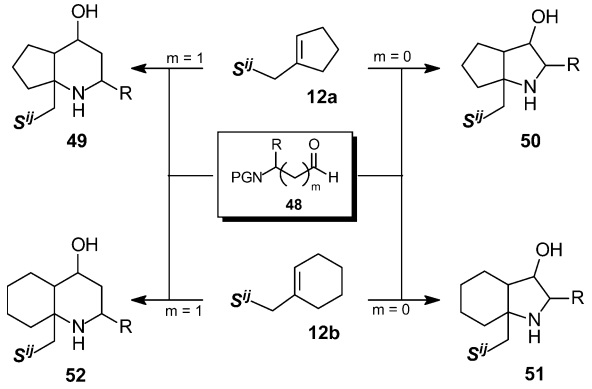
**Type-100 Heterocycles: 2-Azabicyclo[x.y.0]alkanes.** The reaction between the cyclic 2-alkenyl sulfoximines **12a** and **12b** and either α-amino aldehydes or $\beta$-amino aldehydes **48** ($m = 0$ or $m = 1$, respectively) should give rise to the formation of substituted 2-azabicyclic derivatives **49**−**52** as depicted in Scheme 11.

**2-Azabicyclo[3.3.0]octanes 50.** For the synthesis of the 2-azabicyclo[3.3.0]octanes **50** we employed three different starting materials differing in the relative and absolute configuration of the stereogenic centers in the sulfur moiety (Scheme 12, boxed structure). As described earlier, the vinyl sulfoximine intermediates obtained after the deprotonation, transmetalation, and $\gamma$-hydroxyalkylation sequence (a−c in Scheme 12) were not isolated but directly converted to the corresponding bicycles using either piperidine (**50a**−**c**, **50h**−**k**) or hydrazine (**50d**−**g**) to induce the cyclization (Scheme 12, Table 2).

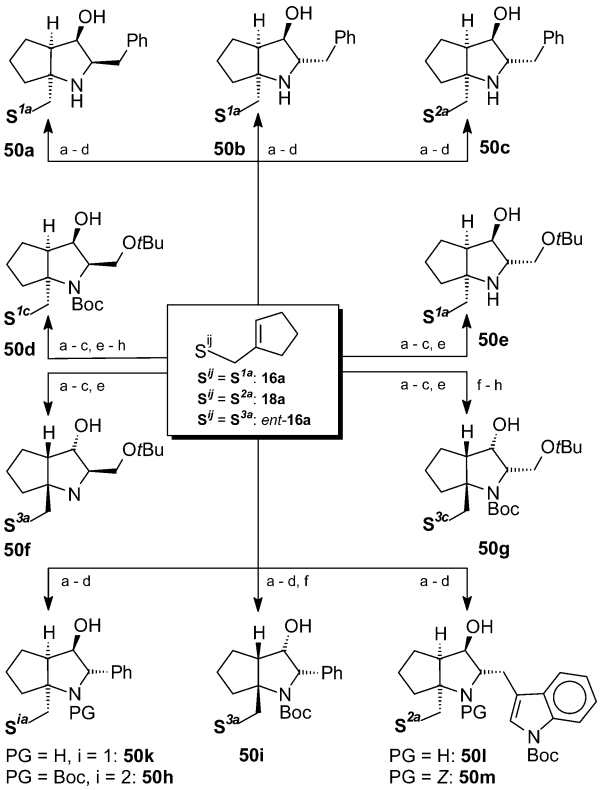
For the synthesis of the serine-derived 2-aza-bicycles **50d**−**50g** we found it advantageous to use the Phth-protected aldehydes **25c** and *ent*-**25c** (Scheme 4) instead of the corresponding Fmoc derivatives. In these cases the cyclization of

(37) Heinrich, T.; Reggelin, M.; Bats, J. W. *Acta Crystallogr.* **1999**, *C55*, IUC9900131.

***Scheme 11.*** General Scheme for the Synthesis of 2-Azabicyclo[x.y.0]alkanes from Cyclic Sulfoximines




***Scheme 12.*** 2-Azabicyclo[3.3.0]octanes[a]




[a] (a) *n*BuLi, toluene, −78 °C. (b) $ClTi(OiPr)_3$, −78 °C to 0 °C. (c) Aldehyde (see Table 2), −78 °C. (d) Piperidine, −78 °C to rt, $(NH_4)_2CO_3$. (e) Hydrazine, −78 °C to rt. (f) EtOH, Δ. (g) 5% HCl in EtOH, rt. (h) $Boc_2O$, $NaHCO_3$, dioxane, rt.

the γ-hydroxyalkylation products was initiated by hydrazine as the deprotecting agent.

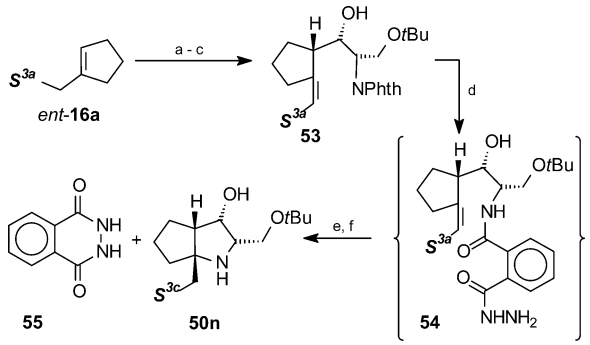
The hydrazine method was developed to circumvent some minor workup problems encumbered with the original piperidine induced deprotection−cyclization sequence using Fmoc-protected amino aldehydes. The latter protocol entails the generation of considerable amounts of a piperidine−fulven adduct which sometimes hampers the isolation of the product. With hydrazine as a deblocking agent the byproduct is phthalhydrazide **55** which is almost insoluble in the reaction medium and therefore can be removed easily by a simple filtration (Scheme 13). Furthermore **55** is able to complex the oxo-titanium compounds generated with the employed $EtOH/H_2O/N_2H_4$ mixture. This greatly facilitates further the workup procedure and avoids the

***Table 2.*** 2-Azabicyclo[3.3.0]octanes[a]

| # | SM | RCHO | Yield [%] | mp [°C] | $[\alpha]_D^{20}$ [b] | *ds* [%] |
|---|---|---|---|---|---|---|
| **50a** | **16a** | *ent*-**25a** | 49 | - | +54.0 (1.2) | ≥98 |
| **50b** | **16a** | **25a** | 35 | oil | -20.68 (1.0) | ≥98 |
| **50c**[c] | **18a** | **25a** | 63 | - | +28.0 (1.0) | ≥98 |
| **50d**[c] | **16a** | *ent*-**25c** | 39 | oil | +28.8 (1.0) | ≥98 |
| **50e**[c] | **16a** | **25c** | 78 | 119.0 | +24.1 (1.0) | ≥98 |
| **50f** | *ent*-**16a** | *ent*-**25c** | 63 | 119.4 | -24.1 (1.0) | ≥98 |
| **50g** | *ent*-**16a** | **25c** | 35 | oil | - | ≥98 |
| **50h** | **18a** | **25b** | 44 | oil | +63.0 (1.0) | ≥98 |
| **50i**[c] | *ent*-**16a** | **25b** | 46 | foam | -6.2 (0.9) | ≥98 |
| **50k** | **16a** | **25b** | 77[d] | 128.5 | +48.8 (1.0) | ≥98 |
| **50l** | **18a** | **25f** | 42 | - | - | ≥98 |
| **50m** | **18a** | **25f** | 60 (from **50l**) | 160.6 | +28.5 (1.0) | ≥98 |

[a] Compounds in shaded rows have been characterized by X-ray structural analysis. [b] (*c* in dichloromethane). [c] X-ray of Boc-protected and desulfurized compounds (Boc-**72x**, see Table 4). [d] Aldehyde addition at 0 °C.

***Scheme 13.*** Potential Problem with the Hydrazine-Induced Cyclization and Its Solution[a]




[a] (a) *n*BuLi, toluene, −78 °C. (b) $ClTi(OiPr)_3$, −78 °C to 0 °C. (c) **25c**, −78 °C. (d) Hydrazine, −78 °C to rt. (e) EtOH, Δ. (f) 5% HCl in EtOH, rt.

sometimes tedious removal of the titanium hydrolysates by $(NH_4)_2CO_3$ solution as is necessary with the original procedure.

Despite these obvious advantages sometimes care must be taken not to isolate intermediates such as **54** resulting from incomplete hydrazinolysis. In these cases, simply refluxing the semihydrazide in EtOH transformed it to the desired product. All 2-azabicyclo[3.3.0]octanes depicted in Scheme 12 are produced as enantiomerically pure diastereomers as judged from the $^1H$ NMR of the crude reaction mixtures. As with the already described pyrrolidines, the reaction proceeded in a completely reagent-controlled manner.

The absolute configurations of the newly created stereogenic centers are a sole consequence of the absolute configuration at sulfur. Again any stereochemical preference of the chiral aldehyde employed is overcompensated by the high level of asymmetric induction exerted by the auxiliary. The absolute configuration at the induced stereogenic centers remains constant for a given absolute configuration at sulfur irrespective of the aldehyde configuration (compare **50a**/**50b**; **50d**/**50e**; **50f**/**50g**). If, on the other hand, the absolute configuration at sulfur is changed, the same is true for the induced stereogenic centers again irrespective of the stereochemical bias exerted by the aldehyde (compare **50d**/**50f**; **50e**/**50g**).

Furthermore, the dominating inductive power of the centrochiral sulfur atom compared to the corresponding influence of

the stereogenic valine derived C-atom in the sulfonimidoyl moiety is demonstrated by the comparison of **50b** with **50c** and **50h** with **50i**.

In **50b** both stereogenic centers in the auxiliary are *S*-configured (*lk*; $S_S$, $S_C$), whereas in **50c** the configuration at carbon is inverted (*ul*; $S_S$,$R_C$). From the identical configuration induced in both compounds the overriding influence of the sulfur configuration is obvious. The same conclusion can be drawn from the product pair **50h** and **50i**. Switching from $S_S$,$R_C$ ($S^{2a}$) to $R_S$,$R_C$ ($S^{3a}$) entails an inversion of the configuration at the newly created stereogenic centers demonstrating again the major influence of the sulfur configuration. It should be mentioned here, that this stereochemical dominance of the sulfur is especially pronounced in the five-membered ring 2-alkenyl sulfoximines. With the six-membered ring sulfoximines the *lk*-configuration in the auxiliary ($S_S$,$S_C$ or $R_S$,$R_C$) was found to be necessary to achieve complete stereocontrol[23] in reactions with α-oxy-aldehydes. Due to the fact that this preferable "intramolecular matched" situation (accompanied by a mutual enhancement of the induction by both stereogenic units) can be easily established by proper choice of the valine isomer, this does not entail any restriction in the configurational scope of the reaction.

Finally the synthesis of three phenyl substituted derivatives (**50h, i, k**) in an isomerically pure state, employing the notoriously configurationally unstable phenylglycinal **25b**, demonstrates the low basicity of the allylic titanium intermediate preventing the aldehyde from racemization.

The configurations of the products shown in Scheme 12 have been confirmed by X-ray structural analysis of **50m**, **50e** and desulfurized **50i**, NBoc-**50c**, NBoc-**50f**, and NBoc-**50d** (Table 4). It is worth mentioning that compounds **50** can be synthesized on a rather large scale. For example, 13.54 g of **50e** have been obtained in 78% yield starting from **16a** without isolation of intermediates via the hydrazine route.

In the course of our efforts to develop a variant of the reaction working on MeOPEG-5000 as a soluble polymeric support,[38] we encountered some solubility problems related to the low reaction temperatures (−78 °C) seemingly necessary for the deprotonation and γ-hydroxyalkylation steps. For this reason we studied the temperature dependence of the resulting azacycles isomeric purity using **50b** and **50k** as examples (Table 3).

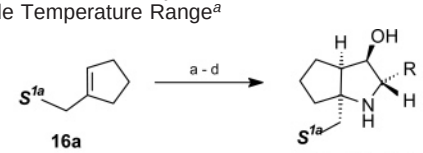
To our delight no erosion of isomeric purity occurred up to 0 °C reaction temperature. Furthermore, it was possible to reduce the reaction time, and we observed an increase in reaction yield especially for **50b** (entries 5 and 6). This turned out to be a general observation as will be demonstrated later (Scheme 16).

### 2-Azabicyclo[x.y.0]nonanes and 2-Azabicyclo[4.4.0]-decane

To broaden the scope of the reaction and to study possible effects on the stereochemical outcome we modified both the aldehyde and the 2-alkenyl sulfoximine. To gain access to bicyclic compounds of type **49**, **51**, and **52** (Scheme 11) we employed combinations of β-amino aldehydes and cyclohexenyl sulfoximines in addition to the already described α-amino aldehydes and cyclopentenyl sulfoximines.

(38) Reggelin, M.; Slavik, S., unpublished results.

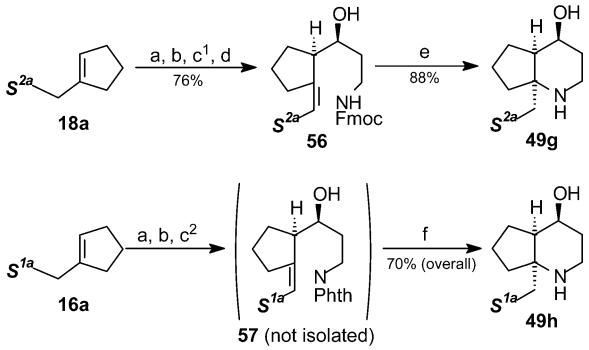
***Table 3.*** Diastereoselectivity of the Reaction Remains Constant over a Wide Temperature Range[a]




| # | R | Ald. | T [°C] | $t_1$ [min] | $t_2$ [h] | yield [%] | *ds* [%] |
|---|---|---|---|---|---|---|---|
| 1 | Ph | **25b** | -78 | 10 | 2 | 66 | ≥98 |
| 2 | Ph | **25b** | -45 | 10 | 2 | 74 | ≥98 |
| 3 | Ph | **25b** | -20 | 5 | 1.5 | 70 | ≥98 |
| 4 | Ph | **25b** | 0 | 5 | 1 | 77 | ≥98 |
| 5 | Bn | **25a** | -78 | 10 | 3 | 35 | ≥98 |
| 6 | Bn | **25a** | 0 | 5 | 1 | 66 | ≥98 |

[a] (a) *n*BuLi, toluene, T, $t_1$. (b) ClTi(O*i*Pr)$_3$, T to 0 °C, 1 h 0 °C. (c) Aldehyde, T, $t_2$. (d) Piperidine, T to rt.

***Scheme 14.*** Synthesis of 2-Azabicyclo[4.3.0]nonanes **49g** and **49h**[a]




[a] (a) *n*BuLi, toluene, −78 °C. (b) ClTi(O*i*Pr)$_3$, −78 °C to 0 °C. (c$^1$) **25g**, −78 °C. (c$^2$) **25h**, −78 °C. (d) $(NH_4)_2CO_3$. (e) Piperidine, THF, 0 °C to rt. (f) Hydrazine, −78 °C to rt.

With the β-amino aldehyde **25g** (Scheme 6) and sulfoximine **18a** we obtained the 2-azabicyclo[4.3.0]nonane **49g** in 67% overall yield using the Fmoc route (Scheme 14).

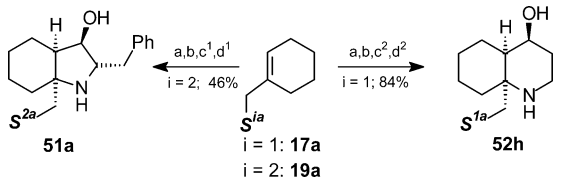
This time the intermediate vinyl sulfoximine **56** was isolated and cyclized in a separate step to make sure that the γ-hydroxyalkylation of **18a** with β-amino aldehyde **25g** proceeded with complete stereocontrol, which was found to be true. To our delight also the final cyclization was completely stereoselective yielding **49g** as a single stereoisomer. With the $S_S$,$S_C$-configured cyclopentenyl methyl sulfoximine **16a** and the Phth-protected aldehyde **25h** the diastereomer **49h** with identical configuration at the induced stereogenic centers was obtained with 70% overall yield without isolation of **57**.

Encouraged by these results we studied the corresponding behavior of the ring enlarged sulfoximine **17a** in its reaction with both α-amino- and β-amino aldehydes (Scheme 15).

The resulting 2-azabicycles **51a** and **52h** were obtained isomerically pure (without isolation of intermediates) in good and very good overall yields, respectively. The latter was prepared on a larger scale (10 g) via the hydrazine route, and its configuration was confirmed by X-ray crystallographic analysis.

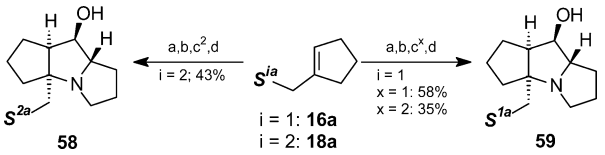
**Type-101, -110, and -111 Azapolycycles.** According to Scheme 3, the combination of a cyclic sulfoximine with

***Scheme 15.*** Synthesis of the 2-Azabicyclo[3.4.0]nonane **51a** and 2-Azabicyclo[4.4.0]decane **52h**[a]



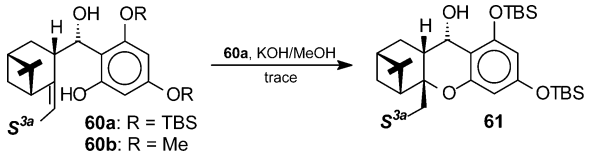

[a] Key: (a) *n*BuLi, toluene, −78 °C. (b) $ClTi(OiPr)_3$, −78 °C to 0 °C. ($c^1$) **25a**, −78 °C. ($c^2$) **25h**, −78 °C. ($d^1$) Piperidine, −78 °C to rt. ($d^2$) Hydrazine, −78 °C to rt.

***Scheme 16*** . Synthesis of Two Type-101 Azapolycycles[a]




[a] Key: (a) *n*BuLi, toluene, −78 °C. (b) $ClTi(OiPr)_3$, −78 °C to 0 °C. ($c^1$) **25e**, 0 °C. ($c^2$) **25e**, −78 °C. (d) Piperidine, $(NH_4)_2CO_3$.

***Scheme 17***




heterocyclic, homocyclic, or heterobicyclic amino aldehydes should lead to tri- or even tetracyclic systems.

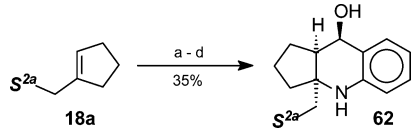
To evaluate the feasibility of such processes we first tried to react the cyclopentenyl sulfoximines **16a** and **18a** (differing only at the C-configuration in the side chain of the auxiliary) with Fmoc-protected (*S*)-prolinal **25e** (Scheme 16).

Applying the standard protocol (aldehyde addition at −78 °C) to the reaction between sulfoximine **18a** and aldehyde **25e**, the tricyclic compound **58** was formed isomerically pure in 43% yield. In accordance with our results in the type-100 series (see Table 3) raising the temperature in the allyl transfer step to 0 °C does not diminish the stereoselectivity as can be deduced from the experiment yielding tricycle **59**. Moreover these reaction conditions entail an increase in yield from 35% to 58%.

In an attempt to synthesize the euglobals G1 and G2 (terrestrial natural products isolated from *Eucalyptus grandis*)[39] we tried to cyclize vinyl sulfoximines **60** to the advanced precursor **61** (Scheme 17).[20] It is worth mentioning here that a sterically hindered tetrasubstituted aromatic aldehyde reacted with the titanated sulfoximine to furnish **60b** in a respectable 62% yield. This is even more surprising if one takes into account that protection of the phenolic hydroxyl was not necessary due to the low basicity of the titanium reagent.

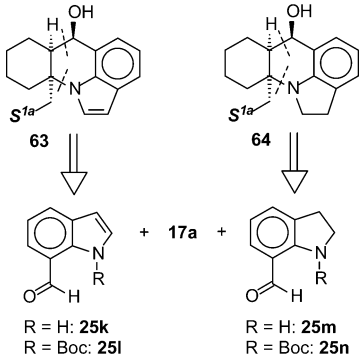
Unfortunately, even after considerable experimentation we were not able to obtain **61** in more than trace amounts. With this disappointing result in mind, we were curious to see whether it should be possible to accomplish cyclization if we replace the phenolic oxygen by nitrogen. In the event we found that the standard Fmoc-based one-pot protocol delivered the benzoannelated model-system **62** in 35% yield as a pure diastereomer (Scheme 18).

***Scheme 18.*** Benzoannelated Piperidine **62** as Example for a Type-110 Heterocycle[a]




[a] Key: (a) *n*BuLi, toluene, −78 °C. (b) $ClTi(OiPr)_3$, −78 °C to 0 °C. (c) **25i**, −78 °C. (d) Piperidine, $(NH_4)_2CO_3$.

***Scheme 19.*** Retrosynthetic Scheme to the Quadricyclic Compounds **63** and **64**




To complete the set of azapolycycles defined in Scheme 3 we explored the possibility to prepare the quadricyclic compounds **63** and **64** from sulfoximine **17a** (Scheme 19) and the bicyclic aldehydes **25k**−**n**, whose preparation has already been described (Scheme 6).

Due to the fact that none of the aldehydes **25k**−**n** is Fmoc- or Phth-protected and due to the peculiarities often encountered with an indole nitrogen, a new cyclization protocol had to be developed. Therefore we decided to prepare the target structures **63** and **64** via their corresponding vinyl sulfoximine intermediates **65**−**67**, which in turn can be used as starting materials for the new cyclization procedure (Scheme 20).

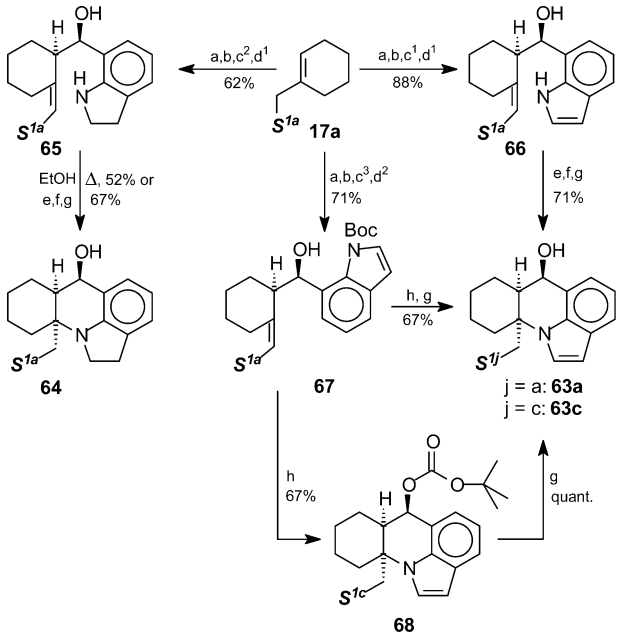
Being aware of the already mentioned low basicity of the titanated sulfoximines[20] (Scheme 17) we expected the reaction to work even with the unprotected aldehydes **25m** and **25k**. Indeed both reacted smoothly to the corresponding vinyl sulfoximines **65** and **66**, respectively, with complete stereocontrol.

Moreover, the former compound cyclized readily in refluxing ethanol to yield the quadricycle **64** in 52% yield again as a single isomer. Unfortunately, but not unexpectedly, the indole derivative **66** failed to cyclize under these conditions. Any attempt to force the system to cyclize by NH-deprotonation failed due to retroaddition. To avoid this unproductive reaction, the hydroxy function in **66** was silylated, and indeed, this time the base induced cyclization worked and, after solvolysis, delivered the desired product **63a** in 71% overall yield as a single isomer. Alternatively we succeeded in synthesizing **63c** via the Boc-protected vinyl sulfoximine **67** which cyclized under the influence of TBAF as the Boc-deprotection agent.[40] Interestingly, this cyclization is accompanied by a Boc-group migration from nitrogen to oxygen, delivering the carbonate **68** as an intermediate, which can be isolated in 67% yield. Solvolysis with $K_2CO_3$ containing methanol delivered **63c** in quantitative yield. The configuration of **66** and **63a** was confirmed by X-ray structural analysis.

(39) Takasaki, M.; Konoshima, T.; Kozuka, M.; Haruna, M.; Ito, K.; Shingu, T. *Chem. Pharm. Bull.* **1994**, *42*, 2591.

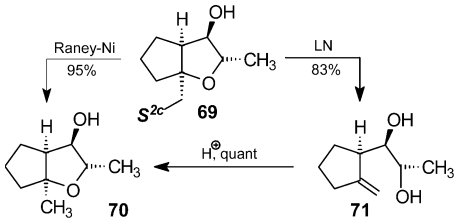
(40) Routier, S.; Sauge, L.; Ayerbe, N.; Coudert, G.; Merour, J. Y. *Tetrahedron Lett.* **2002**, *43*, 589.

***Scheme 20.*** Two Examples of Type-111 Azapolycycles[a]




[a] Key: (a) *n*BuLi, toluene, −78 °C. (b) $ClTi(OiPr)_3$, −78 °C to 0 °C. ($c^1$) **25k**, 0 °C. ($c^2$) **25m**, 0 °C. ($c^3$) **25l**, −78 °C. ($d^1$) Phthalhydrazide, EtOH, $H_2O$. ($d^2$) $(NH_4)_2CO_3$. (e) $Me_2N-SiMe_3$, Δ, 2 h. (f) *t*BuOH, *t*BuOK, Δ, 2 h. (g) $K_2CO_3$, MeOH. (h) TBAF, THF, rt.

***Scheme 21.*** Desulfurization of **69** with Raney-Nickel and Lithium Naphthalenide (LN)




**Removal of the Auxiliary.** Since sulfoximines can be taken as aza-analogues of sulfones, it is obvious that desulfurization methods applicable for the latter should also work for the former. For that reason we started our work on the removal of the sulfonimidoyl moiety using reagents known to effect the desulfurization of sulfones.

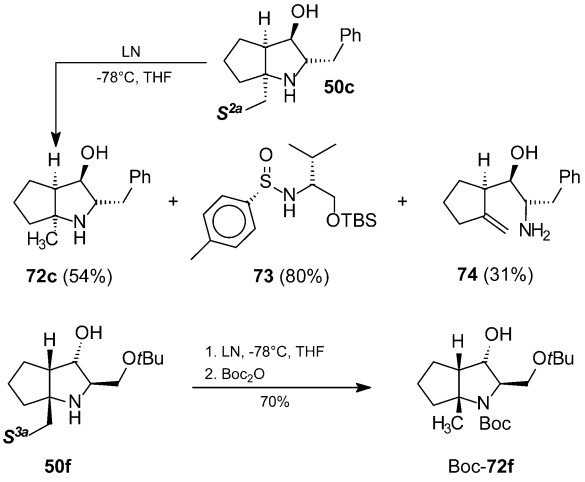
In the course of our work on the synthesis of 2-oxabicyclo-[3.3.0]octanes[20] we found Raney-nickel to be the reagent of choice for the desulfurization of these compounds (Scheme 21).

With **69** as a model compound Raney-nickel delivered the desulfurized 2-oxabicycle **70** with nearly quantitative yield. On the other hand treatment of **69** with lithium naphthalenide (LN) produced the sulfur-free, albeit ring-opened homoallylic alcohol **71** in 83% yield. This latter compound can be converted stereoselectively to the target bicycle **70** in a quantitative manner, simply by acid treatment.

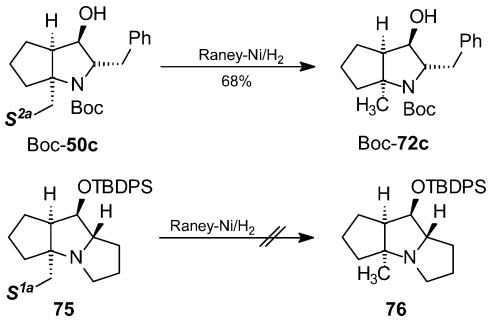
From these experiments we learned that every desulfurization method accompanied by an increase in electron density at the carbon adjacent to the sulfur atom may initiate a $\beta$-elimination destroying the bicyclic framework.

On the other hand for the azacyclic compounds under consideration here, the LN method may be feasible due to the reduced nucleofugacity of the nitrogen. Therefore we tried to desulfurize sulfoximines **50c** and **50f** with LN (Scheme 22). Indeed, the derived angular methyl-substituted derivatives **72c**

***Scheme 22.*** LN-Mediated Desulfurizations of 2-Azabicyclo[3.3.0]octanes




***Scheme 23.*** Successful and Unsuccessful Desulfurization with Raney-Nickel




and Boc-**72f** were produced with 54% and 70% yield, respectively. The former was accompanied by 31% of the ring-opened homoallylic alcohol **74** reflecting the residual nucleofugacity of the amine.

The reduced auxiliary **73** was isolated in about 80% yield with complete retention of the sulfur configuration as was shown by comparison with an independently prepared sample. Although this result confirmed our initial assumptions concerning the diminished nucleofugacity of the amide, the reaction was not really satisfying. This is all the more true because the unsaturated amine **74**, contrasting the behavior of the related alcohol **71** (Scheme 21), cannot be converted to the target structure **72c** by acid treatment, as expected.

Despite the fact that Raney-nickel (RN) proved to be a rather unreliable desulfurization agent with the sulfonimidoyl-substituted pyrrolidines,[21] we tried this reagent with the bi- and tricyclic sulfoximines Boc-**50c** (derived from **50c**) and **75** (derived from **59**), respectively (Scheme 23).

Whereas it was possible to desulfurize Boc-**50c** yielding 68% Boc-**72c**, which was characterized by X-ray structural analysis, the reaction failed to work with **75**. Again we encountered problems with the reliability and the constitutional scope of the RN-mediated desulfurization, and therefore we decided to explore the possibility of applying the $SmI_2$ reduction we developed for the sulfonimidoyl-substituted pyrrolidines some years ago (Scheme 24).[21]

For the $SmI_2$ method to work, it is necessary to have the *N*-atom Boc-protected and the side chain of the auxiliary deprotected, as already discussed.[21] Therefore, the substrates

***Scheme 24***

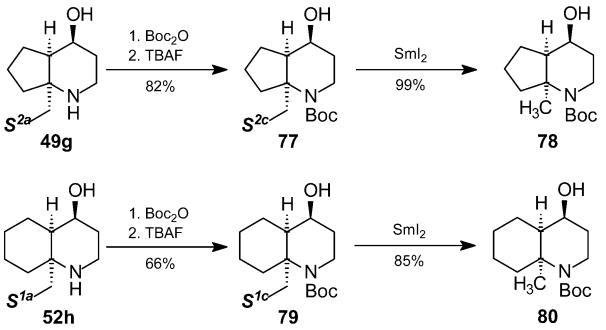
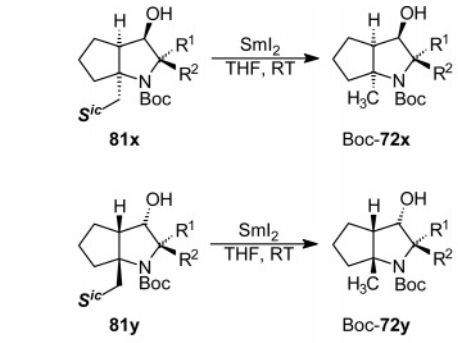



***Table 4.*** Desulfurization of 2-Azabicyclo[3.3.0]octanes with $SmI_2$[a]




| entry | x | y | i | $R^1$ | $R^2$ | Y[%] | $[\alpha]_D^{20}$ [b] |
|---|---|---|---|---|---|---|---|
| 1 | **c** | - | **2** | Bn | H | 74 | +8.4 |
| 2 | **h** | - | **2** | Ph | H | 78 | +34.5 |
| 3 | - | **i** | **3** | Ph | H | 70 | +50.7 |
| 4 | **e** | - | **1** | *t*BuOCH$_2$ | H | 53 | +65.87 |
| 5 | **d** | - | **1** | H | *t*BuOCH$_2$ | 31 | -27.6 |
| 6 | - | **g** | **3** | *t*BuOCH$_2$ | H | 46 | +27.6 |

[a] Compounds in shaded rows have been characterized by X-ray structural analysis. The .cif files can be found in the Supporting Information (#.cif). [b] (*c* in dichloromethane).

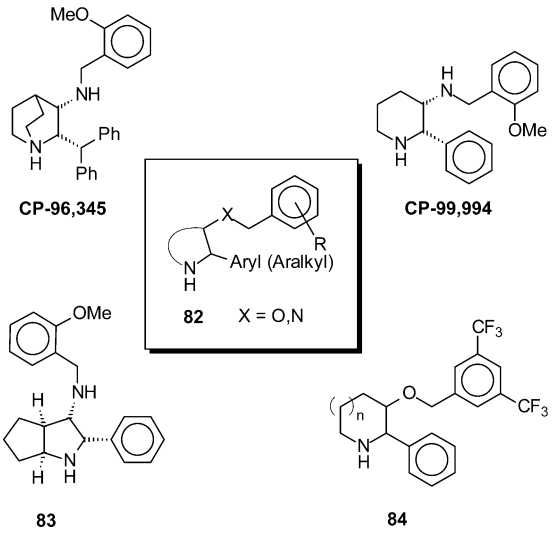
**49g** and **52h** were converted to the *N*-protected and desilylated derivatives **77** and **79**, respectively. To our delight both compounds were desulfurized with $SmI_2$ in THF with excellent yields delivering the azabicycles **78** and **80** as single isomers. Moreover, using this reaction we were able to desulfurize all 2-azabicyclo[3.3.0]octanes (Scheme 12) after the above-mentioned functional group interconversions (Table 3).

The yields given in Table 4 are not optimized and can be regarded as the lower limit. This is especially true for entries 4−6 which can be traced back to our lack of experience with the preparation of the $SmI_2$ reagent at the time the experiments were made. Nevertheless it should be noted that we were not able to desulfurize the tricyclic compounds **58** and **59** including several derivatives thereof. The reasons for these failures are not clear so far.

**NK1 Receptor Antagonists.** In the context of research directed toward the synthesis of nonpeptidic neurokinin subtype I (NK1) receptor antagonists, the 2-phenyl-3-heterobenzyl and the 2-phenylalkyl-3-heterobenzyl ethylamine subunits contained in **82** were identified as important structural motifs (Chart 4).[41]

(41) Desai, M. C.; Lefkowitz, S. L.; Thaideio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911.

***Chart 4.*** NK1 Receptor Antagonists Containing the Common Structural Subunit **82**




Quite a number of compounds have been synthesized incorporating this or similar structural motifs.[5,42,43] Many of them are based on either the quinuclidine nucleus (e.g., **CP-96,345**)[5,42] or the 1-azabicyclo[3.3.0]-scaffold (e.g., **83**) or are pyrrolidine (**84**, $n = 0$) or piperidine (**84**, $n = 1$) derivatives.[43,44] From these studies it became obvious that the biological activity of these compounds not only was dependent on the nature of the scaffold but also was sensitive to the substitution pattern and the configuration of the carbon atoms displaying the pharmacophoric groups. For these reasons and the fact that the compounds depicted in Chart 4 are all within the constitutional and configurational scope of the method described above, we decided to study its applicability within the context of NK1 antagonism. Toward this end we synthesized the substituted pyrrolidine **85** and the bicyclic derivative **86** (Scheme 25).

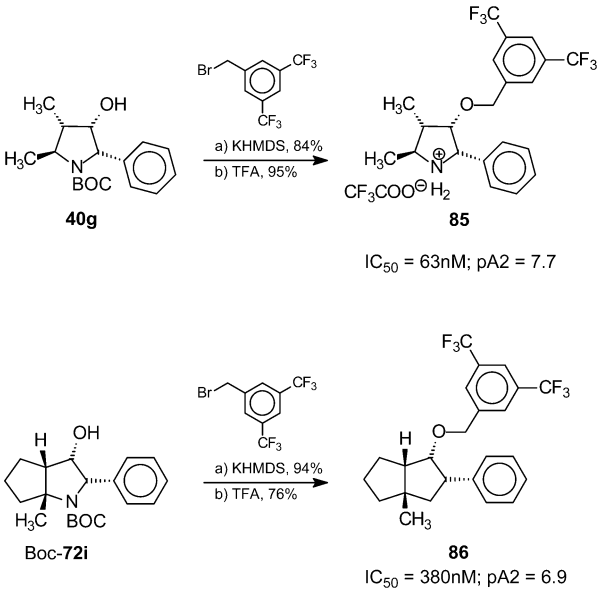
The absolute configuration of **85** was confirmed by X-ray structural analysis of the corresponding *p*-toluenesulfonic acid salt which in turn secures the structural assignment of **40g** too. Although both compounds do not reach the high level of activity of **CP-96,345**, the pyrrolidine **85** comes quite close. Taking this result as an encouraging starting point, we are currently exploring changes in ring sizes, substitution pattern, and configuration of the side chains presented, thereby exploiting the potential of the synthetic approach presented in this article to superimpose structural diversity from the side chains and the scaffold simultaneously.

## Conclusions

Starting from the cyclic sulfonimidates **1a** and **1b** and their enantiomers (Scheme 2, **1a** and *ent*-**1a** are commercially available; Aldrich # 54099−4 and 54412−4 respectively) the open chain and cyclic 2-alkenyl sulfoximines **16** to **21** can be

(42) Lowe, J. A., III; Drodzda, S. E.; Snider, R. M.; Longo, K. P.; Zorn, S. H.; Morrone, J.; Jackson, E. R.; McLean, S.; Bryce, D. K.; Bordner, J.; Nagahisa, A.; Kanai, Y.; Suga, O.; Tsuchiya, M. *J. Med. Chem.* **1992**, *35*, 2591.
(43) Appell, K. C.; Fragale, B. J.; Loscig, J.; Singh, S.; Tomczuk, B. E. *Am. Soc. Pharmacol. Experim. Therapeut.* **1992**, 772.
(44) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545.
(45) Craig, D. A. *Trends Pharmacol. Sci.* **1993**, *14*, 89.
(46) We thank Dr. R. Brückner (Solvay Pharmaceuticals, Hannover, Germany) for providing us with the biological data for **85** and **86**.

***Scheme 25.*** Synthesis of NK1 Receptor Antagonists[a]




[a] In vitro binding affinity of **85** and **86** for the NK1 receptor as measured by the reduction of substance P induced relaxation in precontracted aortic rings isolated from guinea pigs.[45,46] Compare with **CP-96,345** under the same conditions: IC50 = 10 nM, pA2 = 8.5.

prepared in high yields and on a multigram scale (e.g., **16a** with 78% overall yield starting from **1a**, Chart 3). The organotitanium compounds derived from these allylic sulfoximines can be hydroxyalkylated with almost complete stereocontrol delivering vinyl sulfoximines of type **13** (Scheme 3) using α- or *β*-amino aldehydes as electrophiles. These can be isolated, but in most cases it was found to be preferable to cyclize them immediately from the crude reaction mixture yielding highly substituted aza-(poly)cyclic compounds of general formula **14**.

With two types of sulfoximines (acyclic/cyclic) and four types of aldehydes (open chain, homocyclic, heterocyclic, heterobicyclic) eight different types of ring systems (type-000 to -111, Scheme 3) can be prepared as single isomers.

According to our goal, the development of a highly flexible entry to a broad range of highly substituted azacyclic compounds as potential peptide mimetics, we synthesized the pyrrolidine derivative **85** and the 2-azabicycle **86** (Scheme 25). Both compounds showed high biological activity in NK1-functional assays.

The sulfonimidoyl moiety can be removed using Raney-nickel, lithium naphthalenide, or $SmI_2$. The latter reagent turned out to be the reagent of choice in most cases, although the auxiliary is destroyed during the reduction.

Our current work is directed toward a functionalization of ring 1 (Scheme 3) and toward a functionalizing desulfurization combining the desulfurization step with the introduction of functional groups at the carbon atom adjacent to sulfur.

Finally, we explore the possibility of "translating" structural data from NMR studies on bioactive peptides to non-peptides of general structure **14** or desulfurized derivatives thereof.

**Acknowledgment.** We thank the Fonds der Chemischen Industrie (Kekulé Fellowship for P.B.) and Solvay Pharmaceuticals (Hannover, Germany) for generous financial support. We also thank Ms. S. Foro (TU Darmstadt) and Dr. J. Bats (University of Frankfurt/Main) for their careful work on the X-ray structures and Prof. H. Fuess (Department of Material Science, TU-Darmstadt) for measuring time on his diffractometer.

**Supporting Information Available:** Experimental procedures and characterization of the products (PDF). Crystallographic information files (CIF) for compounds **39d**, 5-*epi*-**39a**, 5-*epi*-**40a**, **40d**, 2-*epi*-**40g**, **43**, **50e**, **50m**, **52h**, **63a**, **66**, Boc-**72c-f**, Boc-**72i**, and **85**. This material is available free of charge via the Internet at http://pubs.acs.org.

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