A Regio- and Stereodivergent Route to All Isomers of *vic*-Amino Alcohols

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Abstract

The first part of this thesis describes a synthetic strategy that provides all eight possible isomers of a given *vic*-amino alcohol starting from vinylepoxides. The value of a general route is evident, as several isomers are needed in investigations of structure-activity relationships for pharmacologically active derivatives, and for optimizing the performance of chiral ligands containing the amino alcohol moiety.

Vinylepoxides, obtained in high enantiomeric excess, were ring-opened both with inversion and retention of stereochemistry, delivering two diastereomeric amino alcohols with high regio- and stereoselectivity. Via ring-closure to aziridines and subsequent regioselective ring-opening with suitable oxygen nucleophiles, the two remaining amino alcohols were selectively achieved.

Within this study, two efficient protocols for the regioselective and stereospecific aminolysis of vinylepoxides have been presented. Compared to previous methods, these procedures use milder reaction conditions, shorter reaction times, generally give higher yields and are applicable to a larger set of substrates. Furthermore, the ring-closure of vic-amino alcohols to the corresponding *N*-H vinylaziridines has been investigated. Three routes have been found useful, which one is preferred depends on substrate and scale.

In the second part of the thesis, the synthetic strategy is applied on the synthesis of Sphingosine and its regio- and stereoisomers. Moreover, a rapid way of determining relative configuration of *vic*-amino alcohols is described, which should be of substantial use when amino alcohols are formed by diastereoselective reactions.

Berit Olofsson; **A Regio- and Stereodivergent Route to All Isomers of vic-Amino Alcohols**. Department of Chemistry, Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden.

Keywords: amino alcohols, vinylepoxides, vinylaziridines, oxazolines, oxazolidinones, ring-opening, regioselective, diastereoselective, sphingosine, configuration, NMR spectroscopy.

Table of contents

Abbreviations

Δ	heat
BINOL	1,1-bi-2-naphtol
Boc	*t*-butoxy carbonyl
Cbz	benzyloxycarbonyl
dba	dibenzylideneacetone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
$(DHQ)_2PHAL$	hydroquinine 1,4-phtalazinediyl diether
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
dr	diastereomeric ratio
ds	diastereoselectivity
es	enantioselectivity
HRMS	high resolution mass spectroscopy
IBX	2-iodoxybenzoic acid
Ipc	isopinocampheyl
KHMDS	potassium hexamethyldisilazane
LDA	litium diisopropylamide
mCPBA	*m*-chloroperbenzoic acid
NMI	1-methylimidazole
Ms	methanesulfonyl
NOE	nuclear Overhauser effect
PMB	*p*-methoxybenzyl
SAE	Sharpless asymmetric epoxidation
TBHP	*t*-butyl hydroperoxide
TFA	trifluoroacetic acid
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Tr	trityl = triphenylmethyl
Ts	*p*-toluenesulfonyl
vic	vicinal

List of publications

This thesis is based on the following publications, in the text referred to by their Roman numerals **I-VII**.

I. **Microwave-assisted Aminolysis of Vinylepoxides**
Berit Olofsson, Ulf M. Lindström and Peter Somfai
Tetrahedron Lett. **1999**, *40*, 9273-9276.

II. **A Regio- and Stereodivergent Synthesis of *vic*-Amino Alcohols**
Berit Olofsson, Uttam Khamrai and Peter Somfai
Org. Lett. **2000**, *2*, 4087-4089.

III. **A Regio- and Stereodivergent Route to All Isomers of *vic*-Amino Alcohols,** Berit Olofsson and Peter Somfai
Latvijas J. Chem. **2002**, *1*, 69-78.

IV. **A Regio- and Stereodivergent Route to All Isomers of *vic*-Amino Alcohols,** Berit Olofsson and Peter Somfai
J. Org. Chem. in press.

V. **Synthesis of *N*-H Vinylaziridines: A Comparative Study**
Berit Olofsson, Roel Wijtmans and Peter Somfai
Tetrahedron **2002**, *58*, 5979-5982.

VI. **Divergent Synthesis of D-*erythro*-Sphingosine, L-*threo*-Sphingosine and their Regioisomers**
Berit Olofsson and Peter Somfai
Manuscript.

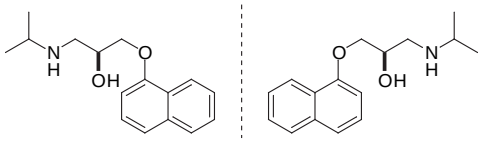
VII. **Determination of the Relative Configuration of *vic*-Amino Alcohols**
Berit Olofsson and Peter Somfai
Submitted.

Introduction

1

One of the main objectives of organic chemistry has always been the synthesis of natural products, as they can often be isolated from Nature only in minor amounts. Very complex molecules have been synthesized as early as in the 1950s, albeit in poor total yields. In the last decades chemists have, besides synthesizing extraordinarily complicated compounds, focused on optimizing already present reactions and developing new reactions which could simplify and shorten these syntheses. Great efforts to develop libraries of efficient reactions for each type of transformation have been made, in order to simplify the design of complex molecules. With these libraries at hand, each subunit of a complex molecule can be synthesized by means of well-known techniques, presupposed that the subunits can be combined in a later stage.

Many natural products contain one or more stereogenic centers, which complicate their syntheses substantially. Asymmetric synthesis is one of the most expanding fields in organic chemistry, since the discovery that the two enantiomers of a chiral compound can have different pharmacological effect. This can be exemplified by propranolol, which was introduced in the 1960s for the treatment of heart disease. The (-)-enantiomer is a potent β-blocker, whereas the (+)-enantiomer acts a contraceptive (Figure 1).[1]



(-)-Propranolol (mirror plane) (+)-Propranolol

Figure 1: The two enantiomers of propranolol.

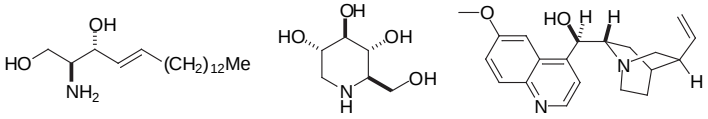
Asymmetric reactions are often developed from well-known procedures. Chiral auxiliaries or catalysts bearing chiral ligands can be utilized to afford induction towards one of the possible isomers. As the research on new

[1] Aitken, R. A.; Kilényi, S. N. *Asymmetric synthesis*; Blackie Academic & Professional: Glasgow, 1992.

asymmetric processes is continuously increasing, the need for novel chiral auxiliaries and ligands is extensive.[2,3]

1.1 Vicinal amino alcohols

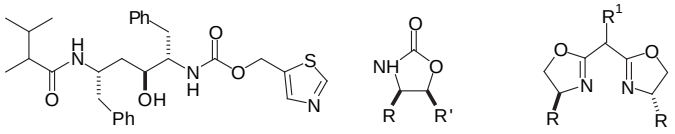
The β-amino alcohol moiety is found in a wide variety of biologically active alkaloids and peptides.[4] The subunit is also present in many synthetic, pharmacologically active molecules. Hydroxyamino acids constitute a major group among the naturally occurring amino alcohols. Lipids and lipid-like molecules often contain an amino alcohol moiety, as exemplified by sphingosine (Figure 2). This compound is the major backbone in glycosphingolipids, which are vital in cell recognition events such as growth, differentiation and immune response. Cyclic amino alcohols constitute a third group, where the amino residue is contained within a ring. Representatives of this group are deoxynojirimycin, which is an α-glycosidase inhibitor with therapeutic potential due to its low cytotoxicity, and quinine that is used as a drug for the treatment of malaria, high fever and other diseases.[4]



Sphingosine Deoxynojirimycin Quinine

Figure 2: Examples of natural products incorporating a *vic*-amino alcohol moiety.

Peptidomimetics are the most common among synthetic, pharmacologically active compounds containing a vic-amino alcohol subunit. This group of peptide analogues is typified by the HIV protease inhibitor saquinavir (Figure 3).[4]



Saquinavir Oxazolidinone Bis(oxazoline)

Figure 3: *Vic*-amino alcohol derivatives used in asymmetric synthesis.

The importance of vicinal amino alcohols is also well recognized in asymmetric synthesis, as many chiral auxiliaries and ligands contain this substructure. Some representative examples of amino alcohol-derived compounds are shown in Figure 3. Evans' oxazolidinones are utilized as chiral auxiliaries in various reactions, e.g. asymmetric alkylations. Bisoxazolines are employed as ligands in enantioselective cyclopropanations and aziridinations.[2,3]

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[2] Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835-875.

[3] Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995.

[4] Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561-2576.

1.2 Synthesis of amino alcohols

Existing synthetic routes to enantiopure amino alcohols rely heavily on the derivatization of the available pool of amino acids, inherently limiting the number of accessible derivatives.[5] The great efforts made to develop asymmetric routes to 1,2-amino alcohols can be divided into two strategically different categories. Amino alcohols formed by concomitant creation of a new C-C bond, i.e. by coupling reactions, constitutes the first class. More commonly, the amino alcohol moiety is constructed without alteration of the carbon skeleton. This category can be further divided into three subclasses, as depicted in Figure 4.[4]

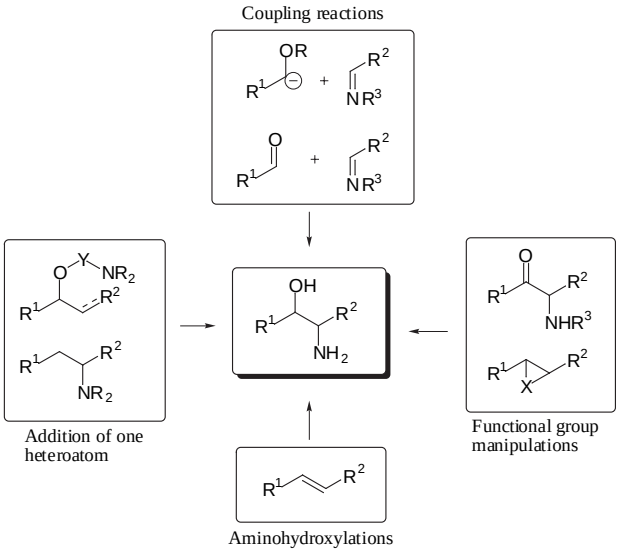


Figure 4: Syntheses of amino alcohols divided into categories.

1.2.1 Reactions forming C-C bonds

The most effective synthesis of amino alcohols should be the coupling of two molecules, one containing an oxygen functionality and the other a nitrogen functionality. As two new stereocenters are created simultaneously, both enantio- and diastereoselectivity must be controlled. The strategy is generally limited by the structural demands on the substrates, in order to obtain high selectivities.

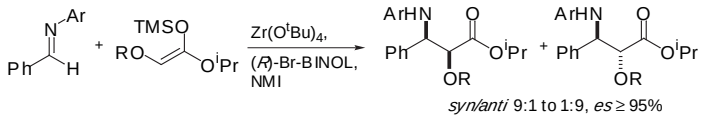
Stereoselective nucleophilic additions to imines afford amino alcohols with high enantioselectivity.[6] In the addition of α–alkoxyenolates to aldimines, the choice of enolate decides which isomer (*syn*/*anti*) will be the major product (Scheme 1).[7] A recent report by Jørgensen describes a proline-catalyzed α-

[5] Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531-1546.

[6] (a) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 2785-2792. (b) Tanaka, Y.; Taniguchi, N.; Uemura, M. *Org. Lett.* **2002**, *4*, 835-838.

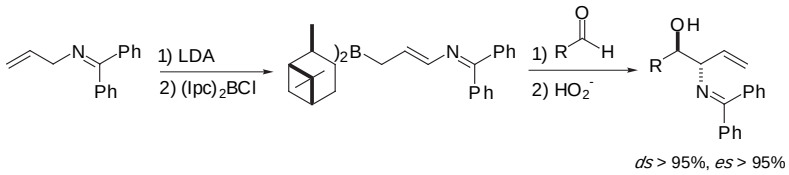
[7] Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431-432.

amination of ketones using an azodicarboxylate as the nitrogen source. The resulting α-hydrazino ketones, which are formed with good enantioselectivities, can be further derivatized into *syn*- or *anti*-amino alcohols by sequential reduction steps.[8]



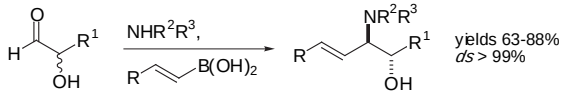
Scheme 1: Nucleophilic addition to an imine.

Additions of allylic imines to aldehydes primarily result in γ-amino alcohols. To obtain α-addition, the imine can be transformed into a 3-aminoallylborane. When chiral boron reagents are used, vinylic 1,2-amino alcohols can be obtained with high enantioselectivities (Scheme 2).[9]



Scheme 2: Aminoallylborane addition to aldehydes.

In a three-component, boronic acid Mannich approach, Petasis recently demonstrated an elegant synthesis of *anti*-amino alcohols (Scheme 3).[10] An α-hydroxyaldehyde is condensed with an amine to form the corresponding imine, which reacts with the boronic acid derivative to provide the *anti*-amino alcohol with excellent diastereoselectivity. The reaction works well with secondary amines, but is less efficient with primary amines and ammonium salts. The major limitation is the need for an aryl or olefinic boronic acid derivative.[11]



Scheme 3: The boronic acid Mannich reaction.

When one of the two stereocenters is set, the other can be created with good diastereoselectivity. This happens in the addition of organometallic nucleophiles to α-aminocarbonyls, derived from chiral amino acids. (Scheme 4).[5] The asymmetric induction obtained in the reaction can be interpreted by means of the Felkin-Anh non-chelation control model. Drawbacks of this method are the

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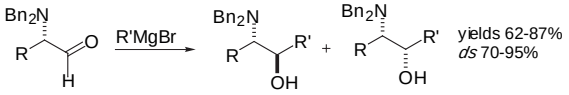
[8] Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254-6255.

[9] Barrett, A. G. M.; Seefeld, M. A.; White, A. J. P. *J. Org. Chem.* **1996**, *61*, 2677-2685.

[10] Petasis, N. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798-11799.

[11] For a similar approach, see List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827-833.

stability problems of α-aminocarbonyls and the sometimes moderate diastereoselectivities obtained.[12]



Scheme 4: Nucleophilic addition to α-aminocarbonyls.

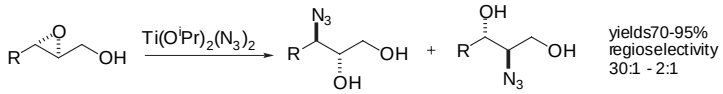
In this category, the addition of α-alkoxyenolates to aldimines is the most flexible reaction, as the choice of enolate decides which isomer (*syn/anti*) will be the major product (see Scheme 1).

1.2.2 Reactions not altering the carbon skeleton

More commonly, the amino alcohol moiety is constructed without alteration of the carbon skeleton. The substrates are primarily alkenes or alkene derivatives, and the reactions often proceed stereospecifically. Regioselectivity is instead a problem, which can be circumvented only when the substrate is substituted by groups having different electronic or steric influences.

Functional group manipulations

With the advancement of diastereo- and enantioselective syntheses of epoxides, cleavage of oxiranes by nitrogen nucleophiles is nowadays one of the most investigated routes to vicinal amino alcohols.[13] Both *syn*- and *anti*-amino alcohols are available by employing *cis*- and *trans*-epoxides, respectively. The strategy is, however, often limited by poor regioselectivity, except with terminal oxiranes. Substituents on the oxirane ring have both steric and electronic influence on the regioselectivity; conjugating substituents, e.g. phenyl and vinyl, usually promote ring opening at the adjacent carbon.[14] Regioselective azide opening of epoxyalcohols can be achieved by employing $Ti(O^iPr)_2(N_3)_2$, which coordinates to the alcohol moiety before nucleophilic attack (Scheme 5).[15]



Scheme 5: Nucleophilic ring-opening of epoxides.

Cyclic sulfates[16] and carbonates,[17,18] derived *via* asymmetric dihydroxylation of

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[12] Veeresha, G.; Datta, A. *Tetrahedron Lett.* **1997**, *38*, 5223-5224.

[13] (a) Hayakawa, H.; Okada, N. M., M.; Miyashita, M. *Tetrahedron Lett.* **1999**, *40*, 4589-4592. (b) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420-7421. (c) Zwanenburg, B. *Pure Appl. Chem.* **1999**, *71*, 423-430.

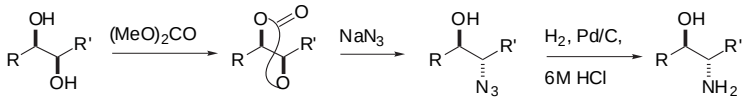
[14] Jaime, C.; Ortuno, R., M.; Font, J. *J. Org. Chem.* **1988**, *53*, 139-141.

[15] Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185-5187.

[16] Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2623-2626. ()Lohray, B. B. *Synthesis* **1992**, 1035-1052.

[17] Chang, H.-T.; Sharpless, B. *Tetrahedron Lett.* **1996**, *37*, 3219-3222.

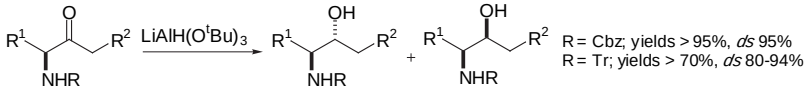
the corresponding alkenes, can be ring-opened with nitrogen nucleophiles to give *anti*-amino alcohols. The opening occurs in the most activated position with overall yields of 70-80% (Scheme 6). In a similar fashion *syn*-diols can be transformed into *syn*-amino alcohols.[18]



Scheme 6: Nucleophilic opening of cyclic carbonates.

Enantioselective aziridination is known to be more difficult than asymmetric epoxidation, and general methods are missing. Ring-openings of aziridines with oxygen nucleophiles to afford 1,2-amino alcohols are consequently not as common as epoxide openings, yet interesting. Nucleophiles employed to date are water, alcohols and carboxylic acids.[19,20]

Reductions of α-amino ketones can be made diastereoselective towards synthesis of either *syn*- or *anti*-amino alcohols, depending on the choice of protective group (Scheme 7).[21] Upon treatment of Cbz-protected substrate with $LiAlH(O^tBu)_3$, the *anti*-isomer is formed with excellent diastereoselectivity. When the same substrate is trityl-protected, the *syn*-isomer is predominantly formed, although sometimes with moderate selectivity. Due to the relative instability of α-hydroxyimines, corresponding reductions of these compounds are seldom performed.[4]



Scheme 7: Diastereoselective reduction.

Aminohydroxylation

The most straightforward route among the functional group manipulations is evidently the asymmetric aminohydroxylation of alkenes. Sharpless has developed a variant of the well-known dihydroxylation that utilizes the same oxidant and ligand system. α,β-Unsaturated esters and phosphonates are the best substrates for this reaction, which delivers *syn*-amino alcohols with high enantioselectivities but often with moderate yields due to poor regioselectivities (Scheme 8).[22]

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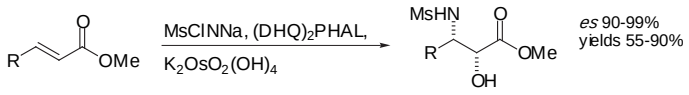
[18] Cho, G. Y.; Ko, S. Y. *J. Org. Chem.* **1999**, *64*, 8745-8747.

[19] Takeuchi, H.; Koyama, K. *J. Chem. Soc., Perkin Trans. 2* **1981**, 121-126.

[20] (a) Ibuka, T.; Nakai, K.; Akaji, M.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *Tetrahedron* **1996**, *52*, 11739-11752. (b) Cantrill, A. A.; Osborn, H. M. I.; Sweeney, J. *Tetrahedron* **1998**, *54*, 2181-2208.

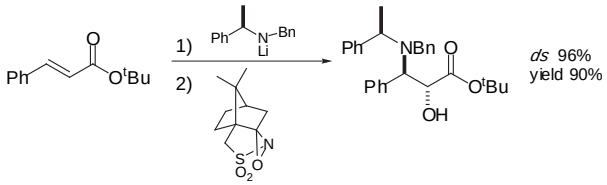
[21] Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045-1056.

[22] (a) Li, G.; Chang, H.-T.; Sharpless, B. K. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451. (b) O'Brien, P. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 326-329.



Scheme 8: Sharpless asymmetric aminohydroxylation.

A complimentary two-step procedure is described by Davies (Scheme 9). In this reaction sequence, a chiral amide anion added to an α,β-unsaturated ester. The resulting enolate was trapped with an oxygen electrophile to yield the *anti*-amino alcohol with excellent diastereoselectivity.[23]

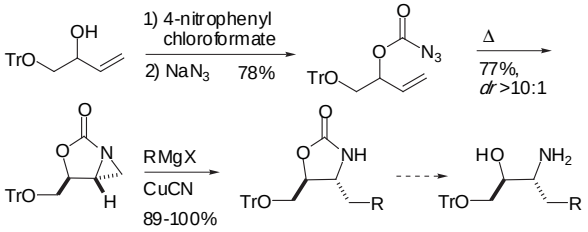


Scheme 9: Two-step aminohydroxylation.

Both of the above methods suffer from very limited substrate tolerance, which can be exemplified by the aminohydroxylation of cyclohexene. The corresponding *syn*-amino alcohol was obtained in 48% yield with 66% enantioselectivity.

Addition of one heteroatom

This strategy is rarely employed, although some examples exist. Chiral auxiliaries are not utilized in these reactions; instead the resident heteroatom directs the nucleophile. The intramolecular addition of an acyloxynitrene to an olefin is an indirect synthetic route to amino alcohols *via* oxazolidinones (Scheme 10).[24] The reaction sequence starts by formation of an azidoformate from the corresponding allylic alcohol. Thermolysis of this species provides a bicyclic aziridine, which can be ring-opened to the corresponding oxazolidinone.



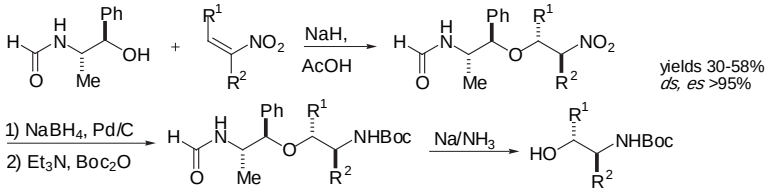
Scheme 10: Intramolecular addition of an acyloxynitrene to an olefin.

The corresponding additions of oxygen nucleophiles to nitrogen-containing molecules are seldom attempted. In the oxa-Michael addition of *N*-formylnorephedrine to nitroalkenes, *anti*-amino alcohols are formed with

[23] Bunnage, M. E.; Chernega, A. N.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2373-2384.

[24] Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1997**, *62*, 4449-4456.

excellent selectivities in a four step sequence (Scheme 11).[25]



Scheme 11: Oxa-Michael addition to nitroalkenes.

1.3 Aim of the study

Despite the great interest in the field of *vic*-amino alcohols, a divergent route from a common starting material towards all possible regio- and stereoisomers of a vicinal amino alcohol is still missing.[2,4] The synthetic planning is thus substantially complicated by the requirement of a separate synthetic route for each isomer. A divergent route leading to all possible isomers would be a great simplification for studies on structure-activity relationships of pharmacologically active derivatives incorporating the amino alcohol moiety. A divergent route would also allow optimization of the performance of chiral ligands containing this structural motif.

We therefore set out to develop a route leading to all eight possible isomers of a given *vic*-amino alcohol, starting from a common substrate that could be readily synthesized. To demonstrate the value of this route, it would then be applied to natural product synthesis.

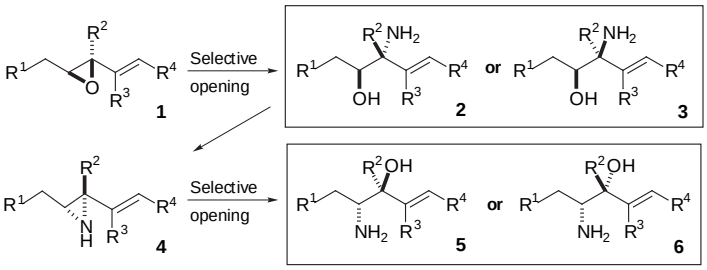
1.4 Synthetic strategy

The requirements of a generally applicable synthetic route are readily available starting materials, flexibility, predictability and high regio- and diastereoselectivity. These demands can be met by choosing vinylepoxides as substrates, as they are known to be ring-opened selectively at the allylic position by hard nucleophiles.[14] Furthermore, both enantiomers are readily available in high enantiomeric excess *via* asymmetric epoxidation strategies.

As depicted in Scheme 12, the synthetic strategy designed to fulfill these specifications starts by ring-opening of epoxides **1** with a nitrogen nucleophile. Selective ring-opening at the allylic position can be performed either with inversion or retention of stereochemistry, yielding *anti*- and *syn*-amino alcohols **2** and **3**, respectively. Amino alcohols **2** can subsequently be ring-closed to the corresponding vinylaziridines **4**. These species can be selectively ring-opened at the allylic position with an oxygen nucleophile, either with inversion or retention, to furnish *anti*- and *syn*-amino alcohols **5** and **6.** The remaining set of

[25] Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877-1894.

enantiomeric amino alcohol isomers can easily be obtained by starting from the enantiomeric vinylepoxides *ent*-**1**.



Scheme 12. Synthetic strategy.

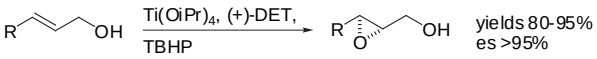
Synthesis of Vinylepoxides 1

(Paper IV)

2

2.1 Introduction

Epoxides are often used as intermediates in asymmetric synthesis, due both to reliable asymmetric epoxidation methods and to facile ring-opening reactions allowing straightforward elaboration to new functionalities.[26] The development of Sharpless asymmetric epoxidation of allylic alcohols in 1980 constitutes a breakthrough in asymmetric synthesis, and to date this method remains the most applied asymmetric epoxidation protocol (Scheme 13).[27] A wide range of substrates can be used in the reaction; (*E*)-allylic alcohols generally give high enantioselectivity, whereas the reaction is more substrate dependent with (*Z*)-allylic alcohols. Conjugated dienols are often problematic substrates due to reduced reactivity. Moreover the products can undergo a Payne rearrangement, which makes them susceptible towards further epoxidation.[28,29] With all reagents commercially available, the main drawback of the SAE-reaction is the substrate limitation to allylic alcohols.



Scheme 13. Sharpless asymmetric epoxidation.

Ten years after Sharpless' discovery, Jacobsen reported an asymmetric

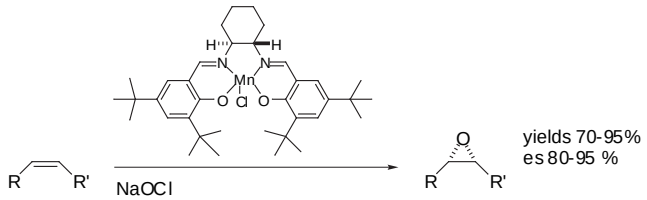
[26] (a) George, T.; Mabon, R.; Sweeney, G.; Sweeney, J. B.; Tavassoli, A. *Journal of the Chemical Society-Perkin Transactions 1* **2000**, 2529-2574. (b) Bonini, C.; Righi, G. *Tetrahedron* **2002**, *58*, 4981-5021.

[27] (a) Katsuki, T.; Martin, V. S. In *Orgainc Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: 1996; Vol. 48, p 1-285. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

[28] Werschofen, S.; Scharf, H.-D. *Synthesis* **1988**, 854-858.

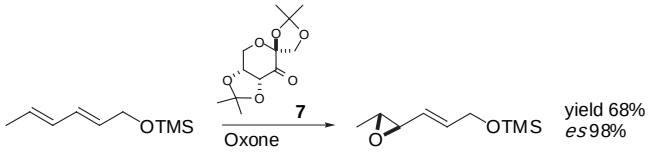
[29] Bernet, B.; Vasella, A. *Tetrahedron Lett.* **1983**, *24*, 5491-5494.

epoxidation of unfunctionalized olefins using chiral Mn-salen catalysts (Scheme 14).[30] This reaction works best on (*Z*)-disubstituted alkenes, although several tri- and tetra-substituted olefins have been successfully epoxidized.[31] The reaction often requires ligand optimization in order to reach high enantioselectivity.



Scheme 14. Jacobsen's asymmetric epoxidation.

Chiral dioxiranes have recently been reported to catalyze epoxidations. The best results have been obtained by Shi, who has developed ketone **7** as catalyst precursor (Scheme 15).[32,33] Although the first results were obtained with (*E*)-alkenes, Shi has now developed reaction conditions suitable for nearly all types of substrates, including (*Z*)-alkenes and terminal olefins.[34] Furthermore, a monoepoxidation of dienes has been reported, where the most electron rich double bond is epoxidized in good selectivity.[35] As this catalyst is rather new, few applications have been published and its potential remains unrevealed.



Scheme 15. Shi's asymmetric monoepoxidation of dienes.

Indirect routes to enantiopure epoxides have also proven valuable in certain cases, i.e. asymmetric dihydroxylation with sequential ring-closure.[36] Aggarwal has recently developed an asymmetric epoxide formation from sulfur ylides and aldehydes.[37]

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[30] Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801-2803.

[31] Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378-4380.

[32] Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235.

[33] This ketone is oxidized to the corresponding dioxirane in the catalytic cycle. **7** is commercially available, **ent-7** can be prepared in five steps from L-sorbose.

[34] (a) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979-2000. (b) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435-2446. (c) Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792-8793.

[35] Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948-2953.

[36] Kolb, H. C.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *48*, 10515-10530.

[37] Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 1430-1433.

Several methods for kinetic resolution and desymmetrisation of epoxides have also evolved.[38]

2.1.1 Ring-opening of epoxides

Ring-opening reactions of epoxides have been performed with a large variety of nucleophiles.[4,39] The regioselectivity can often be controlled by appropriate choice of substituents on the oxirane ring; with alkyl substituents ring-opening proceeds at the sterically least hindered carbon atom, whereas conjugating substituents, e.g. phenyl and vinyl groups, promote ring opening at the adjacent carbon atom.[40] In reactions with vinylepoxides, hard nucleophiles tend to add in a 1,2-fashion, while soft nucleophiles prefer 1,4-addition.[14,41]

2.2 Synthesis of vinylepoxides 1

In the present study, six substrates were designed to represent variations in substitution pattern and electronic influence (Figure 5). Vinylepoxides **1a**,**b** exemplify differences in electronic character, whereas substrates **1b**,**c** depict variation of olefin substitution (terminal vs. internal). Influence of substitution at the allylic position is exemplified by **1d** vs. **1e**. This is an important feature, as the ring-opening reactions should take place regioselectively at this carbon atom. Finally the position of the vinyl group substituent was varied (**1c-e** vs. **1f**). The substrates are represented by the general structure **1**.

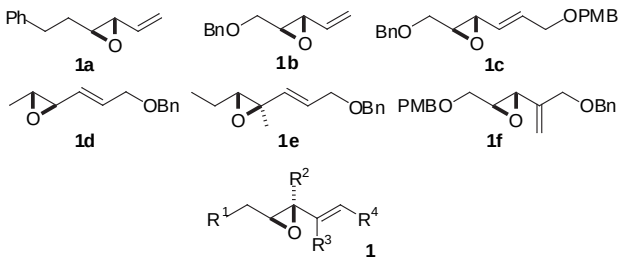

Figure 5. Vinylepoxides used in the present study.

The synthesis of vinylepoxides **1** is briefly described in Schemes 16 and 17. The epoxidation step in each route is the key step of the synthesis, as the enantioselectivity obtained will be preserved throughout the remaining

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[38] (a) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *46*, 14361-14384. (b) Schaus, S. E.; Brandes, B. D.; LArrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307-1315.

[39] (a) Prestat, G.; Baylon, C.; Heck, M.-P.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 3829-3831. (b) Sabitha, G.; Babu, S.; Rajkumur, M.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2001**, *42*, 3955-3958.

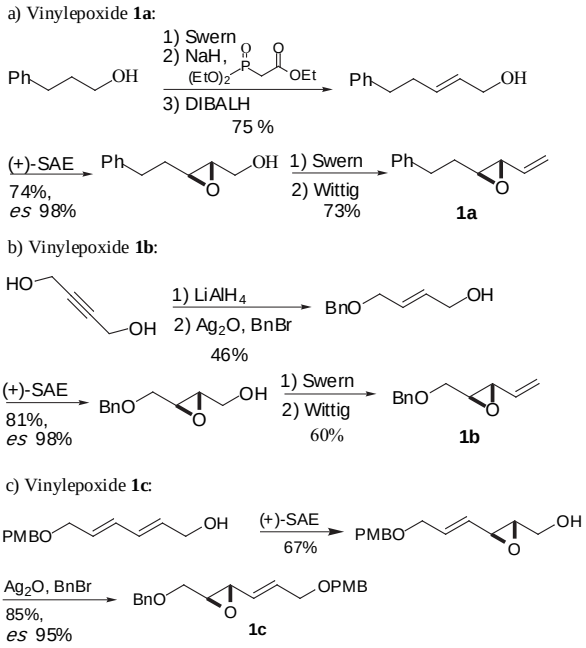
[40] Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 5386-5389.

[41] Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503-1511.

transformations leading to amino alcohols **2**, **3**, **5** and **6** (see Scheme 12).[42]

The synthetic routes to vinylepoxides **1a-c** were designed to employ Sharpless asymmetric epoxidation (SAE). Hence **1a** was obtained from 3-phenyl-propanol by a Swern/Horner-Emmons procedure followed by reduction to the corresponding allylic alcohol. This species was epoxidized under SAE conditions followed by Swern/Wittig to give **1a** (Scheme 16a).[43] Epoxide **1b** was obtained from 2-butyne-1,4-diol by reduction and monobenzylation[44] to reach the corresponding allylic alcohol, which was treated as above to yield **1b** (Scheme 16b).[43]

Although being rather straightforward, this approach suffers from moderate yields in the final Wittig reaction, and is furthermore limited to synthesis of terminal vinylepoxides. Disubstituted (*E*)-olefins can be selectively obtained only with stabilized Wittig reagents, whereas non-stabilized Wittig reagents predominantly afford the undesired (*Z*)-isomers.[45]



Scheme 16. Synthesis of vinylepoxides **1a-c.**

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[42] Vinylepoxides are rarely crystalline, which renders it difficult to increase the *es* by recrystallization. It is therefore of great importance to utilize epoxidation conditions that give high enantioselectivity.

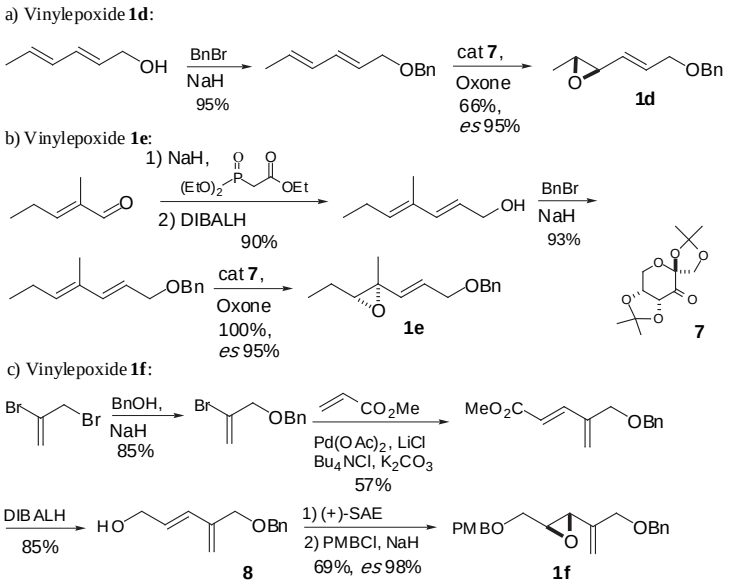
[43] Lindström, U. M.; Somfai, P. *Synthesis* **1998**, 109-117.

[44] Löfstedt, J.; Pettersson-Fasth, H.; Bäckvall, J.-E. *Tetrahedron* **2000**, *56*, 2225-2230.

[45] Only (*E*)-vinylepoxides can be employed within this strategy, as isomerization might occur during the Pd(0)-catalyzed ring-opening of (*Z*)-vinylepoxides, see Chapter 4.1 and Tsuji, J. Palladium reagents and catalysts. Innovations in organic synthesis; John Wiley & Sons Ltd: Chichester, 1995.

Hence a modification of the route was needed to reach substrate **1c** (Scheme 16c). SAE was thus performed on PMB-monoprotected hexa-2,4-dien-1,6-diol, which was produced from the corresponding ester.[46] As described in Chapter 2.1, conjugated dienols are often poor substrates for SAE. The reaction was indeed sluggish, resulting in 45% epoxyalcohol and 37% starting material, i.e. 67% yield based on recovered dienol. Moreover, benzylation of this species was problematic, as standard conditions gave decomposition.[47] Finally **1c** could be isolated in 85% yield based on recovered starting material (45%) using the milder BnBr /Ag_2O conditions.[48]

The synthesis of **1c** was clearly unsatisfactory, and other routes were examined to obtain vinylepoxides **1d-f**. Shi's monoepoxidation of dienes seemed ideal, as TMS-protected hexadienol could be epoxidized in good yield (see Scheme 15).[35] Hexadienol was thus benzylated and exposed to catalyst **7**, yielding 66% of **1d** together with 10% of the corresponding regioisomer (Scheme 17a).[49] Substrate **1e** was synthesized from 2-methyl-2-pentenal by a Horner-Emmons reaction followed by reduction and benzylation. Epoxidation occurred with complete regioselectivity, reflecting the electronic influence exerted by the methyl group, and **1e** was isolated in 100% yield (Scheme 17b). This synthetic strategy was clearly superior to the previous one, being both shorter and having high-yielding steps.



Scheme 17. Synthesis of vinylepoxides **1d-f.**

---

[46] Lindström, U. M.; Somfai, P. *Tetrahedron Lett.* **1998**, *39*, 7173-7176.

[47] BnBr, NaH, THF or DMF, heat.

[48] Bouzide, A.; Sauvé, G. *Tetrahedron Lett.* **1997**, *38*, 5945-5948.

[49] As **1d** was unstable on silica, the yield decreased upon separation from the regioisomer.

Vinylepoxide **1f** was synthesized before **1d**,**e** using a reported strategy.[50] Starting from 2,3-dibromopropene, dienol **8** was made by sequential Williamson reaction, Heck coupling and reduction. This dienol was epoxidized under SAE-conditions, after which PMB-protection resulted in **1f** (Scheme 17c).[51]

In the microwave-assisted aminolysis study (Chapter 3.2), several additional vinylepoxides were used to investigate the scope and limitations of the reaction. These substrates (**1g-k**) were prepared from the corresponding allylic alcohols as described for **1a**,**b** (Figure 6).[43,52,53]

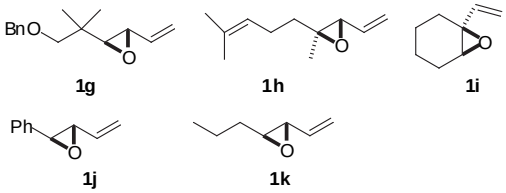


Figure 6. Structures of vinylepoxides **1g-k.**

2.2.1 Determination of enantiomeric purity

The enantiomeric purity of vinylepoxides **1a-c,f** was estimated from measurements on the corresponding epoxyalcohols. Epoxidation of the allylic alcohols with mCPBA yielded the corresponding racemic epoxyalcohols, needed for HPLC-determination of *es*. Vinylepoxides **1d**,**e** were compared with the corresponding racemic vinylepoxides, which were prepared by mCPBA-epoxidation of the dienes.

ChiralCel OJ or OD-H columns were used in the HPLC-analysis, revealing enantioselectivities of 98% for vinylepoxides **1a**,**b**,**f** and of 95% for **1c**-**e**. The enantioselectivities obtained in the Shi epoxidation, yielding **1d**,**e,** were thus slightly lower than in the epoxidation of the corresponding TMS-protected dienols (see Scheme 15). No attempts were made to optimize the selectivity.

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[50] Weigand, S.; Bruckner, R. *Synlett* **1997**, 225-228.

[51] Lindström, U. M.; Somfai, P. *Chem. Eur. J.* **2001**, *7*, 94-98.

[52] Lindström, U. M., Stockholm University, 2000.

[53] Vinylepoxide **1i** is racemic and was prepared by mCPBA-epoxidation instead of SAE.

Aminolysis of Vinylepoxides 1 to *anti*-Amino Alcohols 2

(Papers I-IV)

3

Epoxides are commonly ring-opened by sodium azide to afford azido alcohols, which can be reduced to the corresponding amino alcohols **4**. When vinylepoxides are treated with sodium azide, however, a mixture of products is obtained due to a thermal [3,3]-rearrangement of the allylic azide initially formed.[43] Alternatively, aminolysis can be performed with benzylamine followed by a deprotection step to give amino alcohols.[2,43] Direct ring-opening with ammonia would be a shorter route to **2**, although the reaction suffers from poor reactivity and high pressure.

3.1 Conventional Aminolysis

Stogryn and Brois showed that monosubstituted vinylepoxides could be ring-opened using ammonium hydroxide.[54] With this procedure, vinylepoxide **1a** gave amino alcohol **2a** in only 13% yield after 10 days (Table 1, entry 1), indicating that the reaction was too slow for synthetic purposes with disubstituted substrates.[55] McManus *et al.* could open simple disubstituted epoxides by heating in neat ammonia with a stoichiometric amount of H_2O.[56] As no reaction took place in the absence of water, they suggested the ammonium ion to be the active species. When **1a** was heated in neat ammonia with water present, a slow reaction resulted in minor amounts of amino alcohol **2a** with diols **9** as major products (entry 2).[55]

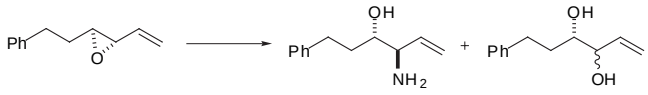
---

[54] Stogryn, E. L.; Brois, S. J. *J. Am. Chem. Soc.* **1967**, *89*, 605-609.

[55] Lindström, U. M.; Franckowiak, R.; Pinault, N.; Somfai, P. *Tetrahedron Lett.* **1997**, *38*, 2027-2030.

[56] McManus, S. P.; Larson, C. Å.; Hearn, R. A. *Synth. Commun.* **1973**, *3*, 177-180.

Table 1. Aminolysis of vinylepoxide **1a** to *anti*-amino alcohol **2a**.



1a **2a** **9**

		Yield (%)	
Entry	**Conditions**	**2a**	**9**
1	NH_4OH, rt → Δ, 10 d	13	0
2	NH_3, 2 equiv H_2O, 80 °C, 3 d	11	62
3	NH_3, 0.05 equiv $TsOH \cdot H_2O$, 130 °C, 3 d	77	10
4	NH_4OH, 25 W, 8 min.	93	0

Gratifyingly, when **1a** was heated in neat ammonia and $TsOH \cdot H_2O$ (0.05 equiv), **2a** could be isolated in 77% yield after 3 days, together with 10% of diols **9** (entry 3).[55,57] The method was applied to several substrates, regioselectively and diastereospecifically affording the corresponding amino alcohols **2** (Table 2).

Although high yields were obtained for unhindered epoxides **1a**,**b**,**f**, the scope of the reaction is limited as it requires prolonged heating in neat ammonia, and when sterically hindered substrates **1g**,**h** are used, the reaction is almost completely retarded (entries 7,8). In order to make the aminolysis more synthetically useful, the development of a reaction less sensitive to steric hindrance and with shorter reaction time was needed.

3.2 Microwave-assisted aminolysis

In recent years, the application of microwave-assisted reactions to organic synthesis has received considerable attention. Compared with conventional heating, microwave irradiation often gives greatly enhanced reaction rates and less byproducts.[58] Pleasingly, when **1a** was treated with ammonium hydroxide under microwave irradiation, **2a** was obtained in 93% yield in only 8 min (Table 1, entry 4). Di-and trisubstituted vinylepoxides **1b**-**k** were also subjected to microwave irradiation in NH_4OH. Complete conversion into amino alcohols **2b**-**g** was generally obtained within 8 min (Table 2).

The yields from unhindered substrates **1a**,**b**,**f** are better or as good as with conventional heating (entries 1,2,6). More sterically hindered substrates also seem to be efficiently converted into amino alcohols, as derivative **1g** gave **2g** in 90% yield compared with only 23% after 4 days in neat ammonia at 130 °C (entry 3). The procedure is effective even with trisubstituted substrates, as exemplified by 2,2,3-trisubstitued vinylepoxide **1h** that afforded **2h** in 76% yield (entry 7). Not surprisingly, 2,3,3-trisubstitued substrates **1e**,**i**, having quaternary allylic carbons, reacted to give **2e**,**i** as regioisomeric mixtures (entries 5,9).

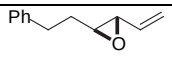
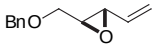
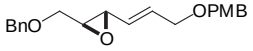
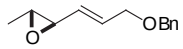
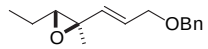
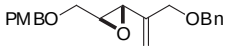
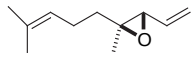
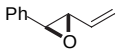
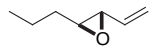
Aminolysis of **1j** resulted in a 2:1 mixture of amino alcohol **2j** and its

[57] Anhydrous TsOH did not catalyze the reaction.

[58] Caddick, S. *Tetrahedron* **1995**, *51*, 10403-10432.

regioisomer, reflecting a competition between the allylic and benzylic positions (entry 10). Unexpectedly, reaction of substrates **1d**,**k** also resulted in regioisomeric mixtures, the explanation being less obvious. Ring-opening in the homoallylic position could be suppressed in both cases by lowering of the irradiation power, which increased the regioisomeric ratios (**1d** 6:1→ 11:1, **1k** 6:1→ 9:1).

Table 2: Comparison of aminolysis yields using conventional or microwave heating.

Entry		Vinylepoxide	Yield (%) / Ratio[a]	
			Conventional[b]	Microwave[c]
1	**1a**		77[d]	93
2	**1b**		93	87
3	**1c**		-	88
4	**1d**		-	88
				11:1
5	**1e**		-	100
				2:1
6	**1f**		86	84
7	**1g**		23[e]	90
8	**1h**		25	76
9	**1i**		-	77
				1:1
10	**1j**		70	98
			2:1	2:1
11	**1k**		75	95
			5:1	9:1

[a]Isolated yields/ regioisomeric ratio. [b]NH_3, $TsOH \cdot H_2O$ (0.05 equiv), 130 °C, 3 days. [c]NH_4OH, 15-30 W, 8-15 min. [d]80 °C. [e]4 days.

With this protocol the synthesis of *anti*-amino alcohols **2** has been greatly improved due to simplified handling, short reaction times and high yielding reactions also with sterically hindered substrates.

3.3 Large Scale Aminolysis

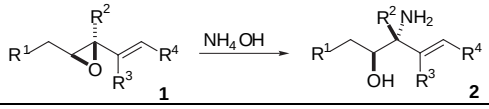
Microwave chemistry can be difficult to perform on a large scale, as the concentration influences the power needed for full conversion.[59] Therefore the

[59] The microwave cavity cannot be scaled up.

aminolysis reaction was further investigated using vinylepoxides **1a**,**b**. As aminolysis of epoxides has been performed in various organic solvents with secondary amines,[60] our first strategy involved the use of protic solvents and excess ammonium hydroxide. Pleasingly, when **1a** was subjected to 10 equiv NH_4OH in EtOH at 70 °C in a sealed flask, slow formation of **2a** occurred. The reaction rate could be increased by the use of a large excess of NH_4OH, which yielded **2a** in 73% after 48 h heating. Addition of a catalytic amount of $TsOH \cdot H_2O$ caused formation of the corresponding diol without increasing the formation rate of **2a**.[61] Compared with the original procedure with neat ammonia, the use of excess NH_4OH in protic solvents simplified the handling without shortening the reaction time.

Not satisfied with these results, we investigated whether there was a microwave effect[62] in the aminolysis reaction, or whether it would proceed with conventional heating. The maximum temperature reached in microwave reactions in NH_4OH at 50W for 8 min was 170 °C, and when vinylepoxide **1b** in NH_4OH was heated to 170 °C in a sealed metal cylinder, **2b** could be isolated in 93% yield after only 4.5 h reaction time (Table 3, entry 2). This procedure was applied to vinylepoxide **1d**, giving **2d** in 72% yield and 6:1 regioselectivity after only 1 h heating (entry 4). The result could easily be improved to 82% and 9:1 regioselectivity by decreasing the temperature to 140 °C, which was sufficient also for the ring-opening of **1e** (entry 5). The reaction temperature could be decreased even further, and amino alcohol **2a** was isolated in excellent yield after 1 h at only 125 °C (entry 1).[63]

Table 3. Aminolysis of vinylepoxides **1** to *anti*-amino alcohols **2**.



Entry	Substrate	R^1	R^2	R^3	R^4	Yield of 2 (%)[a]	
						Microw.[b]	Oilbath[c]
1	**1a**	$PhCH_2$	H	H	H	93	91[d]
2	**1b**	BnO	H	H	H	87	93
3	**1c**	BnO	H	H	CH_2OPMB	88	-
4	**1d**	H	H	H	CH_2OBn	100[d]	82[e]
5	**1e**	Me	Me	H	CH_2OBn	89[f]	78[f]
6	**1f**	PMBO	H	CH_2OBn	H	84	-

[a]Isolated yields. [b]20-30 W, 8-15 min. [c]125-170 °C, 1-4.5 h. [d]Regioisomeric mixture 11:1. [e]Regioisomeric mixture 9:1. [f]Regioisomeric mixture 2:1

[60] (a) Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 287-289. (b) Cristau, H.-J.; Pirat, J.-L.; Drag, M.; Kafarski, P. *Tetrahedron Lett.* **2000**, *41*, 9781-9785.

[61] Change of solvent to 2-methoxyethanol, to increase the boiling point, did not improve the results.

[62] Kuhnert, N. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1863-1866.

[63] Due to difficulties in monitoring reactions in sealed tubes, reaction temperatures and times were not optimized further.

These results clearly indicate the absence of a microwave effect; the reaction probably takes place instantly when the temperature needed to dissolve the vinylepoxides has been reached. The regioisomeric mixtures obtained with some substrates can most likely be further optimized by fine-tuning of reaction temperature and time. This novel aminolysis method is the first practical large-scale protocol described for ring-opening of vinylepoxides with ammonia. The reaction is fast, stereospecific and highly regioselective. Furthermore, no special equipment is needed, as the pressure reached at 125 °C in NH_4OH is moderate.[64]

[64] We now use glass tubes with plastic screw-caps; a metal cylinder is not needed.

Pd(0)-catalyzed Epoxide Opening leading to *syn*-Amino Alcohols 3

(Papers II-IV)

4

Syn-amino alcohols **3** can be obtained by ring-opening of vinylepoxides **1** with retention of configuration (see Scheme 12). This can be achieved via a palladium-catalyzed reaction that proceeds with double inversion.

4.1 Pd(0)-catalyzed Ring-Opening of 1

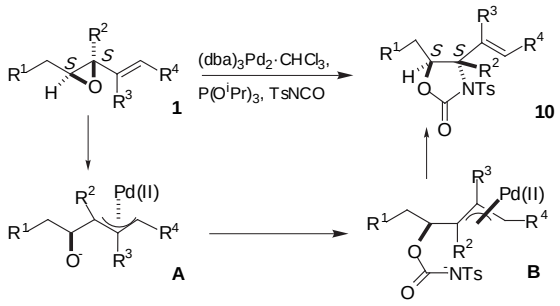
Palladium-catalyzed, nucleophilic ring-openings of vinylepoxides are discussed in a recent review.[65] The reaction is initiated by formation of a π-allyl palladium complex, which is attacked by the nucleophile. 1,4-Addition is often encountered, although this can be avoided by choice of an appropriate nucleophile.

Pd(0)-catalyzed ring-opening of vinylepoxides **1** in the presence of tosyl isocyanate results in formation of oxazolidinones **10**, as depicted in Scheme 18.[66,67] Tosyl isocyanate reacts with the π-allyl palladium complex **A** initially formed, to give intermediate **B**. This species subsequently ring-closes with retention of the original configuration to *N*-tosyl oxazolidinones **10**. 1,4-Addition of the nucleophile is thus avoided by attachment to the oxygen prior to attack.

[65] Trost, B. M. *Chem. Rev.* **1996**, *96*, 395-422.

[66] Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792-3794.

[67] Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1988**, *110*, 7933-7935.



Scheme 18: Palladium(0)-catalyzed epoxide opening with tosyl isocyanate.

When the terminal vinylepoxides **1a,b** were treated with Pd(0), oxazolidinones **10a,b** were obtained in good yields, although as unseparable diastereomeric mixtures (Table 4, entries 1,2). Optimization of the reaction conditions only resulted in a slight improvement of the diastereoselectivity.[68]

Gratifyingly, the initial product mixtures could be equilibrated at reflux, thus favoring the more stable[67] *trans*-oxazolidinones. In this manner, the kinetically obtained, poor ratios could be significantly enhanced (**1a** *dr* 2:1→6:1, **1b** *dr* 2:1→14:1).[69] A recently published study of a Pd(0)-catalyzed transformation of vinyloxazolidinones into vinyloxazolines showed the same equilibration trend; when R^1 changed from alkoxy to alkyl the selectivity decreased.[70] To prove this trend further, vinylepoxide **1k** (see Chapter 2) was exposed to the reaction conditions. The corresponding oxazolidinone was indeed formed with poor diastereoselectivity (*dr* 1.7), which could not be improved by equilibration attempts.[71]

Table 4. Synthesis of oxazolidinones **10**.

Entry	Substrate	R^1	R^2	R^3	R^4	Yield of 10 (%)[a]
1	**1a**	$PhCH_2$	H	H	H	82[b]
2	**1b**	BnO	H	H	H	88[c]
3	**1c**	BnO	H	H	CH_2OPMB	87
4	**1d**	H	H	H	CH_2OBn	62[d]
5	**1e**	Me	Me	H	CH_2OBn	94
6	**1f**	PMBO	H	CH_2OBn	H	93

[a]Isolated yields. [b]*dr* 6:1. [c]*dr* 14:1. [d]See text.

Pleasingly, when **1** contained additional vinylic substituents (**1c-f,** entries 3-6), conversion of **1** to **10** took place with complete diastereoselectivity (>95%), except in the case of oxazolidinone **10d**, which was formed along with *(Z)*-4,5-

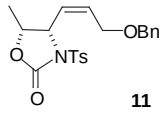
[68] Temperature, amounts of catalyst, ligand and TsNCO were varied independently.

[69] Equilibration was performed with the catalyst at reflux for 2-5 days, where longer reflux time gave better *dr* but also caused more degradation of the product.

[70] Cook, G. R.; Shanker, S. *Tetrahedron Lett.* **1998**, *39*, 3405-3408.

[71] For *ab initio* calculations on the mechanism of η^3-η^1-η^3 isomerizations in allylpalladium complexes, see Solin, N.; Szabó, K. J. *Organometallics* **2001**, *20*, 5464-5471.

cis-oxazolidinone **11** (Figure 7). To the best of our knowledge, an *E*→*Z* isomerization had not previously been reported in this reaction. As opposed to the equilibration results above, the byproduct ratio could be improved by decreasing the temperature (3:1→9:1).



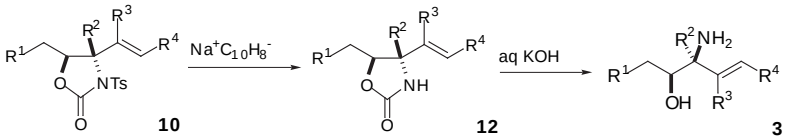
11

Figure 7. *(Z)*-4,5-*cis*-oxazolidinone **11**.

4.2 Detosylation and Hydrolysis

Amino alcohols **3** could in principle be obtained from **10** either by sequential detosylation and hydrolysis, or by hydrolysis prior to detosylation. The latter sequence proved inferior; as the corresponding *N*-tosyl amino alcohols were less reactive than **10** in the detosylation, they could not be selectively deprotected.

Detosylation of oxazolidinones **10** to *N*-H oxazolidinones **12** was effected by titration with sodium naphthalide solution at -78 °C (Scheme 19, Table 5).[72] At this stage the diastereomers of **12a**,**b** could be separated by flash chromatography. Due to troublesome purification of *N*-tosyl oxazolidinone **10d** from byproduct **11**, the best yield from **1d** to **12d** was obtained when **10d** was not isolated (entry 4).



10 **12** **3**

Scheme 19: Detosylation of **10** into **12** and hydrolysis to *syn*-amino alcohols **3**.

Subsequent hydrolysis of *N*-H oxazolidinones **12** into *syn*-amino alcohols **3** was examined both under basic and acidic conditions. The basic hydrolysis was superior, giving **3** in excellent yields (Scheme 19, Table 5). Hydrolysis of **12e** was retarded due to sterical hindrance; 8 h reflux were needed for completion compared to 1 h for **12a-d**,**f** (entry 5).

[72] To avoid degradation/ debenzylation, the reaction time should be kept short. See Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548-1562.

Table 5. Detosylation and hydrolysis to *syn*-amino alcohols **3**.

Entry	Substrate	R^1	R^2	R^3	R^4	Yield (%)[a]	
						12	**3**
1	**1a**	$PhCH_2$	H	H	H	93[b]	100
2	**1b**	BnO	H	H	H	75[b]	97
3	**1c**	BnO	H	H	CH_2OPMB	72	91
4	**1d**	H	H	H	CH_2OBn	61[c]	95
5	**1e**	Me	Me	H	CH_2OBn	80	98
6	**1f**	PMBO	H	CH_2OBn	H	84	86

[a]Isolated yields. [b]Before separation of diastereomers. [c]Yield from **1d**.

Ring-closure of *anti*-Amino Alcohols 2 to Vinylaziridines 4

(Papers II-V)

5

The two remaining amino alcohols, **5** and **6**, are the regioisomers of **2** and **3**. We envisaged the synthesis of **5** and **6** by regioselective ring-opening of *N*-H vinylaziridines **4**, which can be obtained from anti-amino alcohols **2** (see Scheme 12).

5.1 Background to aziridines

Aziridines are versatile synthetic intermediates, as the relief of ring-strain provides a driving force for efficient ring-opening or ring-expansion reactions.[73,74] The importance of aziridines is also well recognized in asymmetric synthesis, where the need for chiral auxiliaries and ligands is continuously increasing.[75]

Vinylaziridines constitute an important subclass of aziridines, and have proven to be useful intermediates for various types of natural and synthetic compounds.[76] Vinylaziridines can be selectively ring-opened at the allylic position (see Chapters 6 and 7), take part in conjugate addition reactions,[77] Wittig and Claisen rearrangements,[51,78] furthermore the vinyl group can be derivatized

[73] (a) Rai, K. M. L.; Hassner, A. *Advances in Strained and Interesting Organic Molecules* **2000**, *8*, 187-257. (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347-1365.

[74] Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 2781-2784.

[75] Tanner, D.; Birgersson, C.; Gogoll, A. *Tetrahedron* **1994**, *50*, 9797-9824.

[76] (a) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Fujii, N.; Nimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 652-654. (b) Somfai, P.; Åhman, J. In *Targets in Heterocyclic Systems*; Italian Society of Chemistry: 1999, p 341-367.

[77] Aoyama, H.; Mimura, N.; Ohno, H.; Ishii, K.; Toda, A.; Tamamura, H.; Otaka, A.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1997**, *38*, 7383-7386.

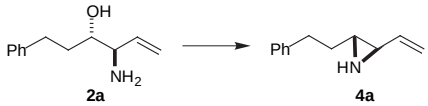
[78] Åhman, J.; Jarevång, T.; Somfai, P. *J. Org. Chem.* **1996**, *61*, 8148-8159.

into interesting functionalities.[79]

Existing enantioselective synthetic routes to aziridines include asymmetric aziridination of alkenes and ring-closure of vicinal hydroxy azides or amino alcohols.[73,80,81] Direct cyclization of β-amino alcohols into *N*-H aziridines is known to be difficult, having neither a nitrogen activating group nor a good leaving group.,[82,83,84] *N*-substituted aziridines can on the other hand be synthesized from amino alcohols in various ways,[80,81] and the plethora of methods encouraged us to perform a comparative study to find out which procedure is the most effective in formation of *N*-H vinylaziridines.

5.2 Investigation of ring-closure strategies

N-H Vinylaziridines are rather acid labile, which limits the number of applicable protocols. We chose amino alcohol **2a** as model substrate, and the desired transformation to aziridine **4a** is shown in Scheme 20.



Scheme 20: Ring-closure of amino alcohol **2a** to aziridine **4a.**

The transformation can be conducted in three general ways: 1) direct ring-closure of amino alcohol **2a** to yield aziridine **4a** is the most effective strategy, but suffers from the low reactivity of **2a** towards ring-closure, as mentioned above. 2) Transformation of the hydroxy group of **2a** into a better leaving group, which should facilitate ring-closure. 3) Protection of the amino moiety of **2a** is expected to increase the reactivity towards ring-closure, although a deprotection step is needed to yield **4a**. To compete with direct ring-closure, the two latter methods need high-yielding reaction steps, as several transformations are needed to achieve the desired product.

5.2.1 Direct ring-closure

Direct ring-closure of amino alcohols to *N*-H aziridines is reported to proceed in moderate yields. This transformation was of major interest in our group, and hence a reaction utilizing Mitsunobu conditions was investigated.[84,85] Initial attempts to ring-close **2a** were disappointing, but moderate yields of **4a** could be

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[79] Patai, S. *The Chemistry of Alkenes*; Wiley: New York:, 1964; Vol. 1.

[80] Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693-1715.

[81] Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 999-1015.

[82] Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. *Pergamon* **1996**, 1-96.

[83] Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599-619.

[84] Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127-164.

[85] Mitsunobu, O. *Synthesis* **1981**, 1-28.

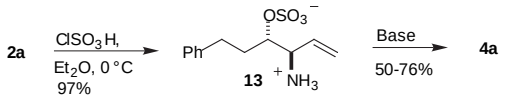
obtained in toluene at reflux.[43] A carbamate byproduct was irregularly formed in considerable amounts due to reaction between the amino alcohol and DEAD;[43,85] this could be prevented by changing the ethyl groups of the azo compound to the bulkier isopropyl groups in DIAD. The reaction rate was increased by change of solvent from toluene to THF; this might reflect the observation of improved solubility of **2a**. Unfortunately, purification of **4a** demanded repeated flash chromatography to remove the triphenylphosphine oxide formed, which decreased the isolated yield considerably.

We suspected *N*-H vinylaziridines to be unstable on silica, and indeed careful purification on deactivated silica could improve the yield of **4a**.[86] Small-scale reactions were purified to give aziridine **4a** in 80% yield, whereas large-scale reactions afforded **4a** in 70% yield. To avoid the tedious purification, polymer bound triphenylphosphine was utilized. As expected, this decreased the reaction rate, but resulted in an easily purified crude product.

5.2.2 Selective activation of the hydroxy group

This strategy relies on the possibility of activating the hydroxy group without substituting the amino group. This limits the number of useful routes considerably, as the amino group is more reactive towards most activating agents e.g. tosyl chloride.

One solution of this delicate problem is reaction of **2a** with chlorosulfonic acid to form sulfate ester **13** (Scheme 21). This compound can subsequently be ring-closed to aziridine **4a** under basic conditions, as reported in formation of 2-vinylaziridine.[54] Formation of salt **13** was nearly quantitative, but ring-closure with excess NaOH at reflux furnished **4a** in moderate yield (Table 6, entry 1). Various solvents and bases were screened, and the best result was achieved with NaOH in toluene/water, which gave aziridine **4a** in 76% isolated yield (entry 2).[87] Attempts using lower temperature, decreased amount of NaOH or other solvents, all decreased the yield (entry 3). The use of *n*-BuLi in THF resulted in 50% yield (entry 4); all other attempts were fruitless (entries 5-8).



Scheme 21: Hydroxy group activation prior to ring-closure.

Ring-closure of **2a** with selective activation of the hydroxy group accordingly yielded **4a** in 74% over two steps, using the conditions stated in Table 6, entry 2.

[86] The drawback of using deactivated silica is decreased separation ability.

[87] Aziridine 4a was found to be volatile, the yield was improved when the toluene was removed carefully, followed by flash chromatography with Et2O instead of EtOAc.

Table 6: Conditions for ring-closure of **13** to **4a**.

Entry	Solvent[a]	Base	Yield of 4a (%)[b]
1	H_2O	NaOH[c]	58
2	Toluene/H_2O	NaOH[c]	76
3	THF/H_2O[d]	NaOH[c]	0
4	THF[e]	*n*-BuLi[f]	50
5	THF	NaOEt[f]	<5
6	Toluene	KO^{t}Bu[f]	0
7	Toluene	Et_3N[g]	<5
8	DMF	K_2CO_3	<5

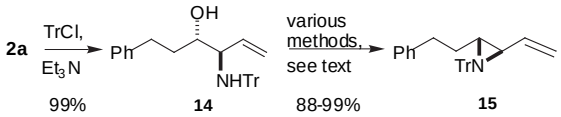
[a]Reactions performed at reflux unless otherwise stated. [b]Isolated yields except in entry 1, which was determined by HPLC. [c]Excess. [d]100 ˚C in sealed flask. [e]-50 ˚C to rt. [f]2.5 equiv. [g]3 equiv.

5.2.3 Selective protection of the amino group

Selective protection of the amino group before ring-closure is facile, thus it is the most common way to synthesize aziridines from amino alcohols. The acid lability of *N*-H vinylaziridines limits the number of useful activating groups, as the conditions needed for deprotection of several activating groups are expected to destroy the aziridine moiety.[88]

Tritylation

Our first choice was the triphenylmethyl (trityl) group, which had been successfully employed in aziridination reactions.[89] Furthermore mild, although acidic, conditions were used for deprotection. Tritylation of **2a** proceeded almost quantatively (Scheme 22),[90] and with trityl amino alcohol **14** in hand, several ring-closing methods could be utilized. The Mitsunobu protocol described above afforded tritylaziridine **15** in 99% yield.



Scheme 22: Amino group activation prior to ring-closure.

Alternatively, the hydroxy group in **14** could be mesylated to provide compound **C** (Scheme 23). This derivative was conveniently ring-closed to yield **15** at elevated temperature.[91] With 1.0 equiv MsCl, tritylaziridine **15** was formed

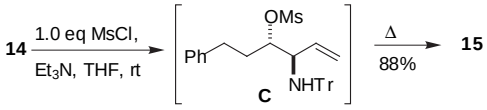
[88] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 3rd ed.; Wiley: New York, 1999.

[89] Kuyl-Yeheskiely, E.; Lodder, M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1992**, *33*, 3013-3016.

[90] Evans, P. A.; Holmes, A. B.; Russell, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3397-3409.

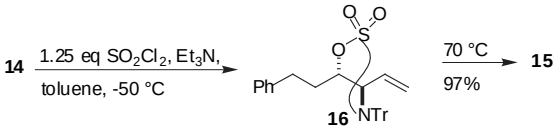
[91] Willems, J. G. H.; Hersmis, M. C.; de Gelder, R.; Smits, J. M. M.; Hammink, J. B.; Dommerholt, F. J.; Thijs, L.; Zwanenburg, B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 963-967.

in 88% yield together with 12% recovered **14**. When an excess of MsCl (1.25 equiv) was employed, **15** was formed along with unidentified byproducts.



Scheme 23: Synthesis of **15** by mesylation and ring-closure.

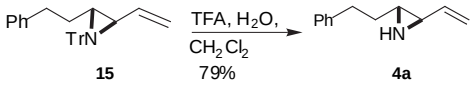
A third possibility employed cyclic sulfamidate **16** (Scheme 24), formed by reaction between **14** and sulfuryl chloride. *In situ* conversion of this type of derivative to the corresponding aziridine was reported to proceed at rt.[89]



Scheme 24: Ring-closure of **14** *via* cyclic sulfamidate **16**.

When trityl amino alcohol **14** was treated with surfuryl chloride, sulfamidate **16** was indeed formed, but ring-closure to aziridine **15** did not take place at rt. Attempted purification by flash chromatography converted **16** to the desired aziridine **15** in 60% yield. The conversion could instead be performed in excellent yield by heating the reaction mixture to 70 ˚C for 1 h.

Removal of the trityl group to *N*-H aziridine **4a** was the most difficult part of the sequence, as *N*-H vinylaziridines are acid labile (Scheme 25). Treatment with TFA and water as a trityl scavenger furnished **4a** in 79% yield.[92,93] Formic acid in methanol worked equally well,[94] whereas the combination of TFA and methanol gave only decomposition products.[95] A recently published reductive detritylation, developed especially for sensitive aziridines, was also employed.[96] Disappointingly this reaction, utilizing TFA and Et_3SiH, proved inferior to the original TFA reaction.



Scheme 25: Detritylation of **15**.

Thus, the three-step transformation of amino alcohol **2a** into aziridine **4a** was achieved in 77% *via* Mitsunobu cyclization, in 69% *via* mesylation and in 76% *via* the cyclic sulfamidate.

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[92] Alsina, J.; Giralt, E.; Albericio, F. *Tetrahedron Lett.* **1996**, *37*, 4195-4198.

[93] The optimal reaction temperature was –10 ˚C; reaction at rt gave 4a in moderate yield whereas lower temperature effected no reaction.

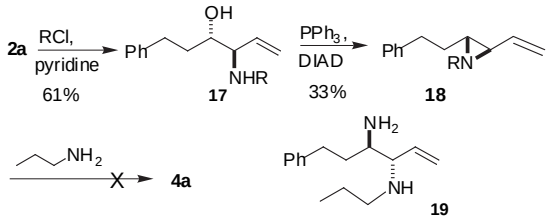
[94] Bosche, U.; Nubbemeyer, U. *Tetrahedron* **1999**, *55*, 6883-6904.

[95] Church, N. J.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1475-1482.

[96] Vedejs, E.; Klapars, A.; Warner, D. L.; Weiss, A. H. *J. Org. Chem.* **2001**, *66*, 7542-7546.

Nosylation

In a similar reaction sequence, the 2,4-dinitrobenzenesulfonyl group was utilized (Scheme 26).[97] Although both protection to **17** and ring-closure to **18** were fast reactions, the yields were poor compared to the tritylation sequence. Furthermore, attempted deprotection of **18** to aziridine **4a** was unsuccessful, instead affording the ring-opened diamine **19**.[98]



Scheme 26: Nosylation strategy, R=2,4-dinitrobenzenesulfonyl.

To summarize the results of this investigation, direct ring-closure under Mitsunobu conditions proved superior to other methods employed for small-scale reactions, as *N*-H aziridine **4a** was formed in 80% yield. This should be compared to 74% via sulfate ester **13** and 69-77% via tritylation of the amino group. For large-scale reactions, the convenience of easy purification could make the sulfate ester route preferable. Although the same advantage is achieved by the use of polymer bound triphenylphosphine in the Mitsunobu reaction, this reagent does not give complete conversion of all substrates (*vide infra*). Furthermore, the choice of strategy is substrate depending, as the substituents on the vinylaziridine influence both the polarity (and hence the ease of purification) and the stability on silica gel.

5.3 Synthesis of vinylaziridines 4b-f

As vinylaziridines **4b-f** were prepared before or in parallel to the investigation described above, only the Mitsunobu conditions were employed in the transformation (Scheme 27). *Anti*-amino alcohols **2** could be ring-closed into vinylaziridines **4** in yields ranging from 80% for **4a** down to 30% for **4b** (Table 7). The poor yield of **4b** could be increased to 72% by careful purification on deactivated silica, indicating that the purification might be more important than the reaction conditions for certain substrates (entry 2).

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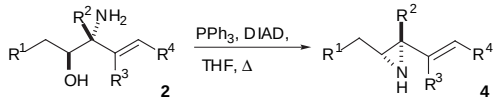
[97] Fukuyama, T.; Cheung, M.; Jow, C. K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831-5834. ()Farràs, J.; Ginesta, X.; Sutton, P. W.; Taltavull, J.; Egeler, F.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron* **2001**, *57*, 7665-7674.

[98] Deprotection with mercaptoacetic acid was not attempted.



Scheme 27: Synthesis of vinylaziridines **4**.

Aziridine **4c** was formed in 93% crude yield according to integration on NMR, but due to its instability even on deactivated silica the isolated yield was poor. This could partially be circumvented by using polymer bound PPh_3, which gave an easily purified crude product but decreased reaction rate. With this protocol, aziridine **4c** could be isolated in 78% yield based on recovered starting material (entry 3). Surprisingly, aziridine **4d** coevaporated with EtOAc, which made purification troublesome as other solvent systems diminished the silica deactivation and gave unpure aziridine (entry 4).[99]

Table 7. Synthesis of aziridines **4**.

Entry	Substrate	R^1	R^2	R^3	R^4	Yield of 4 (%)[a]
1	**2a**	$PhCH_2$	H	H	H	80
2	**2b**	BnO	H	H	H	72
3	**2c**	BnO	H	H	CH_2OPMB	60[b]
4	**2d**	H	H	H	CH_2OBn	62[c]
5	**2e**	Me	Me	H	CH_2OBn	80[d]
6	**2f**	PMBO	H	CH_2OBn	H	63

[a]Isolated yields. [b]23% **2c** was recovered. [c]Isolation problems, see text. [d]13% **2e** was recovered.

Syntheses of trisubstituted *N*-H aziridines are rare and described yields are moderate.[100] This may be due to difficulties both in forming precursors as **2e** and in subsequent ring-closure to aziridines, the reaction rates being retarded by sterical hindrance.

To our delight, ring-closure of **2e** to trisubstituted aziridine **4e** under Mitsunobu conditions proceeded smoothly. Although the reaction stopped before full conversion,[101] this substrate surprisingly gave the best results to date in the ring-closure. The methyl substituent rendered **4e** relatively unpolar, which simplified the purification and **4e** could be isolated in 80% yield with remaining **2e** readily recovered (entry 5). The yield based on recovered **2e** was thus an excellent 92%.

[99] Careful removal of EtOAc by distillation from a –78 °C cooling bath gave loss of product whereas high-vacuum on the isolated compound did not result in losses.

[100] (a) Viallon, L.; Reinaud, O.; Capdevielle, P.; Maumy, M. *Tetrahedron* **1996**, *52*, 13505-13614. (b) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088-6089.

[101] Optimization attempts failed; neither prolonged reaction time nor large excess of reagents improved the conversion, instead a byproduct was formed.

When regioisomeric mixtures of amino alcohols **2** and **5** were obtained in the aminolysis (see Chapter 3), separation of the isomers was needless as ring-closure of both species resulted in aziridines **4**. Surprisingly, the mixture of **2e** and **5e**, obtained by aminolysis of **1e**, could also be ring-closed to **4e** in good yield despite the sterical hindrance in **5e**.

Solvolysis of Vinylaziridines 4 to *anti*-Amino Alcohols 5

(Papers II-IV)

6

6.1 Introduction

Ring-opening of activated aziridines[102] has recently become a field of major interest. Yadav and Singh have focused on Lewis acid-catalyzed ring-openings of *N*-tosyl aziridines with various amines, alcohols and carboxylic acids.[103,104,105] The nucleophilic attack normally takes place on the least hindered carbon atom with moderate regioselectivity, the exception being aryl-substituted aziridines that are regioselectively ring-opened in the benzylic position.

Hydrolysis of activated aziridines mediated by Brønstedt acids normally proceeds with rather poor regioselectivity.[19,106,107] Ibuka has employed organocopper reagents to obtain S_N2' addition to vinylaziridines.[108] There are no reports on hydrolysis of *N*-H aziridines, which may be due both to the low reactivity of unactivated aziridines and to the difficulty of synthesizing *N*-H aziridines.[83]

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[102] Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Otaka, A.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **1995**, *60*, 2044-2058.

[103] Yadav, J. S.; Reddy, B. V. S.; Jyothirmai, B.; Murty, M. S. R. *Synlett* **2002**, 53-56.

[104] Yadav, J. S.; Reddy, B. V. S.; Abraham, S.; Sabitha, G. *Tetrahedron Lett.* **2002**, *43*, 1565-1567.

[105] Prasad, B. A. B.; Sanghi, R.; Singh, V. K. *Tetrahedron* **2002**, *58*, 7355-7363.

[106] Prasad, B. A. B.; Sekar, G.; Singh, V. K. *Tetrahedron Lett.* **2000**, *41*, 4677-4679.

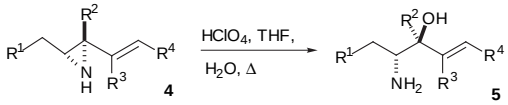
[107] Tamamura, H.; Yamashita, M.; Nakajima, Y.; Sakano, K.; Otaka, A.; Ohno, H.; Ibuka, T.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2983-2996.

[108] Toda, A.; Aoyama, H.; Mimura, N.; Ohno, H.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1998**, *63*, 7053-7061.

6.2 Solvolysis of vinylaziridines 4

Anticipating that the vinyl moiety would activate the aziridine towards ring-opening, we set out to find suitable conditions for a Brønstedt acid-mediated solvolysis reaction. As the aziridine becomes protonated, the allylic bond weakens and ring-opening becomes facilitated. To elude loss of diastereoselectivity, the formation of a carbocation must be avoided. Furthermore, the amine nitrogen is more basic than the aziridine nitrogen, which renders the use of a catalytic amount of acid difficult.

To our delight, *N*-H vinylaziridines **4** could be hydrolyzed into *anti*-amino alcohols **5** (Scheme 28) under acidic conditions. Initial hydrolysis attempts with **4a** were performed with a catalytic amount of tosic acid in THF/H_2O, which indeed resulted in a catalytic amount of **5a**. When a stoichiometric amount of TsOH was utilized, **5a** was obtained as a 9:1 regioisomeric mixture in moderate yield. This result could be improved with perchloric acid, furnishing **5a** with complete regioselectivity (>20:1) in 80% yield (Table 8, entry 1).[109]



Scheme 28: Solvolysis of vinylaziridines **4**.

When aziridines **4b-d,f** were treated with perchloric acid, *anti*-amino alcohols **5b-d,f** were obtained in good yields (Table 8). The reaction proceeded, as expected, with clean S_N2 inversion for substrates **4a-c**, **f**. Surprisingly, amino alcohol **5d** was formed in a 10:1 diastereomeric ratio (entry 4), the reason for which is unclear.

Table 8. Synthesis of *anti*-amino alcohols **5**.

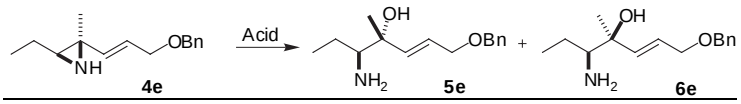
Entry	Substrate	R^1	R^2	R^3	R^4	Yield of 5 (%)[a]
1	**4a**	$PhCH_2$	H	H	H	80
2	**4b**	BnO	H	H	H	84
3	**4c**	BnO	H	H	CH_2OPMB	82
4	**4d**	H	H	H	CH_2OBn	74[b]
5	**4e**	Me	Me	H	CH_2OBn	67[c]
6	**4f**	PMBO	H	CH_2OBn	H	71

[a]Isolated yields. [b]*dr* 10:1. [c]The reaction was performed with $BF_3{\cdot}OEt_2$, *dr* 2.5:1.

Due to the methyl group situated at the allylic position, we were expecting trisubstituted vinylaziridine **4e** to behave differently than **4a-d,f** under acidic conditions. Indeed, amino alcohol **5e** was formed in a 1:1 diastereomeric mixture with **6e** (Table 9, entry 1) and optimization attempts with perchloric acid failed. The lack of selectivity could be explained by the stabilizing effect of the methyl group on a carbocation intermediate.

[109] Catalytic conditions failed also with perchloric acid.

Table 9. Solvolysis of **4e** in THF /H_2O.



4e **5e** **6e**

Entry	Acid	Equiv	Conditions	Ratio 5e:6e
1	$HClO_4$	1	rt	1:1
2	$LiClO_4$	1	reflux	1:1.4
3	$InCl_3$	0.1	rt, pH 4	1:2.1
4	$BF_3{\cdot}OEt_2$	2	rt	2.5:1
5	$BF_3{\cdot}OEt_2$	2	-20 °C →0 °C	no reaction
6	$BF_3{\cdot}OEt_2$	0.2	rt → reflux	1.3:1
7	BBr_3	2	rt	see text

Turning to Lewis acids, we hoped that the carbocation formation would be retarded and the diastereoselectivity thus enhanced. However, $LiClO_4$, which had been reported to mediate similar transformations, was ineffective for this reaction at rt. At reflux temperature, a poor yield of a 1:1.4 mixture of **5e** and **6e** was obtained (entry 2).[103,110] $InCl_3$ at pH 4 gave a 1:2 mixture of **5e** and **6e**, i.e. the unwanted diastereomer was again the major product (entry 3). This might be explained by internal delivery of water from $In(H_2O)_6^{3+}$ coordinated to nitrogen.[104,111] Fortunately, employment of 2 equiv $BF_3{\cdot}OEt_2$ in THF/H_2O 10:1 yielded **5e** in a 2.5:1 ratio (entry 4).[106] Reducing the temperature or the amount of acid did not improve this result (entries 5, 6). When **4e** was treated with BBr_3 no product was isolated, instead partly epimerized **4e** could be recovered (entry 7).

[110] Parrodi, C. A.; Vazquez, V.; Quintero, L.; Juraristi, E. *Synth. Commun.* **2001**, *31*, 3295-3302.

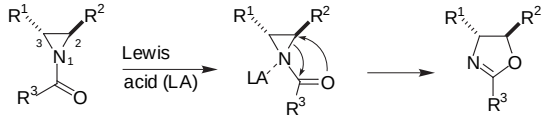
[111] Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 3554-3558.

Aziridine Rearrangement leading to *syn*-Amino Alcohols 6

(Papers II-IV)

7

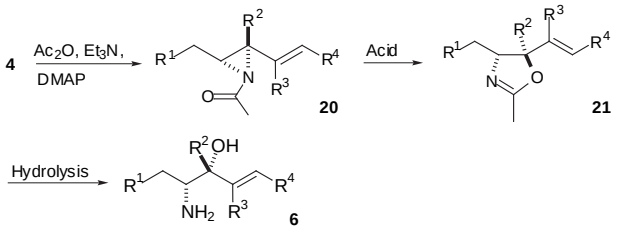
Regioselective ring-opening of aziridines **4** with retention of configuration would yield *syn*-amino alcohols **6** (see Scheme 12). This can be achieved either by a reaction proceeding with double inversion or by an intramolecular rearrangement. The Lewis acid-catalyzed rearrangement of acylaziridines into the corresponding oxazolines is reported to proceed with an S_Ni mechanism to give retention of stereochemistry, as outlined in Scheme 29.[112] The Lewis acid coordinates to the aziridine nitrogen, which is more basic than the carbonyl oxygen, and weakens the C2-N bond. C2 is then attacked by the carbonyl oxygen in a front-side manner, giving the corresponding oxazoline with retention of configuration. The regioselectivity observed in the two cases reported (R^1=H and R^2=Me or Ph) can be explained by a partial positive charge on C2 being more stabilized than on C3. When both R^1 and R^2 are alkyl groups, the regioselectivity may become problematic. Brønstedt acids can also be used to effect the reaction, although the mechanism in these cases might be different.



Scheme 29: Rearrangement of acylaziridine with S_Ni mechanism.

Applying this reaction to vinylaziridines **4**, the reaction sequence leading from **4** to *syn*-amino alcohols **6** is depicted in Scheme 30.

[112] Hori, K.; Nishiguchi, T.; Nabeya, A. *J. Org. Chem.* **1997**, *62*, 3081-3088.



Scheme 30: Transformation of **4** to *syn*-amino alcohols **6**.

7.1 Acetylation

Acetylation of aziridines **4a-d**, **f** proceeded with nearly quantitative yields under standard conditions (Ac_2O, Et_3N, 0.05 equiv DMAP). As *N*-acetylaziridines are unstable on silica gel,[113] compounds **20a-d**, **f** were used as crude products in the subsequent rearrangement.

The acetylation of trisubstituted aziridine **4e** was troublesome, affording a mixture of **20e** and an unidentified byproduct.[114] When **4e** was treated with Ac_2O and Et_3N without DMAP catalysis, the reaction rate was considerably lower and solely byproduct was formed. When the acetyl source was changed to AcCl, the reaction was instant, yet only the same byproduct was formed.[115] The byproduct formation could be diminished by addition of a large excess of Et_3N (20 equiv) under DMAP catalysis. Surprisingly, clean acetylation could be acheived with Ac_2O and a stoichiometric amount of DMAP. At this point only the removal of DMAP remained problematic; acidic workup or flash chromatography destroyed the product, whereas remains of DMAP in the crude product would interfere in the rearrangement. Luckily, the acetylation proceeded equally well with polymer bound DMAP.

7.2 Rearrangement

Several methods reported to cause the rearrangement to oxazolines **21** were scanned with *N*-acetylaziridine **20a** (Scheme 30, R^1=$PhCH_2$, R^2, R^3, R^4=H). Reflux in chloroform was unsuccessful[116] and $TsOH \cdot H_2O$ in toluene instead afforded hydroxyamide **22a** (Figure 8a) in moderate yield, with minor amounts of **21a**.[117] Early attempts with sodium iodide gave oxazoline **21a** as a

[113] Lindström, U. M.; Somfai, P. *J. Am. Chem. Soc.* **1997**, *119*, 8385-8386.

[114] The ratio of byproduct was independent of the reaction time, suggesting that it was formed from **4e** rather than from **20e**.

[115] This indicates that although the anion might take part in the reaction, is not present in the byproduct.

[116] Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *Tetrahedron Lett.* **1997**, *38*, 6953-6956.

[117] Nishiguchi, T.; Tochio, H.; Nabeya, A.; Iwakura, Y. *J. Am. Chem. Soc.* **1968**, *91*, 5835-5845.

diastereomeric mixture,[118] but fine-tuning of the reaction conditions caused a slow but clean rearrangement to **21a**.[119] Turning to Lewis acids, copper triflate caused a slow rearrangement to **21a**.[120] Treatment with $BF_3 \cdot OEt_2$[112] in toluene resulted in a mixture of oxazoline **21a** and ring-closed byproduct **23**, the formation of which could be suppressed by lowering the temperature (Figure 8b).[121]

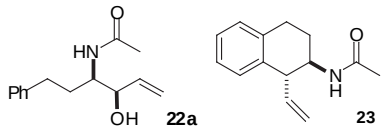
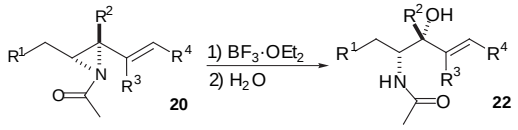


Figure 8. a) Hydroxyamide **22a**. b) Ring-closed byproduct **23**.

7.2.1 *In situ* hydrolysis

Despite the clean rearrangement with $BF_3 \cdot OEt_2$, oxazoline **21a** could only be isolated in 55% yield. Unexpectedly, **21a** was partly hydrolyzed during purification, furnishing a mixture of **21a** and hydroxyamide **22a** after flash chromatography.[88,122] To avoid this loss, we turned our attention to a two step, one pot formation of **22a** from **20a** (Scheme 31). Returning to the $TsOH \cdot H_2O$-mediated reaction (*vide supra*), the results indicated initial formation of **21a** followed by partial hydrolysis to **22a**. Indeed, treatment of oxazoline **21a** with $TsOH \cdot H_2O$ afforded **22a** in high yield. Apparently, water caused byproduct formation when present during the rearrangement,[123] but seemed necessary for the reaction to proceed, as rearrangement was retarded with anhydrous TsOH or camphorsulfonic acid.



Scheme 31. Rearrangement and *in situ* hydrolysis to hydroxyamides **22**.

As Brønstedt acids seemed ineffective for the hydrolysis to **22**, we speculated whether *in situ* hydrolysis of **21a** to **22a** would be possible also in the $BF_3 \cdot OEt_2$ rearrangement. After complete formation of **21a** in toluene, water was added to the reaction mixture, which indeed caused slow formation of hydroxyamide **22a** along with byproducts (Scheme 31). A change of solvent to THF considerably

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[118] Foglia, T. A.; Gregory, L. M.; Maerker, G. *J. Org. Chem.* **1970**, *35*, 3779-3785.

[119] This reaction proceeds with double inversion of configuration.

[120] Ferraris, D.; Drury, W. J., III; Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 4568-4569.

[121] Compound **23** is probably the result of a Friedel-Craft's type of ring-opening, see Taylor S. K. et al, *Synthesis* **1998**, 1133-1136 for comparable reactions of epoxides.

[122] Lee, K.-Y.; Kim, Y.-H.; Park, M.-S.; Oh, C.-Y.; Ham, W.-H. *J. Org. Chem.* **1999**, *64*, 9450-9458.

[123] The combined yield of **21a** and **22a** was moderate in the TsOH·H2O-mediated reaction of **20a**.

increased the hydrolysis rate, and **22a** could be isolated in 71% yield from **4a** (Table 10, entry 1).

The rearrangement proceeded as expected with complete diastereoselectivity (*dr* >20:1), and gratifyingly also with complete regioselectivity (>20:1). The latter could be rationalized by the stabilizing effect of the vinyl group on the transition state, thus favoring an attack of the carbonyl oxygen at the allylic position.

Table 10. Synthesis of *syn*-amino alcohols **6**.

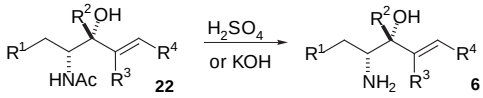
Entry	Substrate	R^1	R^2	R^3	R^4	Yield (%)[a]	
						22	**6**
1	**4a**	$PhCH_2$	H	H	H	71	95[b]
2	**4b**	BnO	H	H	H	73	92[b]
3	**4c**	BnO	H	H	CH_2OPMB	73	91[c]
4	**4d**	H	H	H	CH_2OBn	74[d]	93[b]
5	**4e**	Me	Me	H	CH_2OBn	70	-[e]
6	**4f**	PMBO	H	CH_2OBn	H	73	84[c]

[a]Isolated yields. [b]Acidic hydrolysis. [c]Basic hydrolysis. [d]*dr* 10:1. [e]See text.

Also acylaziridines **20b-f** could be rearranged and hydrolyzed into hydroxyamides **22b-f**, which were formed in ≥70% yield over two steps (entries 2-6). The diastereoselectivity was complete in all cases apart from **22d** (*dr* 10:1), the reason for which is unclear.[124]

7.3 Hydrolysis

Being very stable compounds, amides are normally hydrolyzed with brute force.[88] However, the presence of a vicinal hydroxy group facilitates the reaction considerably,[88] and hydrolysis of hydroxyamides **22** could be performed under mild conditions. Amides **22a**,**b** were hydrolyzed in 5% aq H_2SO_4, giving *syn*-amino alcohols **6a**,**b** in excellent yields (Scheme 32, Table 10). Due to the acid lability of the PMB group, hydroxyamides **22c**,**f** were hydrolyzed in 1M KOH, which gave a slower reaction (entries 3,6). As expected, the reaction proceeded without alterations of the stereochemistry in all cases.



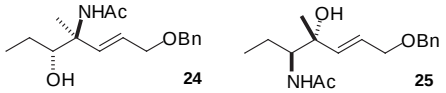
Scheme 32: Hydrolysis of hydroxyamides **22**.

Hydrolysis of **22e** was severely retarded by sterical hindrance (compare Chapter 4.2). Several reaction conditions were screened without success; acidic

[124] Interestingly, when **20e** was rearranged with byproduct present (see Chapter 7.1), hydroxyamide **22e** was formed as a diastereomeric mixture, the ratio of which depended on the amount of byproduct present in the starting material.

media caused no reaction at rt and only decomposition at higher temperatures.[125] Basic media generally caused no reaction, the exceptions being hydrazine, which instead reduced the double bond (see Chapter 9), and Ca/NH_3 that cleaved both amide and benzyl groups.[126]

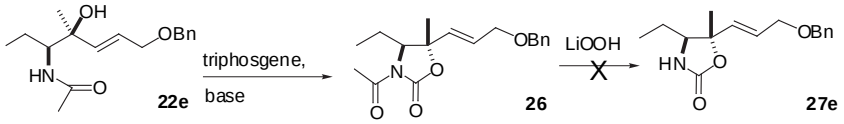
The different reactivity of regioisomeric hydroxyamide **24** compared with **22e** is noteworthy (Scheme 33). This compound can be hydrolyzed under normal basic conditions, whereas the diastereomeric amide **25** is as unreactive as amide **22e**.



Scheme 33: Isomeric hydroxyamides **24** and **25**.

7.3.1 Alternative strategies to reach amino alcohol 6e

In Evans' asymmetric alkylations, the chiral auxiliary can be removed by LiOOH treatment, which cleaves the amide bond rather than the oxazolidinone.[127] As oxazolidinones are easily hydrolyzed to amino alcohols (see Chapter 4.2), this would be a possible strategy towards **6e**. Unexpectedly, when **22e** was converted to the corresponding acyloxazolidinone **26** followed by LiOOH treatment, oxazolidinone **27e** was not formed, but amide **22e** was recovered (Scheme 34).



Scheme 34: Hydrolysis attempt *via* acyloxazolidinone .

Routes avoiding amide **22e** were then examined. Oxazoline **21e** could be isolated in 89% yield,[128] but reduction of this species with $NaBH_3CN$ in acidic medium to the corresponding oxazolidine **D**, followed by hydrolysis to **6e** was unsuccessful (Scheme 35).[129]

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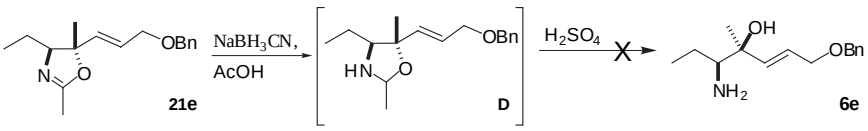
[125] Acidic conditions: 5% aq H_2SO_4, rt to reflux; 5% H_2SO_4 in THF/H_2O 1:1, rt to reflux; 5 equiv $BF_3{\cdot}OEt_2$ in THF/H_2O 10:1, rt to reflux; 10 equiv TsOH·H_2O in THF, rt to reflux.

[126] Basic conditions: 1M KOH in EtOH/H_2O 1:1, 150 °C; NH_4OH in EtOH/H_2O 1:1, 140 °C; NH_4OH in H_2O, 50W 15 min; LiOH, H_2O_2 in THF/H_2O 3:1, reflux; NaOEt in EtOH, reflux; $NH_2NH_2{\cdot}H_2O$, reflux; Ca, NH_3, EtOH, DME, -30 °C.

[127] Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448-3467.

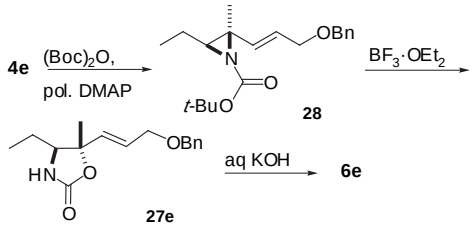
[128] This was possible as hydrolysis to **22e** was retarded due to steric hindrance.

[129] Gosmann, G.; Guillaume, D.; Husson, H.-P. *Tetrahedron Lett.* **1996**, *37*, 4369-4372.



Scheme 35: Reduction of oxazoline **21e**.

Instead **6e** was obtained *via* Boc-protection of aziridine **4e** to compound **28** (Scheme 36).[130] Crude **28** was rearranged with $BF_3 \cdot OEt_2$ to oxazolidinone **27e**, which was obtained as a separable mixture of diastereomers (*dr* 2.3:1) in 66% combined yield from **4e**. Oxazolidinone **27e** was easily hydrolyzed with 1M KOH to *syn*-amino alcohol **6e** in 98% yield.



Scheme 36. Rearrangement to oxazolidinone **27e** followed by hydrolysis to **6e**.

[130] Sepulveda-Arques, J.; Armero-Alarte, T.; Acero-Alarcon, A.; Zaballos-Garcia, E.; Solesio, B. Y.; Carrera, J. E. *Tetrahedron* **1996**, *52*, 2097-2102.

Synthesis of Sphingosine and its Regio- and Stereoisomers

(Paper VI)

8

Having developed the divergent synthesis of *vic*-amino alcohols described in the previous chapters, we turned our attention to finding a suitable natural product, on which to apply the route. Ideally, not only the compound itself but also its diastereo- and regioisomers should be interesting targets of total synthesis. These demands could be met by D-*erythro*-sphingosine.

8.1 Background

Glycosphingolipids are ubiquitous membrane components of all eucaryotic cells, located in plasma membranes as well as in some intracellular organelles. The backbone of sphingolipids consists of long-chain aliphatic 2-amino-1,3-diols, of which D-*erythro*-sphingosine is the most common (**29**, Figure 9). Sphingolipids, as well as sphingosine itself, are important in such diverse biological phenomena as cell-cell-recognition and signaling within and between cells.[131] Numerous structurally related sphingoid base structures are present in nature, such as phytosphingosines and sphingofungins (Figure 9). The vast distribution of sphingolipids in both plants and animals has led to an immense interest of this compound class in medical research.

[131] (a) Karlsson, K.-A. *Trends Pharm. Sci.* **1991**, *12*, 265-272. (b) Liscowitch, M.; Lavie, Y. *Trends. Glycosci. Glycothechn.* **1990**, *2*, 470-485. (c) Hannun, Y.; Bell, R. M. *Science* **1989**, *243*, 500-507.

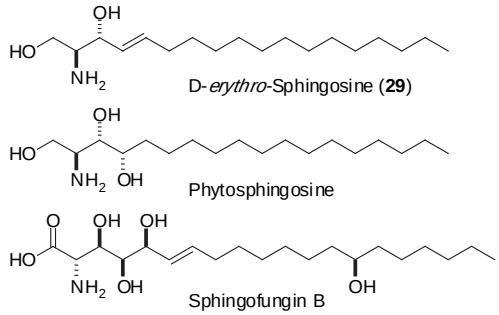


Figure 9. Various sphingoid bases.

Sphingosine and its isomers have been targets of synthetic interest for decades, and well over 50 total syntheses have been published. Most asymmetric syntheses have relied on the chiral pool, starting from sugars or amino acids. Other investigations have made use of asymmetric reactions, often Sharpless asymmetric epoxidation or aldol reactions with a chiral auxiliary, to create the two stereocenters.[132] Divergent syntheses have been rare, though Hudlicky recently presented an elegant synthesis of sphingosine and its diastereomers.[133] No divergent route from a common starting material towards all possible regio- and stereoisomers of sphingosine has been documented.

Application of our synthesis scheme starting from vinylepoxide **1l** (Scheme 37) would lead to D-*erythro*-sphingosine (**29**, Figure 10) and its diastereo- and regioisomers (**30**-**32**). The remaining four sphingosine isomers (*ent*-**29** to *ent*-**32**) can simply be obtained by starting from vinylepoxide *ent*-**1l**.

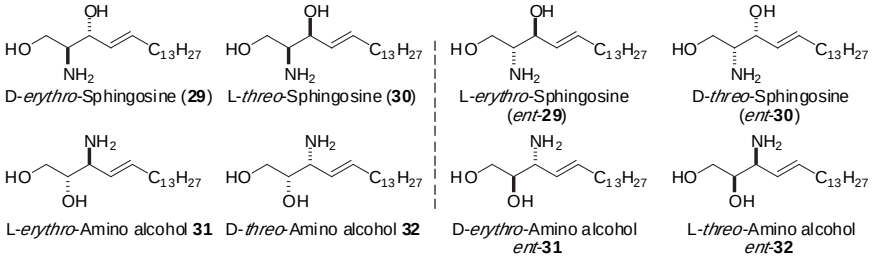


Figure 10. All possible regio- and stereoisomers of sphingosine.

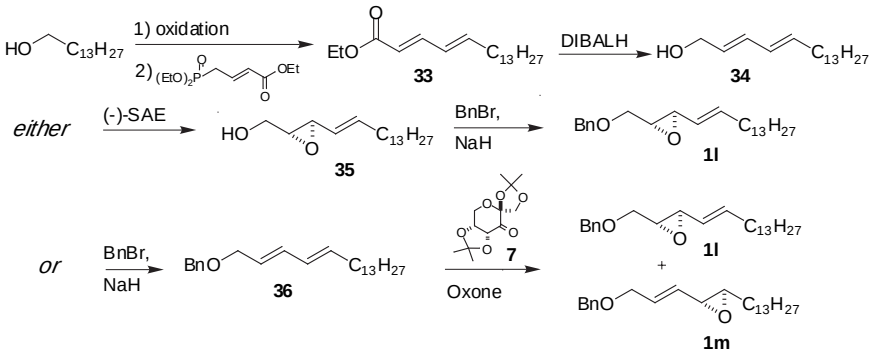
8.2 Synthesis of vinylepoxide 1l

We envisaged the synthesis to begin with commercially available tetradecanol, which could be transformed into **1l** in four steps (Scheme 37). A Swern/Wittig

[132] Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075-1091.

[133] Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510-520. For other divergent approaches, see Shultz, M. D.; Kiessling, L. L. Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30 2001, ORGN-055 and Lee, J.-M.; Lim, H.-S.; Chung, S.-K. *Tetrahedron: Asymmetry* **2002**, *13*, 343-347.

procedure would give the unsaturated ester **33**, which would be reduced to dienol **34**. Catalytic Sharpless symmetric epoxidation to epoxyalcohol **35** could be attempted on this species, although the stoichiometric SAE has been reported to cause decomposition.[29] Alternatively, **34** could be benzylated to **36** prior to epoxidation using Shi's catalyst **7**, although this would give rise to two regioisomeric vinylepoxides (**1l** and **1m**).[35]



Scheme 37. Synthesis of vinylepoxide **1l**.

Due to the lipid chain present throughout the reaction scheme, solubility problems were often encountered at low temperatures. Thus, Swern oxidation gave poor yield of the corresponding aldehyde. TPAP[134] or IBX[135] oxidation performed at rt gave better results. IBX was the method of choice due to simplified workup and thus better yield of the aldehyde, which was used as crude product in the subsequent olefination. In our experience, diene esters like **33** could be unstable on silica, which rendered the Horner-Emmons procedure a better choice than the classical Wittig reaction. When the reaction was performed with KHMDS (or NaH) and triethyl phosphonocrotonate, a complicated mixture of products was obtained. This might be explained by poor solubility at low reaction temperature and too high reactivity upon increased temperature.

To avoid this problem a different approach using LiOH, triethyl phosphonocrotonate and molecular sieves in refluxing THF was attempted.[136] With this procedure, **33** was formed in quantitative crude yield and good *E,E* selectivity.[137] Crude diene ester **33** could be reduced with DIBALH at –40 ˚C to dienol **34**, which was isolated in 59% yield from tetradecanol.

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[134] Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639-666.

[135] For synthesis of IBX see Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537-4538. For oxidation with IBX see Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272-7276.

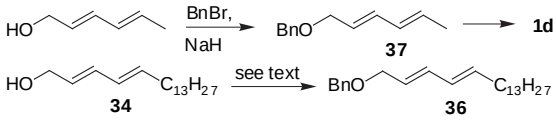
[136] Takacs, J. M.; Jaber, M. R.; Clement, F.; Walters, C. *J. Org. Chem.* **1998**, *63*, 6757-6760.

[137] 10:1 ratio *(E,E*-isomer to other isomers). The ratio could not be improved by iodine isomerization.

8.2.1 Epoxidation strategies

Sharpless epoxidation of dienes is often troublesome, as discussed in Chapter 2. Not surprisingly, catalytic SAE of dienol **34** resulted in a mixture of compounds lacking double bonds, as in the stoichiometric attempt previously reported.[29] No optimization attempts of the SAE were made; instead we aimed at Shi epoxidation of diene **36**.

Benzylation of **34** proved more difficult than expected, as the reaction stopped before completion under standard conditions.[138] As *E,E*-hexadienol could be benzylated to compound **37** in 98% yield (Scheme 38), the lipid chain might be the origin of these problems. Extended reaction time, increased temperature, excess reagents or slow addition of **34** to avoid possible micelle formation all resulted in no improvement. Other procedures were scanned; both Ag_2O/BnBr[48] (see Chapter 2) and benzyl trichlorotriacetimidate/ triflic acid[139] gave a complex mixture of products. Finally, addition of Bu_4NI to the original protocol sufficed to give benzylated diene **36** in 95% yield.[140]



Scheme 38: Benzylation of hexadienol and **34**.

Shi epoxidation works well on protected dienols, epoxidizing the most electron rich double bond with good selectivity.[35] Epoxidation of diene **37**, which differs from **36** only by the length of the carbon chain (Scheme 38), resulted in a 4:1 mixture of regioisomers, favoring reaction at the 4,5-double bond (see Chapter 2). We were thus doubtful whether **1l**, which is expected to be the minor isomer, could be formed in synthetically useful yields with this method. With diene **36** at hand, Shi's epoxidation was performed. Surprisingly, epoxides **1l** and **1m** were formed in a 1:1 ratio, i.e. with far better selectivity than expected. Again, the difference in reaction outcome could be due to the lipid chain, which might shield the 4,5-double bond.

The conversion was initially poor and could not be improved by longer reaction time or increased temperature. However, the conversion proved dependent on the amount of catalyst used. When a stoichiometric amount of **7** was utilized, both enantioselectivity and yield were enhanced (*es* 87-95%).[141] The catalyst is believed to undergo Bayer-Villiger oxidation in the presence of Oxone, and Shi recently described a method using hydrogen peroxide instead of

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[138] BnBr, NaH in THF or DMF, reflux.

[139] Fleming, I.; Lawrence, N. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, *17*, 2679-2686.

[140] Kulkarni, B. A.; Sankaranarayanan, A.; Subbaraman, A. S.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1571-1577.

[141] The catalyst is now commercially available from Lancaster as D-Epoxone, but this material gave low conversion and poor enantioselectivity.

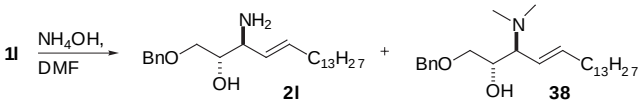
Oxone to avoid this.[142] However, when used on **36** these conditions failed to give any reaction.

Vinylepoxides are known to be unstable on silica,[35] and separation of epoxides **1l** and **1m** was possible only at the expense of decreased yield.[143] To avoid this loss, we aimed at separating the isomers at a later stage in the synthesis (*vide infra*).

8.3 Ring-openings of vinylepoxide 1l

8.3.1 Synthesis of *anti*-Amino Alcohol 2l

Vinylepoxide **1l** was unreactive towards initial aminolysis attempts in NH_4OH and demanded heating to 170 °C for any reaction to take place. At these rather severe conditions, an unidentified byproduct was formed along with amino alcohol **2l**. As we suspected solubility problems to be the reason for the low reactivity, DMF was utilized as co-solvent. Indeed, this resulted in a lowering of the required reaction temperature to 130 °C; furthermore the byproduct formation was suppressed. Surprisingly, a new byproduct, which might be amino alcohol **38**, was instead formed in a minor amount (Scheme 39).[144] With THF as co-solvent, the reaction proceeded without byproduct formation, giving anti-amino alcohol **2l** in 98% yield with complete regioselectivity (>20:1).



Scheme 39. Aminolysis of **1l** with DMF as co-solvent.

Also vinylepoxide **1m** (see Scheme 37) was subjected to aminolysis in ammonium hydroxide. Surprisingly, this compound was even less reactive than **1l**, which might be explained by the lipid chain being closer to the allylic position than in **1l**. This finding caused us to investigate whether a mixture of vinylepoxides **1l** and **1 m** could be used in the aminolysis, with selective formation of **2l**. By decreasing the reaction temperature, the reaction could indeed be made selective in NH_4OH/THF, which meant that separation of vinylepoxides **1l** and **1m** before aminolysis, with subsequent loss of material, could be avoided.

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[142] Suhu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213-5218.

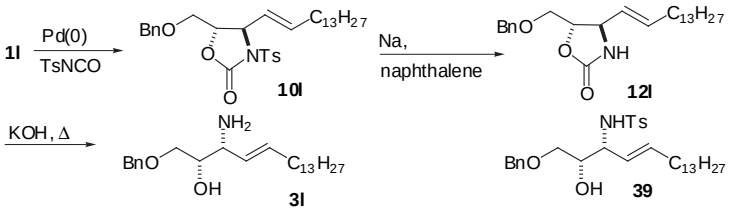
[143] 90% combined crude yield, 50% combined isolated yield.

[144] The presence of **38** could be explained by partial decomposition of DMF to dimethylamine under basic conditions and heat, see Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; 4th ed.; Butterworth-Heinemann: Oxford, 1996.

8.3.1 Synthesis of *syn*-Amino Alcohol 3l

Pd(0)-catalyzed ring-opening of vinylepoxide **1l** in the presence of tosyl isocyanate gave oxazolidinone **10l** in 75% yield (Scheme 40). Detosylation by titration with sodium naphthalide to **12l** was slow, and immediate quench caused formation of amino alcohol **39** by basic hydrolysis of unreacted **10l**. After 20 min reaction time, *N*-H oxazolidinone **12l** was isolated in 88 % yield. Basic hydrolysis of **12l** resulted in *syn*-amino alcohol **3l** in nearly quantitative yield.

When a mixture of vinylepoxides **1l** and **1m** (see Scheme 37) was used in the reaction sequence, oxazolidinones **12l** and **12m** could easily be separated without loss in yield. This rendered the separation of **1l** and **1 m** redundant, as ring-opening to amino alcohols **2l** and **3l** could be performed without interference of **2m** and **3m**.

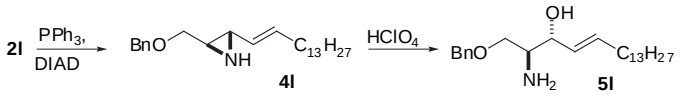


Scheme 40. Ring-opening of **1l** with retention of configuration.

8.5 Synthesis and ring-openings of vinylaziridine 4l

8.5.1 Synthesis of Bn-protected D-*erythro*-Sphingosine 5l

N-H vinylaziridine **4l** was obtained from *anti*-amino alcohol **2l** by ring-closure under Mitsunobu conditions (Scheme 41). As described in Chapter 5, purification of vinylaziridines is often troublesome due to their instability on silica. As isolation of **4l** resulted in a major loss of product, a mixture of **4l** and reduced DIAD was used in the following reactions.[145]



Scheme 41. Formation and ring-opening of vinylaziridine **4l**.

When aziridine **4l** was treated with perchloric acid in THF/H_2O, *anti*-amino alcohol **5l** was surprisingly formed in a 1:1 ratio with 1,4-amino alcohols **40** (Figure 11). Gratefully, when the solvolysis was performed with TFA and H_2O in CH_2Cl_2, the ratio of **5l** to **40** increased to 3:1 and **5l** could be isolated in 62% yield from **2l**. The hydrolysis proceeded *via* amide **41**, which was easily hydrolyzed to **51** under basic conditions.

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[145] Because of the unpolar character of **4l**, removal of Ph_3P=O was easy, whereas reduced DIAD was almost inseparable from **4l**.

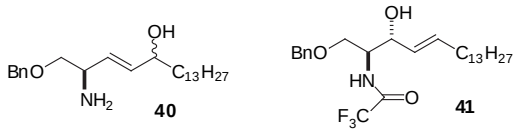
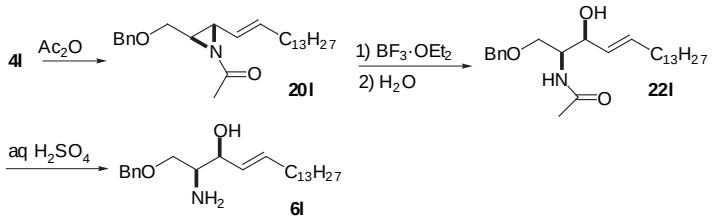


Figure 11. 1,4-amino alcohols **40** and amide **41**.

8.5.2 Synthesis of Bn-protected L-*threo*-Sphingosine 6l

Acetylation of **4l** proceeded in nearly quantitative yield, and *N*-acetylaziridine **20l** was used as crude product in the subsequent reaction (Scheme 42). Rearrangement of **20l** was performed with $BF_3{\cdot}OEt_2$ followed by *in situ* hydrolysis to hydroxyamide **22l**, which was isolated in 43% yield from **2l**. The rearrangement proceeded, as expected, with complete diastereo- and regioselectivity (>20:1). Hydroxyamide **22l** was hydrolyzed in refluxing 5% aq H_2SO_4, giving *syn*-amino alcohol **6l** in good yield.



Scheme 42. Ring-opening of **4l** with retention of configuration.

The synthesis was completed by removal of the benzyl group from amino alcohols **2l**, **3l** and **5l** (debenzylation of **6l** remains). This was performed by means of sodium in liquid ammonia, giving sphingosine isomers **29**, **31** and **32** (see Figure 10) in 91-92% yield.

Determination of Regiochemistry and Relative Stereochemistry of *vic*-Amino Alcohols

(Papers IV,VII)

9

9.1 Introduction

The regiochemistry of vinylic β-amino alcohols can easily be revealed by ^{1}H NMR, as the allylic proton shifts approximately 0.5 ppm downfield compared with the homoallylic proton. Determination of the relative stereochemistry (*syn*/*anti*) is more laborious, demanding complexation or derivatization prior to analysis. Shapiro recently reported an NMR method of determining enantiomeric purity and relative configuration by complexation to (R)-(+)-*t*-butylphenylphosphinothioic acid, which is not commercially available.[146] The absolute configuration can be determined by circular dichroism measurements of various amino alcohol–metal complexes.[147]

Most methods to determine configurations of β-amino alcohols require derivatization before NMR or CD analysis,[148] e.g. transformation with Mosher's acid.[149] Several procedures of configurational assignment rely on the rigidity of certain heterocycles. 1,3-Diols can be converted to acetonides, the ^{13}C-NMR

[146] Gunderson, K. G.; Shapiro, M. J.; Doti, R. A.; Skiles, J. W. *Tetrahedron: Asymmetry* **1999**, *10*, 3263-6266.

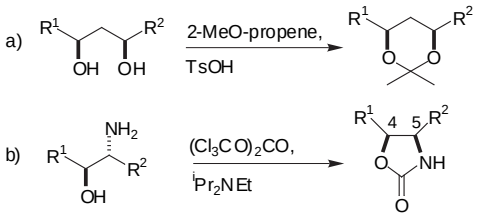
[147] See Frelek, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2809-2816 and references therein.

[148] Zahn, S.; Canary, J. W. *Org. Lett.* **1999**, *1*, 861-864.

[149] Benson, S. C.; Cai, P.; Colon, M.; Haiza, M. A.; Tokles, M.; Snyder, J. K. J. Org. Chem. **1988**, *53*, 5335-5341. For a similar approach, see Apparu, M.; Ben Tiba, Y.; Leo, P. M.; Hamman, S.; Coulombeau, C. *Tetrahedron: Asymmetry* **2000**, *11*, 2885-2898.

shifts of which depend on *cis*- or *trans* configuration (Scheme 43a).[150] Similarly, amino alcohols can be transformed to the corresponding oxazolidinones. (Scheme 43b).[9,151] The ring protons (H_4,H_5) of these compounds have coupling constants that are larger for *cis*- than for *trans*-configuration, typically ranging from 7-9 Hz and 3-7 Hz, respectively. The configuration can also be confirmed by NOE experiments.[9]

Accordingly, by converting amino alcohols into the corresponding oxazolidinones their relative stereochemistry can be revealed, as *syn*-amino alcohols give *trans*-oxazolidinones and *anti*-amino alcohols give *cis*-oxazolidinones. As the differences in coupling constants and NOE interactions between *cis*- and *trans*-oxazolidinones can be small, both isomers of the amino alcohol are often needed for positive assignment. This is true especially for vinyl-substituted oxazolidinones, which often have coupling constants in the range of 7-8 Hz for both isomers.[152]



Scheme 43: Transformation of an *anti*-amino alcohol into a *cis*-oxazolidinone.

9.2 Synthesis of Oxazolidinones

The relative configuration of amino alcohols **2**, **3**, **5** and **6** was determined by conversion to the corresponding oxazolidinones (Scheme 43b, Table 11). When *anti*-amino alcohols **2a-d**,**f**,**l**,**m** and **5a-d**,**f**,**l**,**m** were converted into oxazolidinones **42a-d**,**f**,**l**,**m** and **43a-d**,**f**,**l**,**m** the coupling constants of the ring protons were 7.8-8.4 and 7.5-8.4 Hz, respectively, which is consistent with *cis*-configuration. Oxazolidinones **12a-d**,**f**,**l**,**m** (see Chapter 4.2 and 8.4), which show the relative configuration of *syn*-amino alcohols **3a-d**,**f**,**l**,**m**, have coupling constants ranging from 5.4 to 7.2 Hz, confirming *trans*-configuration. Finally, *syn*-amino alcohols **6a-df**,**l**,**m** yielded oxazolidinones **27a-d**,**f**,**l**,**m** with coupling constants between 5.5 and 6.8 Hz, agreeing with *trans*-configuration. The relative configurations of **12e**, **27e**, **42e** and **43e** were confirmed by NOESY experiments. Interactions between the ring proton (H_4) and the methyl group at C_5 were present for oxazolidinones **42e** and **43e**, indicating *cis*-configuration.

Also the additional *anti*-amino alcohols **2g-k** used in the microwave

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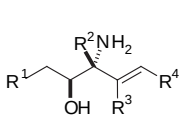
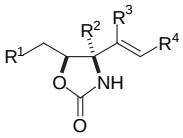
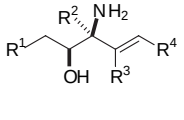
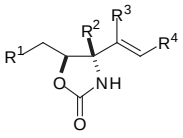
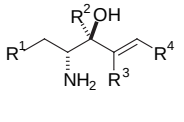
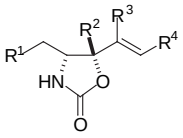
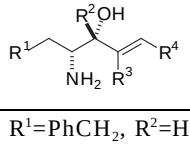
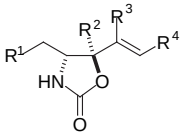
[150] Rychnovsky, S. D.; Richardson, T. I.; Rogers, B. N. *J. Org. Chem.* **1997**, *62*, 2925-2934.

[151] Bergmeier, S. C.; Stanchina, D. M. *Tetrahedron Lett.* **1995**, *36*, 4533-4536.

[152] (a) Ayad, T.; Génisson, Y.; Baltas, M.; Gorrichon, L. *Synlett* **2001**, 866-868. (b) Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150-1158.

aminolysis study (see Chapter 3.2) were transformed into oxazolidinones. Oxazolidinones **42g**,**j**,**k** had ring coupling constants of 7.8-8.1 Hz, agreeing with *cis*-configuration and NOE-experiments on **43h**,**i** revealed *cis*-configuration.[43,52]

Table 11: Coupling constants of oxazolidinone ring protons H_4,H_5 (J_{AB}).

	Amino alcohol Substrate[a]	**Oxazolidinone**	**J_{AB} (Hz) or NOE effect**							
			a	**b**	**c**	**d**	**e**	**f**	**l**	**m**
2		**42** 	8.2	8.2	8.3	7.9	NOE	8.4	8.2	7.8
3		**12** 	7.0	6.6	6.8	7.2	no NOE	5.4	6.8	7.2
5		**43** 	8.0	8.3	7.5	7.5	NOE	7.8	8.4	8.1
6		**27** 	6.6	6.6	6.3	6.5	no NOE	5.5	6.8	6.5

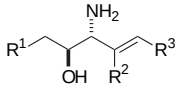
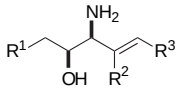
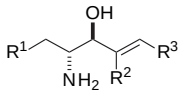
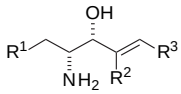
[a] **a**: R^1=$PhCH_2$, R^2=H, R^3=H, R^4=H; **b**: R^1=BnO, R^2=H, R^3=H, R^4=H; **c**: R^1=BnO, R^2=H, R^3=H, R^4=CH_2OPMB; **d**: R^1=H, R^2=H, R^3=H, R^4=CH_2OBn; **e**: R^1=CH_3, R^2=CH_3, R^3=H, R^4=CH_2OBn **f**: R^1=PMBO, R^2=H, R^3=CH_2OBn, R^4=H; **l**: R^1=BnO, R^2=H, R^3=H, R^4=$C_{13}H_{27}$; **m**: R^1=$C_{13}H_{27}$, R^2=H, R^2=H, R^4=BnO.

9.3 NMR determination

As the transformation of all amino alcohols to oxazolidinones was a rather time-consuming operation, we sought a simplified method of configuration assignment without need for derivatization. Since we had analysis data of a large amount of amino alcohols at hand, we started looking for trends in ^{13}C NMR or coupling constants that could be used to distinguish *syn*- and *anti*-amino alcohols.

Substrates **a**-**d**,**f**,**l** and **m**, each with four amino alcohol isomers (**2**, **3**, **5** and **6**), were used in the study.[153] ^{13}C NMR data and coupling constants of methine protons H_3 and H_4 were examined, but to our disappointment no such trends were found (Table 12).

Table 12: Coupling constants and ^{13}C shifts of vinylic amino alcohols **2**, **3**, **5**, **6**.

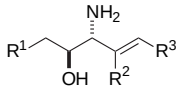
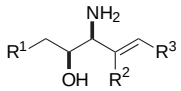
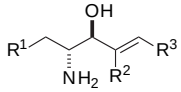
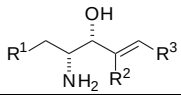
	Amino alcohol	J_{AB} **(Hz)/** ^{13}**C shift** C**H**-O/ C**H**-N **(ppm)**						
	Substrate[a]	**a**	**b**	**c**	**d**	**f**	**l**	**m**
2		4.0 73.2 59.0	m 73.9 57.0	m 72.7 55.6	3.8 72.0 58.3	6.0 73.0 57.4	4.7 72.9 56.0	m 74.2 57.6
3		7.4 73.2 59.5	6.9 73.5 56.2	m 73.3 55.3	7.0 72.8 60.4	m 73.0 56.2	m 73.5 58.5	m 74.0 53.5
5		m 75.0 54.5	5.9 74.6 54.6	5.6 74.4 55.7	4.2 75.3 50.7	6.3 73.2 55.3	5.1 74.8 54.9	m 74.0 55.5
6		6.0 75.4 54.9	5.3 73.4 54.7	4.8 72.6 54.5	6.4 73.6 51.1	m 73.2 55.3	m 73.4 55.3	5.6 73.5 55.7

[a]**a**: R^1=$PhCH_2$, R^2=H, R^3=H; **b**: R^1=BnO, R^2=H, R^3=H; **c**: R^1=BnO, R^2=H,R^3=CH_2OPMB; **d**: R^1=H, R^2=H, R^3=CH_2OBn; **f**: R^1=PMBO, R^2=CH_2OBn, R^3=H; **l**: R^1=BnO, R^2=H, R^3=$C_{13}H_{27}$; **m**: R^1=$C_{13}H_{27}$, R^2=H, R^3=BnO.

Surprisingly, there was instead a trend in the ^1H NMR shifts, where H_3 and H_4 shifted more downfield in *anti*-amino alcohols **2** and **5** than in the corresponding *syn*-amino alcohols **3** and **6**. For example, the shifts of C**H**-O in **2a** and **3a** were 3.61 and 3.32 ppm, respectively. For the same compounds, the shifts of C**H**-N were 3.36 and 3.14 ppm, respectively (Table 13).

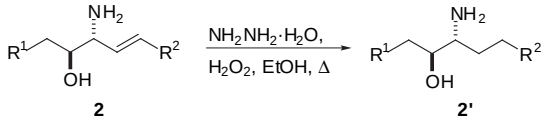
[153] Substrate **e** was excluded as it lacks the allylic proton.

Table 13: ^{1}H NMR shift (ppm) of C<u>H</u>-O / C<u>H</u>-N protons in vinylic *vic*-amino alcohols.

	Amino alcohol[a]	Shift (ppm) of C<u>H</u>-O / C<u>H</u>-N protons a	b	c	d	f	l	m
2		3.61 3.36	3.78 3.50	3.77 3.51	3.73 3.29	3.83 3.63	3.74 3.42	3.53 3.40
3		3.32 3.14	3.50 3.40	3.58 3.43	3.45 3.06	3.70 3.40	3.53 3.34	3.29 3.14
5		4.07 2.94	4.11 3.06	4.15 3.06	4.00 3.00	4.10 3.12	4.04 3.03	4.24 2.85
6		3.85 2.67	4.08 2.97	4.08 2.94	3.73 2.81	3.92 3.04	3.96 2.88	3.91 2.72

[a]**a**: R^1=$PhCH_2$, R^2=H, R^3=H; **b**: R^1=BnO, R^2=H, R^3=H; **c**: R^1=BnO, R^2=H, R^3=H; **d**: R^1=H, R^2=H, R^3=CH_2OBn; **f**: R^1=PMBO, R^2=CH_2OBn, R^3=H; **l**: R^1=BnO, R^2=H, R^3=$C_{13}H_{27}$; **m**: R^1=$C_{13}H_{27}$, R^2=H, R^3=BnO.

Satisfied with this observation, we wanted to see whether the trend was applicable also to saturated *vic*-amino alcohols. Amino alcohols **2**, **3**, **5** and **6** of substrates **a**, **b, d**, **l** and **m** were reduced with hydrazine and hydrogen peroxide to the corresponding saturated compounds **2'**, **3'**, **5'** and **6'** (Scheme 44).[154,155]



2 **2'**

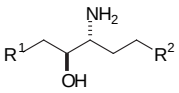
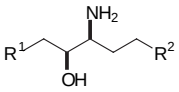
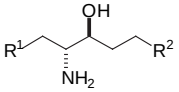
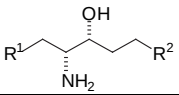
Scheme 44: Hydrazine reduction of the vinyl group.

To our delight, the saturated amino alcohols **2'**, **3'**, **5'**, **6'** showed the same trend in ^{1}H NMR shifts (Table 14). Thus, complexation or derivatization of *vic*-amino alcohols is not needed for determination of relative configuration. Instead simple ^{1}H NMR analysis is sufficient to reveal *syn*/*anti* relationship when both of the isomers of a given amino alcohol are present, as the ^{1}H NMR shifts of C<u>H</u>-O and C<u>H</u>-N protons are more downfield in the *anti*-amino alcohol than in the corresponding *syn*-isomer.

[154] Yadav, J. S.; Sreenivasa Rao, E.; Sreenivasa Rao, V. *Synth. Commun.* **1989**, *19*, 705-711.

[155] Substrate **c** was excluded due to lack of material, substrate **f** as is would give two diastereomers upon reduction.

Table 14: ^{1}H NMR shift of C**H**-O / C**H**-N protons in saturated *vic*-amino alcohols.

		Shift of C**H**-O / C**H**-N protons (ppm)				
	Amino alcohol[a]	**a**	**b**	**d**	**l**	**m**
2'		3.50 2.64	3.67 2.79	3.72 2.78	3.65 2.87	3.46 2.77
3'		3.31 2.52	3.53 2.73	3.41 2.44	3.51 2.80	3.25 2.55
5'		3.39 2.81	3.47 3.02	3.43 2.96	3.55 3.00	3.47 2.76
6'		3.24 2.60	3.42 2.91	3.19 2.73	3.48 2.86	3.26 2.53

[a]**a**: R^1=$PhCH_2$, R^2=H; **b**: R^1=BnO, R^2=H; **d**: R^1=H, R^2=CH_2OBn; **l**: R^1=BnO, R^2=$C_{13}H_{27}$, **m**: R^1=$C_{13}H_{27}$, R^2=BnO.

Concluding remarks

A synthetic strategy that provides a straightforward route from vinylepoxides **1** to the four isomeric *vic*-amino alcohols **2**, **3**, **5** and **6** has been presented. Since *ent*-**1** is available from the same starting material as **1**, all eight possible isomers of a given amino alcohol can be synthesized using this procedure. As an application of the presented route towards amino alcohols, the synthesis of sphingosine and three of its isomers has been detailed.

The synthesis of vinylepoxides **1** has been simplified by application of an enantioselective monoepoxidation of dienes, making the starting materials used in this route readily available in both enantiomeric forms. Moreover, two efficient protocols for the regioselective and stereospecific aminolysis of vinylepoxides have been presented. Compared to previous methods, these procedures use milder reaction conditions, shorter reaction times, generally give higher yields and are applicable to a larger set of substrates.

Furthermore, the ring-closure of *vic*-amino alcohols to the corresponding *N*-H vinylaziridines has been investigated. Three routes were found useful, which one is preferred depends on substrate and scale.

Finally, a rapid way of determining the relative configuration of *vic*-amino alcohols has been developed, which should be of substantial use when amino alcohols are formed by diastereoselective reactions.

Acknowledgements

Jag skulle vilja tacka alla som stöttat och hjälpt mig genom denna, tidvis mycket roliga och tidvis rätt jobbiga, fyraårsperiod. Ett särskilt tack till…

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…alla nuvarande och gamla medlemmar av PS-gruppen, särskilt U*lf*, för all hjälp och bra konserter och *Janne*, som hållit ordning och fixat bra musik på lab!

…alla avdelningskollegor på SU och KTH; mer innebandy till folket!

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…*Janne* och *Gunhild Aulin-Erdtman* för korrelturläsning av denna avhandling.

…alla vänner för att ni stått ut fastän jag nästan aldrig har haft tid. Speciellt tack till *Reneé* och *Leffe* för Emmy, trevliga söndagar och festfixande och till *Bengt* för all hjälp med Umbra.

…min familj, för att ni alltid finns där när det behövs.

...*Peter* & *Emmy*, ni är dom bästa som finns!

Appendix A

The following is a description of my contribution to publications **I**-**VII**, as requested by KTH:

I. I shared lab work and writing of the paper with Dr. U. M. Lindström.

II. I performed all initial reaction optimizations, did the transformations of substrates **a**-**c** to the corresponding amino alcohols and the analyses of compounds **a**-**d**. Dr. U. Khamrai prepared and reacted substrate **1d**. I wrote the article.

III. This paper was written on invitation, and is a more detailed form of paper **II**. I wrote the article.

IV. I performed all lab work apart from what is described above for paper **II**. I wrote the article.

V. I supervised the diploma worker R. Wijtmans, who made the initial investigations apart from the Mitsunobu chemistry. I optimized the reactions, did the analysis work and wrote the article.

VI. I performed all lab work and wrote the article.

VII. I performed all lab work and wrote the article.

Appendix B

This appendix contains experimental details for paper **VII** and analytical data of compounds **1k**, **2m-6m**, **10m**, **12m**, **16-19**, **20m**, **21e**, **22m**, **23-26**, **27m**, **40m** and **41m**.

B.1 Compounds "m" in the Sphingosine route (Chapter 8)

Amino alcohols **2m**, **3m**, **5m** and **6m** were used in the NMR-study described in Chapter 9, and synthesized according to the general procedures described in publications IV and VI.

(*2E,4S,5R*)-4-Amino-1-benzyloxy-octadec-2-en-5-ol (2m):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 5.77 (m, 2H), 4.52 (s, 2H), 4.04 (m, 2H), 3.53 (m, 1H), 3.40 (m, 1H), 1.77 (br s, 3H), 1.37 (m, 2H), 1.26 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.3, 133.2, 128.7, 127.8, 127.7, 74.2, 72.3, 70.4, 57.6, 33.0, 31.9, 29.8, 29.7, 29.7, 29.7, 29.7, 29.6, 29.6, 29.4, 26.0, 22.7, 14.1; IR (neat): 3320, 2915, 2849 cm^{-1}.

(*2E,4S,5S*)-4-Amino-1-benzyloxy-octadec-2-en-5-ol (3m):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 5.77 (dt, 1H, *J* = 15.7, 4.6 Hz), 5.71 (dd, 1H, *J* = 15.7, 6.0 Hz), 4.52 (s, 2H), 4.02 (d, 2H, *J* = 4.6 Hz), 3.29 (m, 1H), 3.14 (m, 1H), 1.81 (br s, 3H), 1.51 (m, 2H), 1.27 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.1, 128.4, 127.9, 127.8, 127.7, 127.6, 74.0, 72.3, 70.3, 53.5, 33.8, 31.9, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.6, 29.3, 25.8, 22.7, 14.1; IR (neat): 3351, 2918, 2847 cm^{-1}.

(*2S,3S*)-2-(3-Benzyloxy-(*E*)-propenyl)-3-tridecyl-aziridine (4m):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.27 (m, 5H), 5.89 (dt, 1H, *J* = 15.5, 5.8 Hz), 5.36 (dd, 1H, *J* = 15.5, 8.4 Hz), 4.54 (s, 2H), 4.03 (dd, 2H, *J* = 5.9, 1.3 Hz), 2.21 (dd, 1H, *J* = 8.3, 2.6 Hz), 1.89 (m, 1H), 1.44 (m, 2H), 1.28 (m, 22H), 0.90 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 134.2, 128.4, 127.9, 127.8, 127.6, 72.3, 70.3, 39.4, 38.5, 33.8, 31.9, 29.7, 29.7, 29.7, 29.7, 29.6, 29.4, 29.4, 29.2, 27.4, 22.7, 14.1; IR (neat): 2925, 2853 cm^{-1}.

(*2E,4R,5S*)-5-Amino-1-benzyloxy-octadec-2-en-4-ol (5m):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.27 (m, 5H), 5.90 (dt, 1H, *J* = 16.1, 5.8 Hz), 5.76 (dd, 1H, *J* = 16.1, 5.9 Hz), 4.52 (s, 2H), 4.24 (m, 1H), 4.06 (d, 2H, *J* = 6.0 Hz), 2.85 (m, 1H), 2.01 (br s, 3H), 1.43 (m, 2H), 1.26 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 131.1, 129.3, 128.4, 127.7, 127.7, 74.0, 72.3, 70.2, 55.5, 33.4, 31.9, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.6, 29.4, 26.4, 22.7, 14.1; IR (neat): 3373, 2926, 2855 cm^{-1}.

(*2E,4S,5S*)-5-Amino-1-benzyloxy-octadec-2-en-4-ol (6m):
^{1}HNMR (400 MHz, $CDCl_3$): δ 7.39-7.26 (m, 5H), 5.91 (dt, 1H, *J* = 15.4, 5.2 Hz), 5.74 (dd, 1H, *J* = 15.4, 5.6 Hz), 4.52 (s, 2H), 4.05 (d, 2H, *J* = 5.0 Hz), 3.91 (t, 1H, *J* = 5.6 Hz), 3.08 (br s, 3H), 2.72 (m, 1H), 1.58 (m, 1H), 1.42 (m, 1H), 1.26 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 133.1, 129.2, 128.4, 127.7, 127.7, 73.5, 72.3, 70.1, 55.7, 33.4, 31.9, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.6, 29.4, 26.1, 22.7, 14.1; IR (neat): 3356, 2925, 2854 cm^{-1}.

(*4S,5S*)-4-(3-Benzyloxy-(*E*)-propenyl)-3-(toluene-4-sulfonyl)-5-tridecyl-oxazolidin-2-one (10m): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, 1H, *J* = 8.4 Hz), 7.38-7.23 (m, 7H), 5.99 (dt, 1H, *J* = 15.4, 4.9 Hz), 5.71 (ddt, 1H, *J* = 15.4, 8.7, 1.7 Hz), 4.55 (s, 2H), 4.52 (m, 1H), 4.13 (m, 1H), 4.07 (dd, 1H, *J* = 4.9, 1.7 Hz), 2.41 (s, 3H), 1.64 (m, 2H), 1.26 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz).

(*4S,5S*)-4-(3-Benzyloxy-(*E*)-propenyl)-5-tridecyl-oxazolidin-2-one (12m):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 5H), 5.85 (dt, 1H, *J* = 15.5, 5.2 Hz), 5.71 (ddt, 1H, *J* = 15.5, 7.7, 1.4 Hz), 5.06 (s, 1H),4.53 (s, 2H), 4.20 (td, 1H, *J* = 7.2, 4.7 Hz), 4.03 (dd, 1H, *J* = 5.2, 1.4 Hz), 3.96 (br t, 1H, *J* = 7.4 Hz), 1.69 (m, 2H), 1.48 (m, 2H), 1.26 (m, 20H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 137.8, 131.4, 129.6, 128.5, 127.9, 127.8, 82.6, 72.8, 69.3, 60.2, 33.8, 31.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.4, 29.3, 24.9, 22.7, 14.1.

1-[2*S*-(3-Benzyloxy-(*E*)-propenyl)-3*S*-tridecyl-aziridin-1-yl]-ethanone (20m):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 6.03 (dt, 1H, *J* = 15.4, 5.6 Hz), 5.26 (ddt, 1H, *J* = 15.4, 5.3, 1.3 Hz), 4.54 (s, 2H), 4.02 (dd, 2H, *J* = 5.6, 1.3 Hz), 2.87 (m, 1H), 2.46 (td, 1H, *J* = 5.6, 2.8 Hz), 2.07 (s, 3H), 1.42 (m, 2H), 1.26 (m, 22H), 1.18 (t, 3H, *J* = 7.2Hz).

(*1S,2S*)-*N*-(5-Benzyloxy-2-hydroxy-1-tridecyl-pent-3-(*E*)-enyl)-acetamide (22m): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.85 (dt, 1H, *J* = 15.6, 5.6 Hz), 5.76 (dd, 1H, *J* = 15.6, 5.8 Hz), 5.90 (br d, 1H, *J* = 9.1 Hz), 4.50 (s, 2H), 4.17 (dd, 1H, *J* = 5.8, 4.0 Hz), 4.02 (d, 2H, *J* = 5.6 Hz), 3.88 (m, 1H), 1.98 (s, 3H), 1.60 (m, 1H), 1.48 (m, 1H), 1.26 (m, 22H), 0.88 (t, 3H, *J* = 7.2 Hz).

(*4S,5S*)-5-(3-Benzyloxy-(*E*)-propenyl)-4-tridecyl-oxazolidin-2-one (27m):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.27 (m, 5H), 5.97 (dt, 1H, *J* = 15.5, 5.0 Hz), 5.83 (ddt, 1H, *J* = 15.5, 7.8, 1.4 Hz), 5.09 (br s, 1H), 4.60 (t, 1H, *J* = 6.5 Hz), 4.54 (s, 2H), 4.07 (dd, 2H, *J* = 5.0, 1.4 Hz), 3.52 (app. q, 1H, *J* = 6.5 Hz), 1.30 (m, 2H), 1.26 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.3, 138.0, 131.8, 128.5, 127.9, 127.8, 127.7, 82.3, 72.6, 69.3, 58.4, 31.9, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 29.3, 25.6, 22.7, 14.1; IR (neat): 3396, 2925, 2854, 1756 cm^{-1}.

(*4S,5R*)-4-(3-Benzyloxy-(*E*)-propenyl)-5-tridecyl-oxazolidin-2-one (42m):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 5.83 (dt, 1H, *J* = 15.5, 5.2 Hz), 5.73 (ddt, 1H, *J* = 15.5, 7.8, 1.2 Hz), 5.03 (br s, 1H), 4.62 (dt, 1H, *J* = 7.8, 4.0 Hz), 4.53 (s, 2H), 4.28 (t, 1H, *J* = 7.8 Hz), 4.04 (dd, 2H, *J* = 5.2, 1.2 Hz), 1.66 (m, 2H), 1.48 (m, 2H), 1.26 (m, 20H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 137.9, 131.9, 128.5, 127.8, 127.7, 127.2, 80.3, 72.6, 69.4, 57.5, 31.9, 30.4, 29.7, 29.6, 29.6, 29.5, 29.4, 29.4, 29.3, 29.3, 25.7, 22.7, 14.1.

(*4R,5S*)-5-(3-Benzyloxy-(*E*)-propenyl)-4-tridecyl-oxazolidin-2-one (43m):
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.99 (dt, 1H, *J* = 15.6, 5.0 Hz), 5.83 (ddt, 1H, *J* = 15.6, 7.5, 1.4 Hz), 5.08 (br t, 1H, *J* = 7.7 Hz), 5.06 (br s, 1H), 4.54 (s, 2H), 4.08 (d, 2H, *J* = 5.0 Hz), 3.82 (td, 2H, *J* = 8.1, 5.8 Hz), 1.45 (m, 2H), 1.26 (m, 22H), 0.88 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.6,138.0, 133.0, 128.5, 127.8, 127.7, 124.6, 80.1, 72.5, 69.3, 56.1, 32.0, 31.0, 29.7, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4, 29.4, 26.2, 22.7, 14.1; IR (neat): 3261, 2922, 2851, 1757 cm^{-1}.

B.2 Reduction of vinylic amino alcohols (Chapter 9)

Typical procedure:
Amino alcohol (0.125 mmol), $NH_2NH_2{\cdot}H_2O$ (122 µL, 2.5 mmol) and H_2O_2 (35 % wt, 80 µL, 0.88 mmol) were dissolved in EtOH (95%, 0.5 mL). the mixture was heated to 100 °C in a sealed tube until finished (very substrate dependent, 1h to 3 days). Water (1 mL) and CH_2Cl_2 (2 mL) were added to the reaction mixture followed by filtration through an Extrelut® NT3 tube. The organic phase was eluted with CH_2Cl_2 (15 mL) and concentrated. No further purification was needed.

B.2.1 Reduction of 2 to 2′

(*3S,4R*)-4-Amino-1-phenyl-hexan-3-ol (2a'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.16 (m, 5H), 3.50 (m, 1H), 2.90 (m, 1H), 2.64 (m, 2H), 1.94 (br s, 3H), 1.67 (m, 2H), 1.48 (dqd, 1H, *J* = 13.8, 7.5, 4.1 Hz), 1.26 (ddq, 1H, *J* = 13.8, 9.1, 7.5 Hz), 0.92 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3, 128.4, 128.3, 125.7, 73.1, 57.2, 33.3, 32.5, 25.2, 11.0; IR (neat): 3341, 2971, 2849 cm^{-1}.

(*2R,3R*)-3-Amino-1-benzyloxy-pentan-2-ol (2b'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 4.55 (s. 2H), 3.67 (m, 1H), 3.61 (dd, 1H, *J* = 9.6, 3.1 Hz), 3.57 (dd, 1H, *J* = 9.6, 3.7 Hz), 2.79 (dt, 1H, *J* = 8.9, 4.5 Hz), 1.95 (br s, 3H), 1.57 (dqd, 1H, *J* = 13.8, 7.5, 4.3 Hz), 1.29 (ddq, 1H, *J* = 13.8, 8.9, 7.5 Hz), 0.96 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.0, 128.4, 127.7, 127.6, 73.5, 72.9, 71.5, 55.2, 26.3, 10.8; IR (neat): 3362, 2964, 2873 cm^{-1}.

(*2R,3S*)-3-Amino-6-benzyloxy-hexan-2-ol (2d'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 4.51 (s, 2H), 3.72 (dq, 1H, *J* = 6.4, 3.8 Hz), 3.50 (t, 2H, *J* = 6.2 Hz), 2.78 (m, 1H), 1.98 (br s, 3H), 1.78 (m, 1H), 1.63 (m, 1H), 1.54 (m, 1H), 1.31 (m, 1H), 1.09 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 128.7, 127.8, 127.6, 73.0, 70.2, 69.7, 55.8, 29.6, 26.8, 17.0; IR (neat): 3296, 2939, 2866 cm^{-1}.

(*2S,3S*)-3-Amino-1-benzyloxy-octadecan-2-ol (2l'):
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H), 4.55 (AB-q, 2H, *J* = 11.9 Hz), 3.65 (m, 1H), 3.61 (dd, 1H, *J* = 9.6, 3.2 Hz), 3.57 (dd, 1H, *J* = 9.6, 6.7 Hz), 2.87 (m, 1H), 1.80 (br s, 3H), 1.47 (m, 2H), 1.26 (m, 26H), 0.88 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.1, 128.5, 127.7, 127.7, 73.6, 73.2, 71.4, 53.7, 33.6, 31.9, 29.7, 29.7, 29.7, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.4, 26.5, 22.7, 14.2; IR (neat): 3361, 2925, 2854 cm^{-1}.

(*4S,5R*)-4-Amino-1-benzyloxy-octadecan-5-ol (2m'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 4.51 (s, 2H), 3.50 (t, 2H, *J* = 6.3 Hz), 3.46 (m, 1H), 2.77 (m, 1H), 1.82-1.48 (m, 7H), 1.27 (m, 24H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 128.4, 127.7, 127.6, 74.4, 73.0, 70.3, 55.3, 31.9, 31.5, 29.8, 29.7, 29.7, 29.7, 29.7, 29.7, 29.6, 29.4, 29.0, 26.9, 26.2, 22.7, 14.1; IR (neat): 3310, 2926, 2854 cm^{-1}.

B.2.2 Reduction of 3 to 3′

(*3S,4S*)-4-Amino-1-phenyl-hexan-3-ol (3a'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.16 (m, 5H), 3.31 (ddd, 1H, *J* = 9.1, 6.0, 3.4 Hz), 2.89 (ddd, 1H, *J* = 13.7, 10.2, 5.3 Hz), 2.70 (ddd, 1H, *J* = 13.7, 10.0, 6.6 Hz), 2.52 (m, 1H), 1.97 (br s, 3H), 1.80 (m, 1H), 1.71 (m, 1H), 1.61 (m, 1H), 1.26 (m, 1H), 0.94 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.4, 128.5, 128.4, 125.8, 72.7, 57.3, 36.4, 32.3, 27.0, 10.5; IR (neat): 3361, 2934, 2876 cm^{-1}.

(*2R,3S*)-3-Amino-1-benzyloxy-pentan-2-ol (3b'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 4.56 (AB-q, 2H, *J* = 12.0 Hz), 3.53 (m, 3H), 2.73 (m, 1H), 1.84 (br s, 3H), 1.55 (m, 1H), 1.29 (m, 1H), 0.95 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.1, 128.4, 127.7, 127.7, 73.5, 72.6, 72.2, 54.2, 27.3, 10.6; IR (neat): 3363, 2932, 2873 cm^{-1}.

(*2R,3R*)-3-Amino-6-benzyloxy-hexan-2-ol (3d'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.27 (m, 5H), 4.51 (s, 2H), 3.50 (t, 2H, *J* = 6.3 Hz), 3.41 (qui, 1H, *J* = 6.3 Hz), 2.44 (m, 1H), 1.89 (br s, 3H), 1.77 (m, 1H), 1.66 (m, 2H), 1.26 (m, 1H), 1.18 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4, 128.4, 127.7, 127.6, 76.8, 73.0, 70.3, 57.3, 31.2, 26.6, 20.1; IR (neat): 3362, 2928, 2857 cm^{-1}.

(*2S,3R*)-3-Amino-1-benzyloxy-octadecan-2-ol (3l'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 4.56 (AB-q, 2H, *J* = 12.0 Hz), 3.58 (dd, 1H, *J* = 7.3, 5.1 Hz), 3.51 (m, 2H), 2.80 (m, 1H), 1.46 (m, 2H), 1.26 (m, 26H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 128.5, 127.7, 127.7, 73.5, 72.7, 72.6, 52.6, 34.6, 32.0, 29.7, 29.7, 29.7, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.4, 26.3, 22.7, 14.2; IR (neat): 3353, 2925, 2854 cm^{-1}.

(*4S,5S*)-4-Amino-1-benzyloxy-octadecan-5-ol (3m'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 4.51 (s, 2H), 3.50 (t, 2H, *J* = 6.2 Hz), 3.25 (m, 1H), 2.55 (m, 1H), 1.75 (m, 1H), 1.65 (m, 1H), 1.48 (m, 2H), 1.26 (m, 24H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 128.4, 127.7, 127.7, 73., 73.0, 70.3, 55.3, 34.4, 31.9, 31.3, 29.8, 29.7, 29.7, 29.7, 29.7, 29.7, 29.6, 29.4, 26.6, 25.9, 22.7, 14.1; IR (neat): 3363, 2932, 2857 cm^{-1}.

B.2.3 Reduction of 5 to 5′

(*3S,4R*)-4-Amino-6-phenyl-hexan-3-ol (5a'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.17 (m, 5H), 3.39 (dt, 1H, *J* = 8.8, 3.9 Hz), 2.81 (m, 1H), 2.60 (ddd, 1H, *J* = 13.8, 9.6, 6.8 Hz), 1.79 (m, 1H), 1.70 (br s, 3H), 1.58 (dtd, 1H, *J* = 13.8, 9.6, 5.4 Hz), 1.42 (m, 2H), 0.97 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 128.4, 128.3, 125.9, 76.0, 54.6, 33.9, 32.9, 24.4, 10.5; IR (neat): 3348, 2963, 2875 cm^{-1}.

(*2S,3S*)-2-Amino-1-benzyloxy-pentan-3-ol (5b'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 5H), 4.53 (AB-q, 2H, *J* = 11.9 Hz), 3.59 (dd, 1H, *J* = 9.3, 4.1 Hz), 3.52 (dd, 1H, *J* = 9.3, 7.0 Hz), 3.47 (dt, 1H, *J* = 8.3, 4.3 Hz), 3.02 (dt, 1H, *J* = 7.0, 4.3 Hz), 1.71 (br s, 3H), 1.46 (m, 2H), 0.99 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.9, 128.5, 127.8, 127.7, 75.4, 73.5, 72.0, 54.1, 26.1, 10.4; IR (neat): 3364, 2937, 2874 cm^{-1}.

(*2S,3R*)-2-Amino-6-benzyloxy-hexan-3-ol (5d'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 4.52 (s, 2H), 3.53 (t, 2H, *J* = 6.2 Hz), 3.43 (dt, 1H, *J* = 9.5, 3.5 Hz), 2.96 (m, 1H), 1.81 (m, 1H), 1.77 (br s, 3H), 1.72 (m, 1H), 1.56 (m, 1H), 1.43 (m, 1H), 1.02 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.3, 128.4, 127.7, 127.6, 74.8, 73.0, 70.5, 50.6, 29.5, 26.6, 17.4; IR (neat): 3354, 2940, 2864 cm^{-1}.

(*2S,3R*)-2-Amino-1-benzyloxy-octadecan-3-ol (5l'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 4.53 (AB-q, 2H, *J* = 11.9 Hz), 3.58 (dd 1H, *J* = 9.3, 4.2 Hz), 3.55 (m, 1H), 3.52 (dd 1H, *J* = 9.3, 7.0 Hz), 3.00 (dt, 1H, *J* = 7.0, 4.2 Hz), 1.85 (m, 3H), 1.53-1.38 (m, 4H), 1.26 (m, 24H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 128.5, 127.8, 127.8, 73.9, 73.5, 71.9, 54.5, 33.3, 32.0, 29.7, 29.7, 29.7, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.4, 26.1, 22.7, 14.2; IR (neat): 3352, 2915, 2848 cm^{-1}.

(±)-5-Amino-1-benzyloxy-octadecan-4-ol (5m'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 4.52 (s, 2H), 3.53 (t, 2H, *J* = 6.1 Hz), 3.47 (dt, 1H, *J* = 9.9, 3.4 Hz), 2.76 (m, 1H), 1.87-1.54 (m, 5H), 1.42 (m, 2H), 1.26 (m, 24H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 128.4, 127.7, 127.6, 74.2, 73.4, 70.5, 55.5, 32.6, 31.9, 29.8, 29.7, 29.7, 29.7, 29.7, 29.6, 29.6, 29.4, 28.6, 26.6, 22.7, 14.1; IR (neat): 3354, 2924, 2854 cm^{-1}.

B.2.4 Reduction of 6 to 6′

(*3R,4R*)-4-Amino-6-phenyl-hexan-3-ol (6a'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.17 (m, 5H), 3.24 (m, 1H), 2.79 (ddd, 1H, *J* = 13.9, 10.0, 5.5 Hz), 2.65 (ddd, 1H, *J* = 13.9, 9.7, 6.6 Hz), 2.60 (m, 1H), 1.89 (m, 4H), 1.55 (m, 2H), 1.40 (m, 1H), 0.97 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.8, 128.5, 128.3, 126.0, 75.1, 54.6, 36.3, 32.7, 27.1, 10.1; IR (neat): 3362, 2935, 2876 cm^{-1}.

(*2S,3R*)-2-Amino-1-benzyloxy-pentan-3-ol (6b'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 4.54 (AB-q. 2H, *J* = 11.9 Hz), 3.58 (dd, 1H, *J* = 9.3, 4.0 Hz), 3.49 (dd, 1H, *J* = 9.3, 6.7 Hz), 3.42 (ddd, 1H, *J* = 9.6, 5.4, 4.3 Hz), 2.91 (m, 1H), 1.89 (br s, 3H), 1.48 (m, 2H), 0.98 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.9, 128.5, 127.8, 127.7, 73.6, 73.5, 73.2, 54.1, 27.2, 10.2; IR (neat): 3370, 2934, 2874 cm^{-1}.

(*2S,3S*)-2-Amino-6-benzyloxy-hexan-3-ol (6d'):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 4.52 (s, 2H), 3.53 (td, 1H, *J* = 6.2, 2.6 Hz), 3.19 (ddd 2H, *J* = 9.3, 6.3, 3.1 Hz), 2.73 (app. qui, 1H, *J* = 6.4 Hz), 1.88-1.62 (m, 3H), 1.55 (br s, 3H), 1.42 (m, 1H), 1.09 (d, 3H, *J* = 6.4 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4, 128.4, 127.7, 127.6, 75.6, 73.0, 70.5, 51.2, 31.2, 26.2, 21.0; IR (neat): 3371, 2944, 2869 cm^{-1}.

(*2S,3S*)-2-Amino-1-benzyloxy-octadecan-3-ol (6l'):
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 4.52 (AB-q, 2H, *J* = 11.3 Hz), 3.61 (m, 1H), 3.55 (m, 1H), 3.48 (m, 1H), 2.86 (dt, 1H, *J* = 6.4, 4.1 Hz), 1.55 (br s, 3H), 1.42 (m, 2H), 1.26 (m, 26H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 128.6, 128.5, 127.8, 127.8, 73.8, 73.5, 71.9, 53.5, 34.6, 31.9, 29.7, 29.7, 29.7, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.4, 26.3, 22.7, 14.1.

(*4S,5S*)-5-Amino-1-benzyloxy-octadecan-4-ol (6m'):
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.26 (m, 5H), 4.52 (s, 2H), 3.52 (m, 2H), 3.26 (ddd, 1H, *J* = 9.0, 5.6, 3.6 Hz), 2.53 (m, 1H), 1.87-1.49 (m, 5H), 1.43 (m, 2H), 1.27 (m, 24H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 128.4, 127.7, 127.6, 73.7, 72.9, 70.5, 55.6, 34.6, 31.9, 29.7, 29.7, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.4, 26.3, 26.3, 22.7, 14.1; IR (neat): 3332, 2924, 2853 cm^{-1}.

B.3 Analysis data of compounds 1k, 16-19, 21e, 23-26, 40, 41

(*2S,3S*)-2-Propyl-3-vinyl-oxirane (1k):
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.58 (ddd, 1H, *J* = 17.2, 9.9, 7.3 Hz), 5.45 (dd, 1H, *J* = 17.2, 1.6 Hz), 5.25 (dd, 1H, *J* = 9.9, 1.6 Hz), 3.09 (dd, 1H, *J* = 7.2, 2.2 Hz), 2.83 (dt, 1H, *J* = 5.9, 2.2 Hz), 1.57-1.47 (m, 4H), 0.96 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 118.7, 60.3, 58.7, 34.1, 19.3, 14.1.

(*4R,5S*)-5-Phenethyl-3-trityl-4-vinyl-[1,2,3]-oxathiazolidine 2,2-dioxide (16):
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (m, 6H), 7.32-7.12 (m, 12H), 7.04 (m, 2H), 5.72 (m, 1H), 4.99 (dd, 1H, *J* = 10.3, 1.1 Hz), 4.93 (dd, 1H, *J* = 16.9, 1.1 Hz), 3.57 (dd, 1H, *J* = 7.3, 1.1 Hz), 3.12 (ddd, 1H, *J* = 7.3, 4.8, 2.2 Hz), 2.67 (m, 1H), 2.52 (m, 1H), 1.81 (m, 2H).

(*3S,4R*)-4-(2,4-Dinitro-benzenesulfonyl)-amino-1-phenyl-hex-5-en-3-ol (17):
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, 1H, *J* = 2.2 Hz), 8.49 (dd, 1H, *J* = 8.6, 2.2 Hz), 8.25 (d, 1H, *J* = 8.6 Hz), 7.29 (m, 2H), 7.22 (t, 1H, *J* = 7.3 Hz), 7.16 (d, 1H, *J* = 7.1 Hz), 6.07 (br s, 1H), 5.65 (ddd, 1H, *J* = 17.4, 10.3, 7.8 Hz), 5.17 (d, 1H, *J* = 17.4 Hz), 5.13 (d, 1H, *J* = 10.3 Hz), 4.06 (dd, 1H, *J* = 7.8, 3.3 Hz), 3.77 (m, 1H), 2.79 (ddd, 1H, *J* = 14.2, 8.7, 6.1 Hz), 2.66 (m, 1H), 1.96 (br s, 1H), 1.80-1.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.6, 147.9, 140.8, 140.2, 132.7, 131.7, 128.6, 128.3, 126.9, 126.2, 120.6, 120.0, 72.8, 61.7, 35.1, 31.7; IR (neat): 3359, 2944, 2878, 1553, 1353 cm^{-1}.

(*2R,3R*)-1-(2,4-Dinitro-benzenesulfonyl)-2-phenethyl-3-vinyl-aziridine (18):
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, 1H, *J* = 2.2 Hz), 8.52 (dd, 1H, *J* = 8.6, 2.2 Hz), 8.38 (d, 1H, *J* = 8.6 Hz), 7.29-7.12 (m, 5H), 5.75 (ddd, 1H, *J* = 17.0, 10.3, 8.8 Hz), 5.43 (d, 1H, *J* = 17.0 Hz), 5.35 (d, 1H, *J* = 10.3 Hz), 3.23 (dd, 1H, *J* = 8.8, 4.7 Hz), 3.13 (dt, 1H, *J* = 7.7, 4.7 Hz), 2.84-2.67 (m, 2H), 2.36 (m, 1H), 1.89 (dq, 1H, *J* = 14.0, 7.8 Hz).

(*3S,4R*)-6-Phenyl-*N*^{3}-propyl-hex-1-ene-3,4-diamine (19):
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (m, 2H), 7.22 (m, 3H), 5.71 (ddd, 1H, *J* = 17.4, 10.5, 8.4 Hz), 2.87 (m, 1H), 2.82 (m, 1H), 2.69-2.58 (m, 2H), 2.50 (m, 1H), 1.79 (m, 3H), 1.62-1.44 (m, 2H), 1.29 (m, 2H), 0.94 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.2, 136.5, 128.4, 128.4, 125.8, 118.3, 66.2, 53.6, 49.2, 36.5, 32.9, 23.1, 11.8; IR (neat): 3297, 2932, 2872 cm^{-1}.

(*4S,5S*)-5-(3-Benzyloxy-(*E*)-propenyl)-4-ethyl-2,5-dimethyl-4,5-dihydrooxazole (21e): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H), 5.84 (m, 2H), 4.53 (s, 2H), 4.06 (d, 2H, *J* = 4.1 Hz), 3.67 (t, 1H, *J* = 6.9 Hz), 2.03 (s, 3H), 1.53 (m, 2H), 1.33 (s, 3H), 1.07 (t, 3H, *J* = 7.3 Hz).

(*1R,2R*)-*N*-(1-Vinyl-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetamide (23):
White solid, mp 145-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.14 (m, 4H), 5.85 (ddd, 1H, *J* = 17.1, 10.1, 8.1 Hz), 5.46 (br s, 1H), 5.24 (dt 1H, *J* = 10.1 Hz), 5.04 (dt, 2H, *J* = 17.0, 1.5 Hz), 4.19 (ddd, 2H, *J* = 16.2, 8.2, 3.0 Hz), 3.34 (br t, 1H, *J* = 7.5 Hz), 2.97 (dt, 1H, *J* = 17.3, 6.4 Hz), 2.86 (dt, 1H, *J* = 17.3, 6.2 Hz), 1.99 (s, 3H), 2.20 (dtd, 1H *J* = 13.3, 6.4, 3.0 Hz), 1.79 (ddt, 1H *J* = 16.2, 13.3, 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 140.0, 135.6, 135.2, 130.1, 129.0, 126.0, 126.0, 117.7, 50.2, 49.1, 26.6, 26.0, 23.6; IR (neat): 3305, 2939, 2850, 1645 cm^{-1}; $[\alpha]_D$: -58.0 (*c* 0.23, CH_2Cl_2); HRMS (CI+): Exact mass calculated for $C_{14}H_{18}NO$ (M+H): 216.1388. Found: 216.1389.

***N*-[4-Benzyloxy-1(*S*)-(1(*R*)-hydroxy-propyl)-1-methyl-2-(*E*)-butenyl]-acetamide (24):** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.81 (d, 1H, *J* = 15.9 Hz), 5.70 (dt, 1H, *J* = 15.9, 5.5 Hz), 5.65 (br s, 1H), 4.52 (s, 2H), 4.31 (br d, 1H, *J* = 9.1 Hz), 4.05 (d, 2H, *J* = 5.5 Hz), 3.34 (m, 1H), 2.00 (s, 3H), 1.55 (m, 2H), 1.47 (s, 3H), 1.01 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 135.5, 128.5, 127.9, 127.9, 127.8, 126.6, 78.7, 72.6, 70.3, 62.2, 24.9, 24.1, 22.5, 11.2; IR (neat): 3307, 2935, 2875 cm^{-1}.

(*1S,2R*)-*N*-(5-Benzyloxy-1-ethyl-2-hydroxy-2-methyl-3-*(E)*-pentenyl)-acetamide (25): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 5.87 (dt, 1H, *J* = 15.6, 5.5 Hz), 5.77 (d, 1H, *J* = 15.6 Hz), 5.48 (br d, 1H, *J* = 9.8 Hz), 4.52 (s, 2H), 4.05 (dd, 2H, *J* = 5.5, 1.2 Hz), 3.80 (td, 1H, *J* = 9.8, 2.8 Hz), 2.29 (br s, 1H), 2.04 (s, 3H), 1.68 (dq, 2H, *J* = 7.4, 2.8 Hz), 1.29 (s, 3H), 0.90 (t, 3H, *J* = 7.4 Hz); ^{13}CNMR (125 MHz, $CDCl_3$): δ 171.1, 138.2, 136.6, 128.4, 127.7, 127.7, 125.8, 75.4, 72.4, 70.1, 58.7, 26.8, 23.3, 23.1, 11.1; IR (neat): 3314, 2932, 2872, 1650 cm^{-1}.

(*4S,5S*)-3-Acetyl-5-(3-benzyloxy-(*E*)-propenyl)-4-ethyl-5-methyl-oxazolidin-2-one (26): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 5.91 (dd, 1H, *J* = 16.0, 0.6 Hz), 5.82 (dtd, 1H, *J* = 16.0, 5.2, 0.6 Hz), 4.51 (s, 2H), 4.06 (d, 2H, *J* = 5.1 Hz), 3.79 (dd, 1H, *J* = 11.2, 2.3 Hz), 2.04 (s, 3H), 1.58 (s, 3H), 1.39-1.21 (m, 2H), 1.02 (t, 3H, *J* = 7.3 Hz).

2-Amino-1-benzyloxy-octadec-3-en-5-ol (40):
Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 5.67 (m, 2H), 4.54 (s, 2H), 4.08 (dt, 1H, *J* = 6.7, 6.1 Hz), 3.63 (m, 1H), 3.49 (m, 1H), 3.29 (td, 1H, *J* = 9.0, 1.6 Hz), 1.57 (br s, 3H), 1.351 (m, 2H), 1.26 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 134.2, 131.7, 128.4, 127.7, 127.7, 75.3, 73.3, 72.6, 52.8, 37.4, 31.9, 29.7, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.4, 25.4, 22.7, 14.1; IR (neat): 3422, 2919, 2848 cm^{-1}.

***N*-((*1S,2R,3E*)-1-Benzyloxymethyl-2-hydroxy-heptadec-3-enyl)-trifluoro-acetamide (41):** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.26 (m, 5H), 7.01 (br d, 1H, *J* = 8.5 Hz), 5.77 (dtd, 1H, *J* = 15.4, 6.9, 1.2 Hz), 5.43 (ddt, 1H, *J* = 15.4, 6.3, 1.2 Hz), 4.51 (AB-q, 2H, *J* = 11.7 Hz), 4.23 (m, 1H), 4.03 (ddt, 1H, *J* = 8.5,

5.1, 2.9 Hz), 3.89 (dd, 1H, *J* = 9.9, 2.9 Hz), 3.62 (dd, 1H, *J* = 9.9, 2.9 Hz), 2.69 (br d, 1H, *J* = 8.4 Hz), 2.02 (q, 2H, *J* = 6.9 Hz), 1.32 (m, 2H), 1.26 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.7, 136.9, 134.8, 128.7, 128.3, 128.2, 127.9, 127.9, 73.8, 73.3, 68.5, 53.1, 32.2, 31.9, 29.7, 29.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 29.0, 22.7, 14.1; IR (neat): 3294, 2919, 2851, 1699, 1183 cm^{-1}.