Development of Simple and Efficient Synthetic Strategies for Production of Fine Chemicals of Pharmaceutical Relevance

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Metal-Mediated Allylation Combined with Applied Catalysis

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Helky laulu Auran rantain
silmä kirkas salamoi,
kaiu maine kauas kantain
minkä kunto kansan voi!
Täällä Suomen synnyinmuistot,
täällä työn ja tiedon puistot
virttä vapauden soi
virttä vapauden soi.
:,: Helky laulu, kaiu maine,
virttä vapauden soi.:,:

Auran rantamilla tähti
syttyi päälle Suomenmaan,
Auran rantamilta lähti
onni maahan ihanaan.
Kristinuskon, tiedon valta
nosti heimot kaikkialta
turvaks armaan synnyinmaan
turvaks armaan synnyinmaan.
:,: Helky laulu, kaiu maine,
virttä vapauden soi.:,:

Puhkes uudet tertut tuomeen,
aika aatteet uudet toi,
Auran rantamilta Suomeen
koitti kirkas huomenkoi.
Täällä Suomen synnyinmuistot,
täällä työn ja tiedon puistot
virttä vapauden soi
virttä vapauden soi.
:,: Helky laulu, kaiu maine,
virttä vapauden soi.:,:

Väinö Kulo (Kolkkala)

PREFACE

The present work was carried out at the Laboratory of Organic Chemistry, Department of Chemical Engineering, Åbo Akademi University between the years 2006 and 2011. Financial support from Åbo Akademi University, the National Graduate School of Organic Chemistry and Chemical Biology, the Swedish Academy of Engineering Sciences in Finland (STV), the Research Institute of the Åbo Akademi Foundation, the Finnish Foundation of Technology Promotion (TES) and the Association of Finnish Chemical Societies is gratefully acknowledged.

I wish to express my sincerest gratitude to my supervisor, Professor Reko Leino. Your enthusiasm is infectious! Thank you for your support during these years and for all the great opportunities you create for all of us! The greatest one during my doctoral studies was certainly the short term visit to Eindhoven University of Technology in late 2007. Professor Dieter Vogt, Professor Christian Müller (currently at The Free University of Berlin) and the whole HomCat group back in those days: thank you for sharing your professionalism what comes to hydroformylations and homogeneous catalysis in general. The time I spent in Eindhoven had an enormous impact on my thesis work! I would also like to thank Professor János Wölfling, Professor Gyula Schneider and Professor István Zupkó at the University of Szeged, Professor Liisa Kanerva and MSc Ari Hietanen at the University of Turku and Dr Johannes Dieterich at the University of Göttingen and all other co-authors and co-workers for the fruitful collaboration that has significantly enhanced the scientific impact of this thesis.

I am very thankful to Professor Pavel Kočovský and Professor Guy Lloyd-Jones for reviewing my thesis and for your valuable comments that encouraged me to improve it. Furthermore, I wish to express my gratitude to Professor Shū Kobayashi for accepting to act as my opponent.

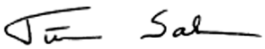
The former and present members of the team United Organic Tigers are all equally acknowledged for making the everyday life in the lab so much more cheerful. Dr Sara Rosenberg, my mentor, is especially acknowledged for introducing me into the world of Barbier-type allylations and for being my big sister at work.

Since January 2008, I have had an honor to be a member of the dynamic Organic Chemistry teaching group. These activities, though not directly visible in this thesis, have taught me a lot. I am truly thankful for all the great discussions and the enormous support from my fellow teachers: Reko, Leif, Pancho, Patrik, Janne, Peter, Axel et al. It has not always been so easy to balance between teaching and doctoral studies, but still, I would not give any moment (or student!) away.

I am truly thankful for all my friends and for all the unforgettable moments I have spent with you during these, someone could call them rather hectic, years. Especially Suski and Johanna (a.k.a. SuJo): life simply feels so much better after our weekly outdoor (and sometimes indoor) activities. Thanks a trillion for your support!

My warmest hugs go to my family. Thank you for always supporting me, whenever, wherever! Mom and Dad: thank you for everything you have given to me since the day I was born, most importantly the roots and the wings! Antti and Anna: thank you for being you! Whatever happens, I know you are near. It feels good to be your little sister! Tuulia, my lovely goddaughter: a very special hug goes to you! But above all, I wish to thank you, Mikki, for your endless support, optimism and understanding during this project. Thank you for waking me up in the mornings and for teaching me what really matters in life.

Åbo, April 2012



ABSTRACT

Development of novel synthesis procedures that can be applied in the synthesis of pharmaceutically relevant targets is of topical interest. The ultimate goal in this context is not only to access the target products but, more importantly, to develop sustainable synthesis routes aiming at fulfilling the criteria for the ideal synthesis. In this doctoral thesis, new synthesis routes for production of fine chemicals with pharmaceutical relevance have been developed by combining virtually simple transformations into novel reaction sequences. All reaction sequences described in this thesis were initiated by Barbier-type metal-mediated allylation of selected aldehydes or aldimines. The obtained products containing a carbon–carbon double bond, accompanied by hydroxyl or amino group, were then further derivatized by utilizing some well-known catalytic tools from the organic chemistry toolbox.

In the first part of this thesis, metal-mediated allylation of unprotected carbohydrates was combined with a hydroformylation reaction yielding, as a result of intramolecular cyclization, highly functionalized lactol products. The reaction sequence can be performed in aqueous media without the need for protective group manipulations thus significantly increasing the attractiveness of this approach. In addition, the conformation of the homoallylic polyols derived from common monosaccharides is briefly discussed.

Barbier-type metal-mediated allylation was likewise applied for transformation of an estradiol based steroid derivative bearing aldehyde functionality. The homoallylic products were then further derivatized by utilizing ring-closing olefin metathesis and catalytic asymmetric dihydroxylation. Furthermore, the cytotoxic activities of the synthesized steroid derivatives with increased hydrophilicity are shortly presented herein.

In the last part of this thesis, synthesis of a series of homoallylic amines by Barbier-type metal-mediated allylation of *N*,*N*-dimethylsulfamoyl protected aldimines followed by facile deprotection by transamination is described. Furthermore, enzymatic kinetic resolution utilizing an acyl donor with a terminal double bond was applied for the racemic amines giving access to highly valuable enantiopure amines and amides that can further be derivatized to enantiopure nitrogen-containing heterocycles using ring-closing olefin metathesis as a key step. Finally, this synthesis route, without the enzymatic kinetic resolution, was applied for the synthesis of naturally occurring tobacco alkaloids (±)-anatabine and (±)-anabasine.

SAMMANFATTNING

Utvecklandet av nya syntesmetoder som kan tillämpas vid syntes av farmaceutiskt relevanta målstrukturer är högaktuellt. I detta sammanhang är den ultimata målsättningen dock inte endast en lyckad syntes av målmolekylen, utan det är allt viktigare att utveckla syntesrutter som uppfyller kriterierna för den hållbara utvecklingen. I denna doktorsavhandling har nya syntesrutter för produktion av finkemikalier med farmaceutisk relevans utvecklats genom att kombinera förhållandevis enkla transformationer till nya reaktionssekvenser. Alla reaktionssekvenser som diskuteras i denna avhandling påbörjades med en metallförmedlad allylering av utvalda aldehyder eller aldiminer. De erhållna produkterna innehållende en kol-koldubbelbindning med en närliggande hydroxyl- eller aminogrupp modifierades sedan vidare genom att tillämpa välkända katalytiska reaktioner.

I avhandlingens första del kombinerades den metallförmedlade allyleringen av oskyddade kolhydrater med en hydroformyleringsreaktion, vilket resulterade i polyhydroxylerade laktolprodukter efter en intramolekylär ringslutning. Reaktionssekvensen kan utföras i vattenmiljö utan skydssgruppsmanipuleringar, vilket gör denna reaktionssekvens avsevärt mera lockande. Utöver detta diskuteras konformationen för utvalda homoallyliska polyoler kortfattat i denna avhandling.

Den metallförmedlade allyleringen tillämpades även för ett estradiolderivat innehållande en aldehydgrupp. De erhållna homoallyliska produkterna derivatiserades vidare genom att använda ringslutningsmetates och asymmetrisk dihydroxylering. Utöver detta presenteras de cytotoxiska aktiviteterna för de syntetiserade steroidderivaten med ökad vattenlöslighet kort häri.

I avhandlingens sista del diskuteras syntesen av en serie homoallyliska aminer genom en metallförmedlad allylering av *N*,*N*-dimetylsulfamoyl-skyddade aldiminer följt av en effektiv klyvning av skyddsgruppen genom transaminering. De motsvarande aminerna kan erhållas i enantioren form efter en framgångsrik enzymatisk kinetisk resolvering. Genom att använda en acyldonor med en terminal kol-koldubbelbindning blir även resolveringsprodukten (amiden) en intressant byggsten för ytterligare modifieringar. Den enantiorena amiden och motsvarande aminen kan omvandlas vidare till kväveheterocykliska föreningar genom att använda ringslutningsmetates som nyckelsteg. Slutligen tillämpades denna syntesrutt för syntes av två naturligt förekommande alkaloider (±)-anatabin och (±)-anabasin.

LIST OF ORIGINAL PUBLICATIONS AND MANUSCRIPTS

I Saloranta, T.; Müller, C.; Vogt, D.; Leino, R. **Converting Unprotected Monosaccharides into Funtionalised Lactols in Aqueous Media: Metal-Mediated Allylation Combined with Tandem Hydroformylation-Cyclisation**, *Chem. Eur. J.* **2008**, *14*, 10539–10542.

II Saloranta, T.; Dieterich, J.; Leino, R. et al. **Conformational Study on the Homoallylic Polyol Derived from Mannose and the Aggregation Behavior of the Same**, *manuscript in preparation.*

III Saloranta, T.; Zupkó, I.; Rahkila, J.; Schneider, G.; Wölfling, J.; Leino, R. **Increasing the Amphiphilicity of an Estradiol Based Steroid Structure by Barbier-Allylation – Ring-Closing Metathesis – Dihydroxylation Sequence**, *Steroids* **2012**, *77*, 110–117.

IV Källström, S.; Saloranta, T.; Minnaard, A. J.; Leino, R**. Indium- and Zinc-Mediated Barbier-Type Allylations of an *N*,*N*-(Dimethylsulfamoyl)-Protected Aldimine and Subsequent Deprotection**, *Tetrahedron Lett.* **2007**, *48*, 6958–6961.

V Hietanen, A.; Saloranta, T.; Rosenberg, S.; Laitinen, E.; Leino, R.; Kanerva, L. T. **Synthesis of Enantiopure Benzyl Homoallylamines by Indium-Mediated Barbier-Type Allylation Combined with Enzymatic Kinetic Resolution: Towards Chemoenzymatic Synthesis of N-Containing Heterocycles**, *Eur. J. Org. Chem.* **2010**, 909–919.

VI Saloranta, T.; Leino, R. **From Building Block to Natural Products: A Short Synthesis and Complete NMR Spectroscopic Characterization of (±)-Anatabine and (±)-Anabasine**, *Tetrahedron Lett.* **2011**, *52*, 4619–4621.

CONTRIBUTION OF THE AUTHOR

This thesis is based on five original publications and one manuscript. The author of this thesis is the main author in four original publications (I, III, V, VI) and in the manuscript (II), and the second author in one publication (IV). The author is responsible for all the experimental work presented in this thesis with the following exceptions: the geometry optimization (Chapter 4), the biological tests (Chapter 5) and the enzymatic work (Chapter 6). However, for these exceptions apply that the author of this thesis contributed in planning of these experiments as well as writing of the results.

RELATED PUBLICATION (not discussed in this thesis)

I Långvik, O.; Saloranta, T.; Kirilin, A.; Liljeblad, A.; Mäki-Arvela, P.; Kanerva, L. T.; Murzin, D.; Leino, R. **Dynamic Kinetic Resolution of *rac*-2-Hydroxy-1-indanone Using Heterogeneous $Ru(OH)_3/Al_2O_3$ Racemization Catalyst and Lipase**, *ChemCatChem* **2010,** *2*, 1615–1621.

LIST OF RELATED CONFERENCE CONTRIBUTIONS

I Källström, S.; Saloranta, T.; Minnard, A. J.; Leino, R. **Indium- and Zinc-Mediated Barbier-Type Allylations of an *N*,*N*-(Dimethylsulfamoyl)-Protected Aldimine**, *The X Spring Meeting of Synthetic Chemistry*, May 23 – May 24 **2007**, Helsinki, Finland. Oral presentation.

II Källström, S.; Saloranta, T.; Minnaard, A. J.; Leino, R. **Synthesis of Spirocyclic Ethers and Substituted Piperidines by Catalytic Ring-Closing Metathesis of Diallyl Substituted Cyclohexanes and Amines**, *Europacat VIII*, August 26 – August 31 **2007**, Turku, Finland. Poster presentation.

III Saloranta, T.; Müller, C.; Leino, R.; Vogt, D. **Metal-mediated Allylation of Unprotected Monosaccharides and Subsequent Hydroformylation**, *Schuit Institute of Catalysis (SKI) Conference*, November 15 – November 16 **2007**, Sint-Michielsgestel, The Netherlands. Poster presentation.

IV Saloranta, T.; Müller, C.; Vogt, D.; Leino, R. **Metal-Mediated Allylation of Unprotected Monosaccharides Combined with Subsequent Hydroformylation**, *COST D40 Innovative Catalysis: New Processes and Selectivities – Innovation II*, May 20 – May 22 **2008**, Tarragona, Spain. Oral presentation.

V Saloranta, T.; Müller, C.; Vogt, D.; Leino, R. **Metal-Mediated Allylation of Unprotected Monosaccharides Combined with Subsequent Hydroformylation**, *International Symposium on Homogenous Catalysis*, July 6 – July 11 **2008**, Florence, Italy. Poster presentation.

VI Saloranta, T. **Conversion of Biomass into Fine Chemicals – Hydroformylation of Carbohydrate Derivatives in Aqueous Media**, *COST D40 Innovative Catalysis: New Processes and Selectivities – Joint Meeting for Young Co-Workers*, April 27 – April 28 **2009**, Bratislava, Slovakia. Oral presentation.

VII Rosenberg, S.; Saloranta, T.; Hietanen, A.; Laitinen, E.; Kanerva, L. T.; Leino, R. **Towards Enantiopure Substituted N-Containing Heterocycles – Catalysis as Toolbox in Organic Synthesis**, *COST D40 Innovative Catalysis: New Processes and Selectivities – Innovation III*, May 26 – May 28 **2009**, Turku, Finland. Poster presentation.

VIII Rosenberg, S.; Saloranta, T.; Hietanen, A.; Laitinen, E.; Kanerva, L. T.; Leino, R. **Synthesis of Enantiopure Substituted N-Containing Heterocycles**, The *XI Spring Meeting of Synthetic Chemistry*, June 8 – June 9 **2009**, Espoo, Finland. Poster presentation.

IX Saloranta, T.; Hietanen, A.; Rosenberg, S.; Kanerva, L. T.; Leino, R. **Synthesis of Enantiopure Benzyl Homoallylamines by Combined Barbier-Type Allylation/Enzymatic Kinetic Resolution: Toward Chemoenzymatic Synthesis of N-Containing Heterocycles**, *239th ACS National Meeting*, March 21 – March 25 **2010**, San Francisco, CA, USA. Oral presentation.

X Saloranta, T.; Rahkila, J.; Schneider, G.; Wölfling, J. Leino, R. **Modification of an Estradiol Based Steroid Structure – Towards Increased Amphiphilicity**, *The XII Spring Meeting of the Division of Synthetic Chemistry*, June 7 – June 8 **2011**, Jyväskylä, Finland. Poster presentation.

XI Saloranta, T.; Leino, R. **A Journey Towards N-Containing Heterocycles – Synthesis of (±)-Anatabine and (±)-Anabasine**, *The 17th European Symposium on Organic Chemistry*, July 10 – July 15 **2011**, Crete, Greece. Poster presentation.

LIST OF ABBREVIATIONS

AD	asymmetric dihydroxylation
BHT	butylated hydroxytoluene
CAL-A	*Candida antarctica* lipase A
CAL-B	*Candida antarctica* lipase B
calcd	calculated
conv	conversion
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DQF-COSY	double-quantum filtered correlation spectroscopy
ee	enantiomeric excess
equiv	equivalent
ESI	electrospray ionization
HMBC	heteronuclear multiple bond correlation
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum coherence
Lipase PS-D	*Burkholderia cepacia* lipase immobilized on Celite
MD	molecular dynamics
mp	melting point
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhouser effect spectroscopy
RCM	ring-closing metathesis
rt	room temperature
SAR	structure–activity relationship
SEM	standard error of the mean
SET	single electron transfer
TBME	*tert*-butyl methyl ether
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TOF	time of flight
p-TSA	*p*-toluenesulfonic acid
vol	volume

CONTENTS

1 PRELUDE

A pivotal milestone in science that started a new era in chemistry dates back to the early 19th century. Synthetic organic chemistry was born as its own discipline. The synthesis of urea from inorganic starting materials by Friedrich Wöhler (1828) and the synthesis of acetic acid from elemental carbon by Hermann Kolbe (1845) initiated a field of science that has evolved remarkably during the last decades and resulted in a number of achievements that have strongly contributed to the well-being of modern societies.[1]

Synthetic organic chemistry can roughly be divided into two subdisciplines: development of synthetic tools (methods) and application of the tools in the synthesis of target molecules. Naturally, the two subdisciplines often overlap and merge back into a single discipline. To exemplify, total synthesis of complex natural products, often regarded as the most challenging endeavor in synthetic organic chemistry, provides not only access to the desired target molecules but also contributes to the evolution and development of more efficient synthetic strategies.[2] However, much of the fundamental research devoted to the development of novel synthetic methodologies is often exemplified by the use of relatively simple model substrates. Nevertheless, the ultimate goal in this research field as well is to contribute to the synthesis of more complex targets with biological and/or pharmaceutical relevance by executing (total) synthesis of natural products or other predefined targets.

In current synthetic chemistry research, the main emphasis is shifting from a successful synthesis of a target to the ideal pathway towards the target. An ideal organic synthesis was described in 1996 by Paul A. Wender as follows: The target molecule is prepared from readily available, inexpensive starting materials in one simple, safe, environmentally acceptable and resource-effective operation that proceeds quickly and in quantitative yield.[3] Despite all the great efforts in the field of synthetic organic chemistry, the ideal synthesis, as described above, will probably never be realized. However, the ideal synthesis as a concept has inspired and guided the development of synthetic methods that could show the way towards this ambitious goal. In this context, one of the most prominent tools is catalysis, more precisely application of catalysis in the synthesis of complex target structures and development of feasible catalytic processes with high efficiency and minimal waste generation.[4]

As stated above, in an ideal organic synthesis, the target molecule is prepared in *one* simple, safe, environmentally acceptable and resource-effective operation. In other words, resource consuming purifications and isolations of the intermediate products should be avoided. The ideal synthesis

hence follows the syntheses performed by *Nature* proceeding as multistep-cascades with maximum selectivity controlled by the sequences of enzymatic transformations.[5] This type of approaches, when applied in chemical syntheses, lead to obvious advantages such as increased safety and efficiency which, consequently, decrease the production costs.

In order to implement a cascade approach in chemical manufacturing, the individual transformation steps must be properly known and mechanistically understood. Moreover, each step should be optimized to work with excellent conversion and selectivity to minimize the formation of side products and to maximize the yield of the final product. Hence, in an optimal reaction sequence, the synthetic organic chemist's toolbox is utilized in such a fashion that each transformation is driven by the most suitable catalytic tool. Moreover, by utilizing catalytic tools that are mutually compatible, practical reaction cascades can be developed and the ultimate goal, *the ideal synthesis,* becomes closer.

1.1 References and Notes

[1] Nicolau, K. C.; Montagnon, T. *Molecules That Changed the World;* Wiley-VCH: Weinheim, 2008.

[2] See for example: (a) Nicolaou, K. C.; Sorensen, E.J. *Classics in Total Synthesis: Targets, Strategies, Methods*; VCH: Weinheim, 1996. (b) Nicolaou, K. C.; Sorensen, E.J. *Classics in Total Synthesis II: More Targets, Strategies, Methods*; Wiley-VCH: Weinheim, 2003. (c) Nicolau, K. C.; Chen, J. S. *Classics in Total Synthesis III: Further Targets, Strategies, Methods*; Wiley-VCH: Weinheim, 2011.

[3] Wender, P. A. *Chem. Rev.* **1996**, *96*, 1–2.

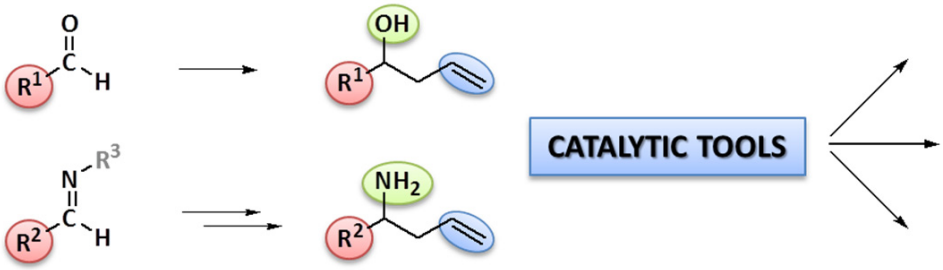
[4] For general introduction, see for example: Cybulski, A.; Moulijn, J. A.; Sharma, M. M.; Sheldon, R. A. *Fine Chemicals Manufacture Technology and Engineering;* Elsevier: Amsterdam, The Netherlands, 2001.

[5] See also: Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193–205.

2 INTRODUCTION

2.1 Aim of This Thesis

In the work discussed in this thesis, new routes towards synthesis of fine chemicals of pharmaceutical relevance were explored by combining virtually simple transformations into novel reaction sequences. Initially, metal-mediated Barbier-type allylation of selected aldehydes and aldimines was examined. The obtained products containing a carbon–carbon double bond, accompanied by a hydroxyl or amino group, tempt to explore some further derivatizations by utilizing the catalytic tools from the organic chemistry toolbox (Scheme 2.1). In this chapter, the toolbox applied in this thesis is generally presented in light of the preceding literature.

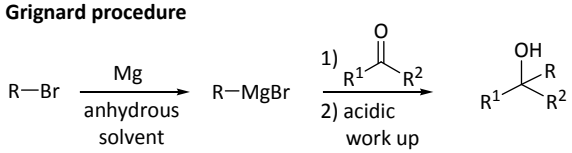


Scheme 2.1. Schematic presentation of the aim of this thesis.

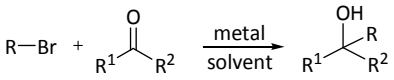
2.2 Barbier Reaction – a Practical Tool for Carbon–Carbon Bond Formation

Formation of new carbon–carbon bonds is one of the key transformations in synthetic organic chemistry. The most utilized way of creating new C–C bonds is to add a carbon nucleophile to a carbonyl group, traditionally carried out by Grignard reaction. Barbier reaction is formally an equivalent to the Grignard reaction with the exception that the organometallic compound does not need to be synthesized in a separate step but the reacting species, stemming from alkyl or allyl halide and a metal, can be formed *in situ* (Scheme 2.2).

Grignard procedure

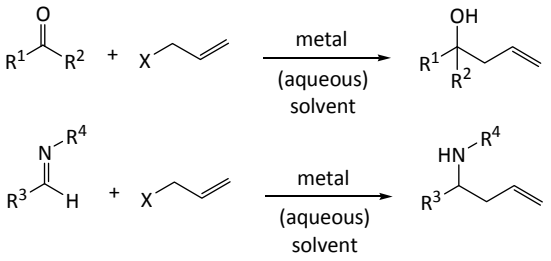


Barbier procedure



Scheme 2.2. Addition of a carbon nucleophile to a carbonyl compound: two-step Grignard versus one-step Barbier procedure.

To be correct, however, the Barbier reaction, named after the French chemist Philippe Barbier, was described for the first time by the Russian chemist Alexander Mikhailovich Zaitsev in the 1870s,[1] as recently pointed out by Lewis.[2] In the original Zaitsev procedure for the synthesis of tertiary alcohols, zinc was employed as the metal. More than 20 years after Zaitsev's first reports, in 1899, Philippe Barbier likewise published a one-pot procedure for the reaction between a ketone and an alkyl halide in the presence of magnesium metal yielding an alcohol,[3] the procedure generally regarded as the original Barbier reaction.[4] One year later, Victor Grignard, a student of Barbier, published a two-step procedure for the same reaction known as Grignard reaction.[5] The Grignard procedure quickly became the leading protocol to create new carbon–carbon bonds,[6] and is still not only a text book favorite, but a widely utilized reaction in synthetic organic chemistry finding applications in industrial processes as well.[7] The main disadvantages associated with the Grignard reaction employing magnesium metal are the anhydrous conditions required, and the fact that a number of common functional groups such as those containing acidic protons (e.g. -OH, -NH_2, -COOH) are not tolerated under the reaction conditions. The Barbier-type procedure, on the contrary, typically mediated by indium, zinc or tin, does not need to be performed under strictly anhydrous conditions but is, in fact, facilitated by water in some cases.[8] The Barbier-type reaction has gained most interest in the coupling of reactive allyl halides to carbonyl compounds or imines (Scheme 2.3).



Scheme 2.3. Barbier-type allylation of carbonyl compound and imine.

2.2.1 Mechanism of the Barbier-Type Allylation

While the Barbier-type allylation is well known in the literature and has been applied for a wide range of substrates, the actual mechanism of the reaction is still under debate. During the past 30 years, a number of contributions dealing with the mechanism of Barbier-type reaction have appeared in the literature.[9] Generally, three alternative mechanisms for the reaction have been proposed:

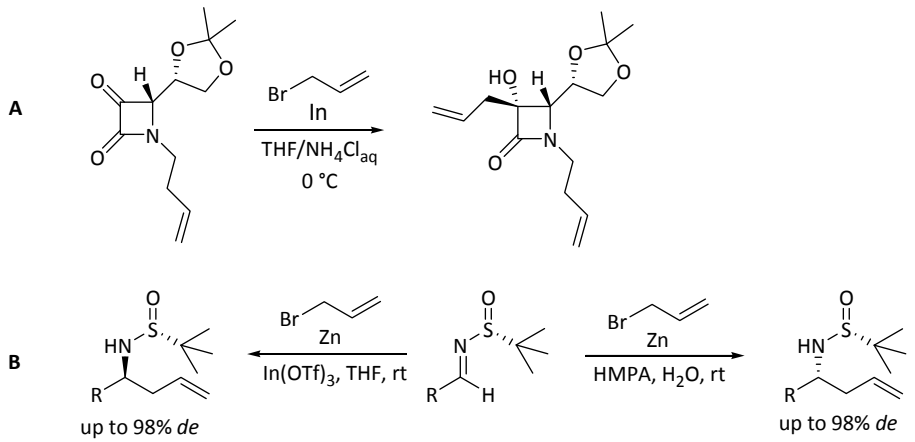
1. Covalent model including discrete allylmetal species
2. Pathway involving a single-electron transfer (SET) with the radical anion coordinated on the metal surface reacting with the carbonyl compound
3. Free radical mechanism

The free radical model is the least probable since it contradicts with the chemoselectivity of the reaction. The covalent model and the SET-pathway seem more probable and the actual mechanism has proven to be dependent at least on the metal and the solvent used. Recently, it has been shown by combined experimental and theoretical mechanistic investigations that the Barbier-type allylation in aqueous media proceeds through a discrete allylmetal species when indium, zinc, tin, antimony or bismuth are used as the mediating metal.[9g] However, when magnesium is used under Barbier conditions, a radical anion is formed as the selectivity determining event indicating an SET-process. This conclusion was supported already by the earlier work of Madsen and Norrby et al., where the zinc-mediated Barbier-type reaction yielding vicinal amino alcohols was studied in detail.[10] The Hammett study performed did not give any indication on radical mechanism but an organometallic reagent was suggested to react with an imine.

2.2.2 Barbier-Type Allylation in Action

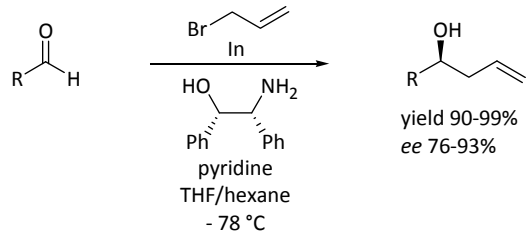
The Barbier-type allylation is applicable for a wide range of substrates bearing aldehyde or ketone functionalities. Likewise, activated imines can be allylated under Barbier-type conditions yielding the corresponding homoallylic amines. The obtained homoallylic alcohols and amines are valuable building blocks as they contain a carbon–carbon double bond accompanied by nearby hydroxyl or amino group that allow a number of further synthetic transformations to be explored.

The stereochemical outcome of the Barbier-type allylation is often substrate dependent and may involve diastereoselective induction. This has been utilized not only in the synthesis of small building blocks, but also in the synthesis of more complex targets. To exemplify, Alcaide et al. have reported a metal-mediated allylation of enantiopure azetidine diones with complete stereocontrol yielding densely functionalized 3-substituted 3-hydroxy-β-lactams (**A**, Scheme 2.4).[11] The Barbier-type allylation of activated imines can be carried out in a diastereoselective fashion by introducing a chiral auxiliary on the nitrogen atom.[12] Remarkably, Xu and Lin have described a diastereoselective allyation protocol of chiral (*R*)-*N*-*tert*-butanesulfinyl imines that allows the preparation of both stereoisomers by simply varying the reaction conditions (**B**, Scheme 2.4).[12c]



Scheme 2.4. Barbier-type allylation in action.

For achiral substrates, the stereochemistry is, in general, difficult to control. In the presence of chiral additives, however, particularly by using chiral amino alcohols, good to excellent enantioselectivities have been obtained in the indium-mediated allylation of achiral carbonyl compounds (Scheme 2.5).[13]



Scheme 2.5. Barbier-type allylation of achiral aldehydes in the presence of a chiral additive.

2.3 Catalytic Tools in Synthetic Organic Chemistry

Development of catalytic methodologies, being applicable in synthetic organic chemistry, has been receiving considerable interest both in the academic community and in the chemical industry. Noteworthy, this field has gained tremendous recognition during the past ten years with three Nobel prizes in chemistry being awarded to its practitioners:[14]

- 2001: William S. Knowles and Ryoji Noyori for their work on chirally catalyzed hydrogenation reactions and K. Barry Sharpless for his work on chirally catalyzed oxidation reactions
- 2005: Yves Chauvin, Robert H. Grubbs and Richard R. Schrock for the development of the metathesis method in organic synthesis
- 2010: Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for palladium-catalyzed cross couplings in organic synthesis

All the above-mentioned processes involve homogeneous catalysis that is discussed in more detail in the following section. The two other main catalysis disciplines, i.e., heterogeneous catalysis and enzyme catalysis are likewise described briefly herein.

2.3.1 Homogeneous Catalysis

By definition, homogeneous catalysis involves catalytic processes where the catalyst is in the same phase with the reactants. Most frequently, the catalyst is dissolved in a solvent and the catalytic reaction takes place in solution. Since the 1950s, homogenous catalysis has been strongly associated with organometallic chemistry finding a broad range of applications in the chemical industry both in fine and bulk chemical production. Homogeneous catalysis is generally associated with processes with high activity and selectivity under mild reaction conditions. Owing to the well-defined structure

of the homogeneous organometallic catalysts, understanding of the mechanism and the catalytic cycle is plausible.

In the context of homogeneous organometallic catalysis, transition metals such as ruthenium, rhodium, palladium and platinum usually gain most attention. The transition metals have a unique bonding ability with a variety of ligands leading to formation of active metal complexes. By tuning the ligand(s), the electronic and steric properties of the metal complexes can be altered and the properties of the catalyst tailored for different applications. Phosphorus based ligands, as exemplified by the chiral phosphines DiPAMP[15] and BINAP[16] in Figure 2.1, are the most commonly applied ligands in organometallic catalysis. Typical reactions applying organometallic transition metal complexes are, for example, hydrogenation, oxidation, hydroformylation and different coupling reactions.[17]

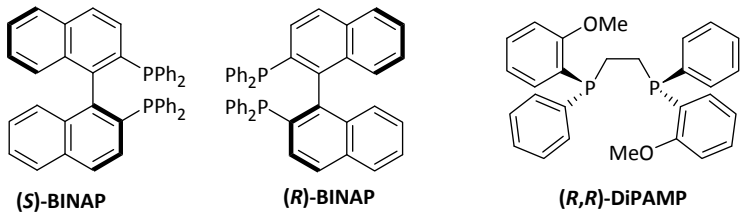
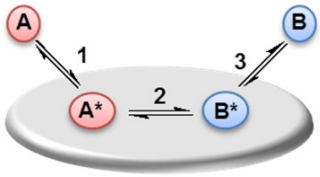


Figure 2.1. Structures of the chiral phosphine ligands (*S*)- and (*R*)-BINAP and (*R*,*R*)-DiPAMP.

2.3.2 Heterogeneous Catalysis

Heterogeneous catalysis, in contrast to homogeneous catalysis, is defined as the catalytic processes where the catalyst is in a different phase than the reactants, most often a solid catalyst in solution or in gas phase reactions. In such heterogeneously catalyzed processes, the reaction takes place on the surface of a catalyst particle thus giving rice to mass transfer issues. Scheme 2.6 shows a general model for a heterogeneously catalyzed reversible reaction consisting of three elementary steps: (1) adsorption of A on an active site; (2) reaction of the adsorbed complex A* to adsorbed complex B*; and, (3) desorption of B from the active site.



Scheme 2.6. Three elementary steps in heterogeneous catalysis.

Heterogeneous catalysis has traditionally been applied in oil refining and bulk chemical production. However, during the recent decades, heterogeneous catalysis has also entered the field of fine chemical industry where heterogeneous transition metal catalysts are today applied in various reactions, including catalytic hydrogenation and dehydrogenation, oxidation and carbon–carbon bond forming reactions.[18]

2.3.3 Enzyme Catalysis

Enzymes, *Nature's* own catalysts, do not only catalyze the crucial biological processes in living organisms, but can also work as active catalysts outside the environment of a living cell. Thus, natural or modified enzymes can be used to catalyze organic transformations characteristically with high chemo- regio- and stereospecificities. However, the high level of specificity also limits the use of a specific enzyme only for certain structures and reactions. Hence, enzymes alone cannot cover the whole diversity of chemical reactions desired in organic chemistry.

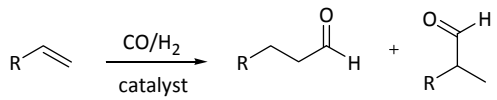
Enzymes utilized in synthetic organic chemistry are divided into six classes: oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases.[19] When applied in organic synthesis, the enzymes are introduced into an unnatural working environment as the reactions usually require partly or pure organic solvents. Organic solvents as the reaction medium and the consequently diminished amount of water around the enzyme will affect the non-covalent forces responsible for the ordered structures of the enzymes. Thus, the protein structures are often stabilized by immobilization that actually gives the enzyme catalysts some heterogeneous character. The main applications for enzymes as synthetic tools are racemate resolution (Section 2.5 in this thesis) and stereospecific synthesis.[20]

2.4 Applied Homogeneous Catalysis Targeting Carbon–Carbon Double Bonds

In this chapter, three catalytic tools targeting carbon–carbon double bonds, i.e., hydroformylation, ring-closing olefin metathesis and asymmetric dihydroxylation, are briefly discussed. In this introduction, the discovery, development and general mechanisms of these reactions are described followed by some representative literature examples of the application of these tools in synthetic organic chemistry.

2.4.1 Hydroformylation

Hydroformylation, the reaction where an alkene is converted to aldehydes in the presence of synthesis gas (CO/H_2) and a metal catalyst, was discovered by Otto Roelen in the late 1930s.[21] A decade after Roelen's initial experiments, a more detailed study, published by Adkins, proved the homogeneous nature of the catalyst.[22] This reaction, initially called oxo-reaction, is a landmark reaction in catalysis being the first reaction to involve homogeneous organometallic catalysis.



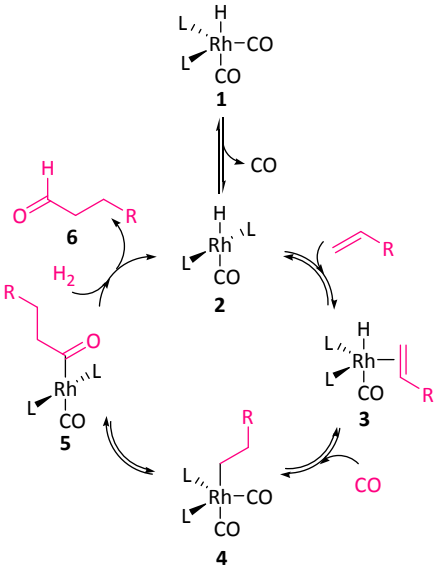
Scheme 2.7. Hydroformylation – a schematic presentation.

The hydroformylation reaction can produce both linear and branched aldehydes as described in Scheme 2.7. The catalyst in the original oxo-reaction was $Co_2(CO)_8$. Rhodium, in turn, was introduced as hydroformylation catalyst for the first time in the late 1950s. The performance of the initially applied unmodified rhodium catalysts can further be enhanced by utilization of phosphorus containing phosphine or phosphite ligands.[23] Both Co- and Rh-catalyzed hydroformylations are operated in industrial scale, making hydroformylation one of the largest homogeneously catalyzed industrial processes today.[24] The obtained aldehydes and the corresponding alcohols are valuable bulk and specialty chemicals finding applications as such or as starting material for further synthesis.

2.4.1.1 Mechanism of Hydroformylation

The generally accepted mechanism for the Co- and Rh-catalyzed hydroformylation was originally proposed in 1961 by Heck and Breslow[25] corresponding to Wilkinson's dissociative mechanism (Scheme 2.8).[26] The mechanism starts with dissociation of CO from complex **1**, yielding a square-

planar intermediate **2** with a vacant coordination site. An alkene is associated with the complex **2** leading to formation of the complex **3**. Migratory insertion of the alkene and the subsequent CO association leads to formation of alkyl species **4**. Complex **4** undergoes a second migratory insertion to give the acyl intermediate **5** that interacts with H_2 via an oxidative addition giving the product aldehyde **6** by reductive elimination. The Rh-hydride species **2** is thus regenerated and the catalytic cycle closed.



Scheme 2.8. The catalytic cycle for Rh-catalyzed hydroformylation.

Regioselectivity of the hydroformylation, defined as linear-to-branched (l/b) ratio of the product, is of utmost relevance in synthetic applications. Formation of the branched aldehyde can be suppressed by using a monodentate phosphine ligand in high excess or by applying bulky bidentate ligands. Representative examples of ligands fulfilling these requirements are the diphosphine ligands BISBI and Xantphos, and the diphosphite ligand BIPHEPHOS (Figure 2.2).[23b,23c]

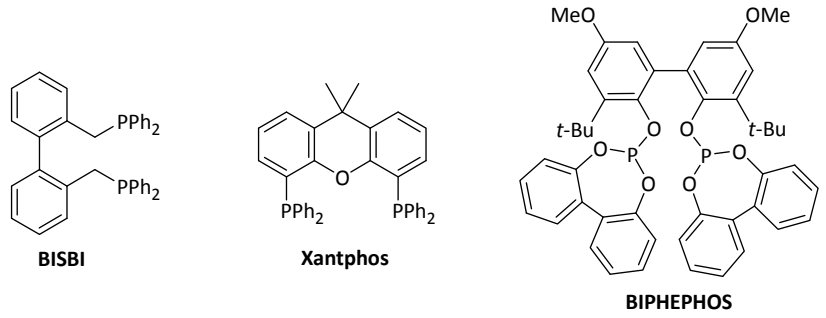
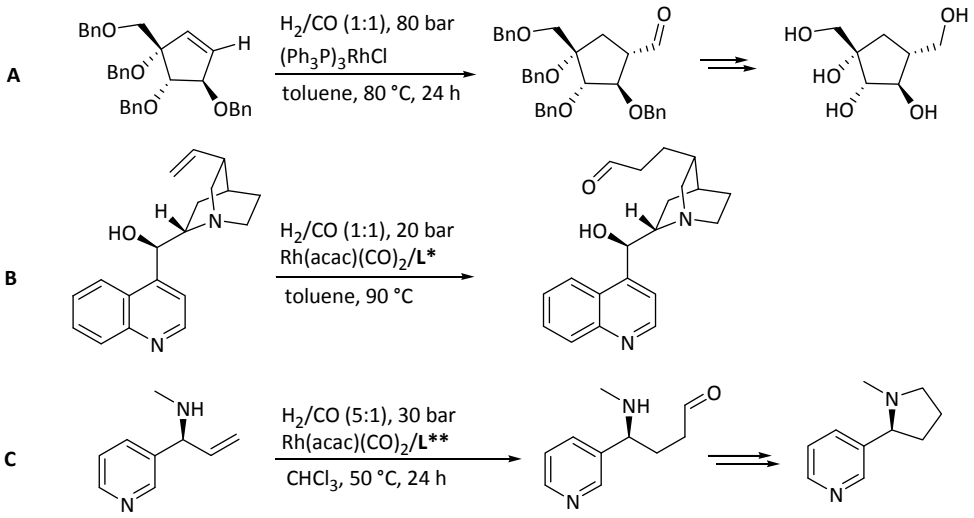


Figure 2.2. Structures of BISBI, Xantphos and BIPHEPHOS ligands.

2.4.1.2 Hydroformylation in Action

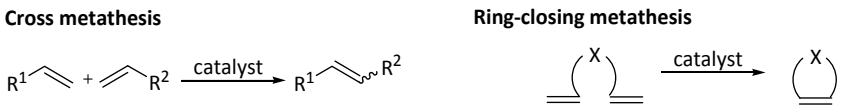
The industrial hydroformylation processes are mainly applied for relatively simple alkenes. However, hydroformylation has also been applied for structurally more complicated structures. To exemplify, Al-Abed et al. synthesized carba-D-fructofuranose utilizing hydroformylation of a polyfunctionalized cyclopentene as a key step (**A**, Scheme 2.9).[27] De Vries performed a highly selective hydroformylation of cinchona alkaloids in the presence of a bulky polyphosphite ligand (**B**, Scheme 2.9).[28] The obtained aldehyde functionalized structures can potentially be anchored on polymeric amines via reductive amination as proposed by the authors. Recently, hydroformylation of allylamines in the presence of phosphine ligands, Xantphos or BIPHEPHOS, was applied in the synthesis of (*S*)-nicotine and other 2-substituted pyrrolidines.[29] The products were obtained as a result of an intramolecular hydroaminomethylation (**C**, Scheme 2.9) demonstrating the versatility of the tandem reaction sequences coupled with hydroformylation.[30]



Scheme 2.9. Hydroformylation in action.

2.4.2 Olefin Metathesis

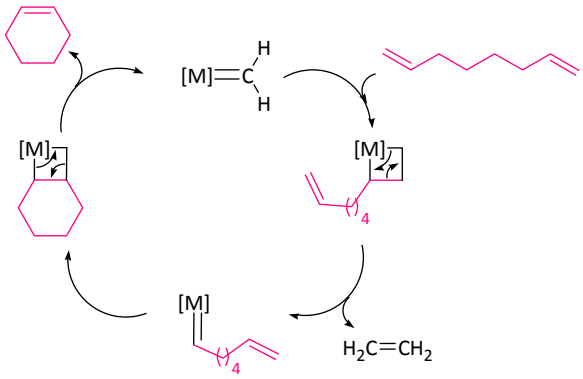
The history of olefin metathesis reaction starts from the first reports of titanium catalyzed polymerization of norbornene yielding a highly unsaturated polymer.[31] According to the definition introduced by Calderon, olefin metathesis is a catalytically induced reaction wherein olefins undergo bond reorganization, resulting in a redistribution of alkylidene moieties.[32] Initiated by these early contributions, the development of olefin metathesis catalysts during the recent decades has enabled the olefin metathesis to become one of the most powerful tools in organic chemistry for formation of new carbon–carbon bonds.[33] Olefin metathesis is commonly divided in three subclasses: cross metahesis (CM), ring-closing metathesis (RCM) and ring-opening metathesis polymerization (ROMP). While cross metathesis often suffers from selectivity issues, the ring-closing metathesis is generally highly selective and applicable for a wide range of substrates (Scheme 2.10).



Scheme 2.10. Olefin metathesis reactions applied in synthetic organic chemistry.

2.4.2.1 *Mechanism of Ring-Closing Olefin Metathesis*

The generally accepted mechanism for olefin metathesis, even described as molecular dance,[34] was first proposed by Chauvin and Hérisson.[35] In Scheme 2.11, the general mechanism for olefin metathesis reaction is exemplified by ring-closing metathesis using 1,7-octadiene as a model substrate. The mechanism starts with [2+2] cycloaddition of an alkene to the metal carbene thus forming a four-membered ring with the metal atom in the ring. In the next step, two single bonds in the metallocyclobutane ring are broken and a new metal carbene is formed and ethene is released. A second [2+2] cycloaddition adds the second alkene leading to the second metallocyclobutane intermediate. In the final step the alkene product is released and the metal carbene is reformed and the catalytic cycle closed.



Scheme 2.11. The catalytic cycle for ring-closing olefin metathesis exemplified with the synthesis of cyclohexene from 1,7-octadiene.

For the ring-closing metathesis, Grubbs-type ruthenium carbenes (Figure 2.3) are transcendent catalysts in terms of versatility and practicability in the hands of a synthetic organic chemist.[36] In particular, the second generation catalysts containing an N-heterocyclic carbene ligand tolerate various functional groups and have been utilized for a wide scope of substrates providing small to medium sized carbocycles and heterocycles with high activity and selectivity.[37]

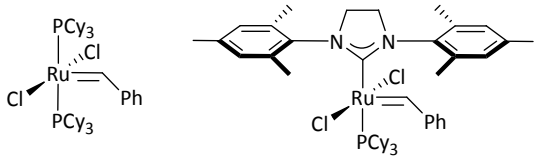
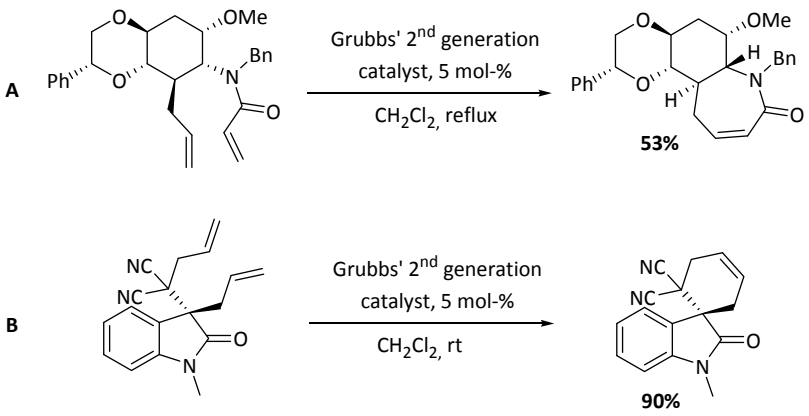


Figure 2.3. Grubbs' 1st generation (left) and 2nd generation (right) Ru-catalysts for olefin metathesis.

2.4.2.2 Ring-Closing Olefin Metathesis in Action

Recent representative literature procedures for construction of complex cyclic targets using ring-closing metathesis as a key step include, for example, synthesis of enantiopure azepinone derivatives on a carbohydrate scaffold (**A**, Scheme 2.12)[38] and synthesis of spiro-indol-2-ones (**B**, Scheme 2.12).[39] Recent developments cover even aqueous olefin metathesis,[40] enabling metathesis reactions to be applied for polar water soluble substrates without protective group manipulations.



Scheme 2.12. Ring-closing olefin metathesis in action.

2.4.3 Catalytic Asymmetric Dihydroxylation

The traditional stoichiometric *syn*-dihydroxylation of a carbon–carbon double bond using OsO_4 can be turned catalytic by utilizing relatively cheap stoichiometric reagents being able to reoxidize the osmium(VI) species. Initially, *N*-methylmorpholine-*N*-oxide (NMO) was applied as a secondary oxidant in catalytic dihydroxylations.[41] NMO has, however, been widely replaced by $K_3Fe(CN)_6$ introduced for the first time in 1990.[42]

The first asymmetric version of catalytic dihydroxylation was reported by Sharpless et al. in the late 1980s.[43] At that time, $K_3Fe(CN)_6$ as secondary oxidant was not known, but NMO was utilized instead. It was noticed that cinchona alkaloid derivatives not only increased the reaction rate, the effect previously known for other tertiary amines, but also induced useful levels of asymmetric control. The reaction protocol was later enhanced by replacing NMO with $K_3Fe(CN)_6/K_2CO_3$ and by utilizing bis-cinchona alkaloids as ligands.[44] The most commonly utilized ligands for asymmetric dihydroxylation are $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ (Figure 2.4). These ligands are even the constituents of the

commercially available mixtures for asymmetric dihydroxylation, AD-mix-α and AD-mix-β, containing $K_2OsO_2(OH)_4$ as a source of osmium and $K_3Fe(CN)_6$ and K_2CO_3 as the secondary oxidant.

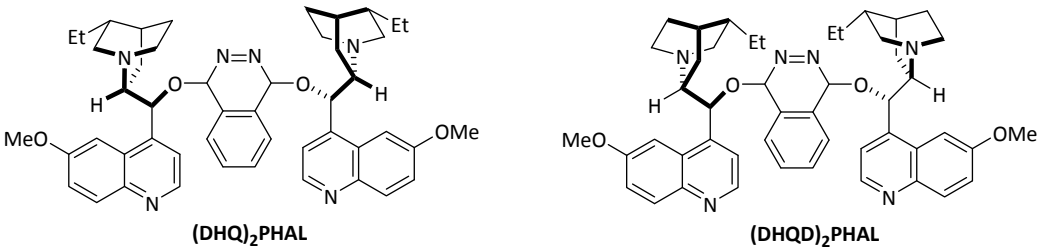
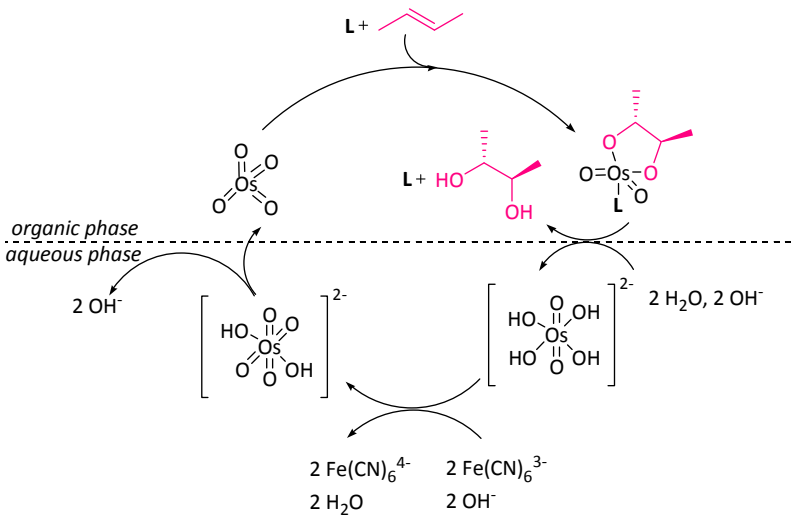


Figure 2.4. Ligands used in AD-mix-α (left) and AD-mix-β (right), respectively.

2.4.3.1 Mechanism of Catalytic Asymmetric Dihydroxylation

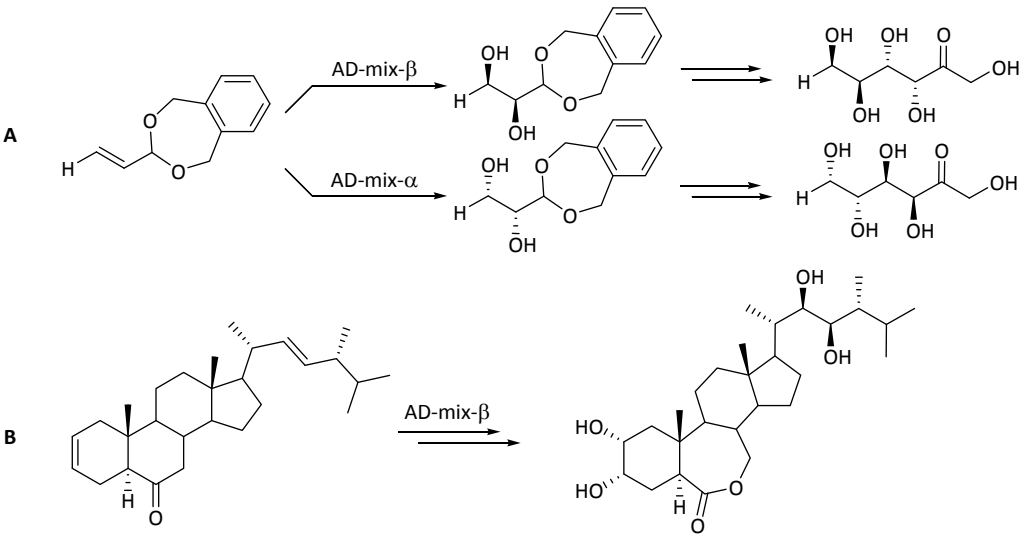
The Sharpless asymmetric dihydroxylation is carried out in biphasic system (*t*-BuOH:H_2O) separating the dihydroxylation and reoxidation of the osmium species into different phases (Scheme 2.13).[45] Addition of methanesulfonamide to the reaction mixture has been shown to increase the reaction rate considerably by accelerating the hydrolysis of the osmium(VI) glycolate.[44]



Scheme 2.13. The catalytic cycle for asymmetric dihydroxylation.

2.4.3.2 Catalytic Asymmetric Dihydroxylation in Action

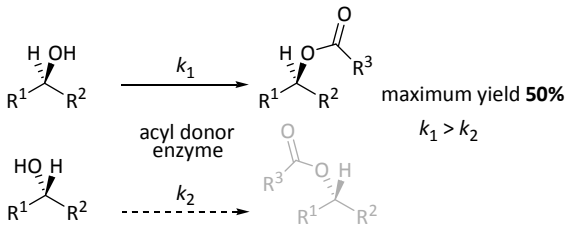
The catalytic asymmetric dihydroxylation is applicable for terminal alkenes as well as for di- tri- and tetrasubstituted alkenes.[46] For example, the Sharpless protocol has been applied in the synthesis of a series of carbohydrates via tandem asymmetric dihydroxylation of unsaturated acetals and enzyme catalyzed aldol reactions (**A**, Scheme 2.14).[47] The method is likewise applicable for steroidal structures as exemplified by the synthesis of 24-epibrassinolide starting from ergosterol with asymmetric dihydroxylation as a key step (**B**, Scheme 2.14).[48]



Scheme 2.14. Catalytic asymmetric dihydroxylation in action.

2.5 Enzymatic Kinetic Resolution

The process, in which pure enantiomers are produced by separating them from a racemic mixture, is called resolution.[49] Such resolution is kinetic when performed by utilizing the different reaction rates of the enantiomers in a certain reaction. Enzymatic kinetic resolution makes use of an enzyme catalyzed reaction that is selective for one enantiomer, optimally leaving the other enantiomer unreacted. Enzymatic kinetic resolution of alcohols employing a selective acylation reaction is illustrated in Scheme 2.15.



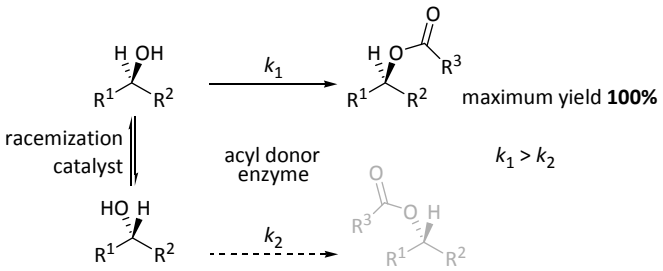
Scheme 2.15. Illustration of enzymatic kinetic resolution of a chiral alcohol ($R^1 \neq R^2$)

Crucial in enzymatic kinetic resolution is that the rate constant for the reacting enantiomer (k_1) is significantly higher than the rate constant for the other enantiomer (k_2). The enzymatic enantioselectivity is measured with enantiomeric ratio (*E*-value) that describes the enzyme's ability to differentiate between the two enantiomers. *E*-value is calculated from enantiomeric excesses of the substrate (ee_S) or product (ee_P) and the conversion of the reaction (c) (Equation 1).[50]

$$E = \frac{\ln[(1-c)(1-ee_S)]}{\ln[(1-c)(1+ee_S)]} = \frac{\ln[1-c(1+ee_P)]}{\ln[1-c(1-ee_P)]} \qquad (1)$$

Theoretically, *E*-value>1000 will provide both the resolution product and the unreacted substrate enantiomer with excellent enantiopurity, ee_P>99% and ee_S>99%, at 50% conversion. However, with high *E*-values even small experimental errors in the determination of *ee*-values and conversions will distort the *E*-value considerably. Thus, in the literature, excellent *E*-values are usually marked *E*>200 or *E*>100.

Kinetic resolution is, however, restricted to maximum 50% conversion and yield. Furthermore, the purification of the reaction mixture might be problematic. These problems can be circumvented by introducing a racemization catalyst that racemizes the slower reacting enantiomer *in situ*, thus leading to maximum yield of 100% of one enantiomer under optimal reaction conditions. This process is called dynamic kinetic resolution (DKR) (Scheme 2.16).



Scheme 2.16. Illustration of dynamic kinetic resolution of a chiral alcohol ($R^1 \neq R^2$).

2.6 Outline of This Thesis

In the first part of this thesis (Chapter 3), a simple synthesis route towards polyhydroxylated lactols starting from unprotected monosaccharides is described.[51] The synthesis route employs a sequence consisting of metal-mediated allylation and hydroformylation reaction. The sequence can be performed in aqueous media, hence reducing the need for resource consuming protection-deprotection operations. In addition, the conformation of the homoallylic polyol derived from mannose will be briefly discussed in Chapter 4.[52]

In Chapter 5, a synthesis route for a series of steroid derivatives with increased amphiphilicity was evaluated. By combining the virtually simple tranfromations, i.e., metal-mediated allylation, ring-closing olefin metathesis and dihydroxylation, into a short reaction sequence, novel hydrophilic steroid based structures were obtained. Furthermore, the structures thus obtained were briefly evaluated in biological assays.[53]

Chapter 6 focuses on the synthesis of nitrogen-containing building blocks relevant for pharmaceutical applications. Initially, metal-mediated Barbier-type allylation of *N*,*N*-dimethylsulfamoyl-protected aldimines followed by facile deprotection by transamination was studied. The racemic amines obtained were subjected for lipase catalyzed kinetic resolution giving access to enantiopure amines and amides that could be further transformed into nitrogen-containing heterocycles using ring-closing olefin metathesis as a key step.[54,55] Finally, the synthesis route developed herein was applied to the synthesis of two natural products (±)-anatabine and (±)-anabasine (Chapter 7).[56]

2.7 References and Notes

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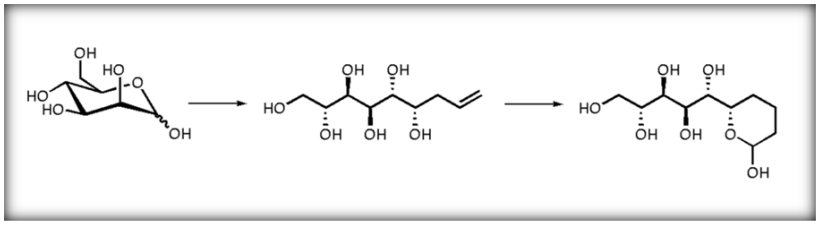
3 METAL-MEDIATED ALLYLATION OF UNPROTECTED MONOSACCHARIDES COMBINED WITH SUBSEQUENT HYDROFORMYLATION



Development of reaction sequences that utilize renewable resources, such as carbohydrates, as starting material is of topical interest. Particularly attractive are reaction protocols where unprotected monosaccharides are applied. In many cases, such reactions may be carried out in aqueous media, hence avoiding the resource consuming protection/deprotection strategies. In this chapter, metal-mediated allylation of unprotected monosaccharides is combined with subsequent hydroformylation, yielding polyhydroxylated lactols mimicking a number of natural products.

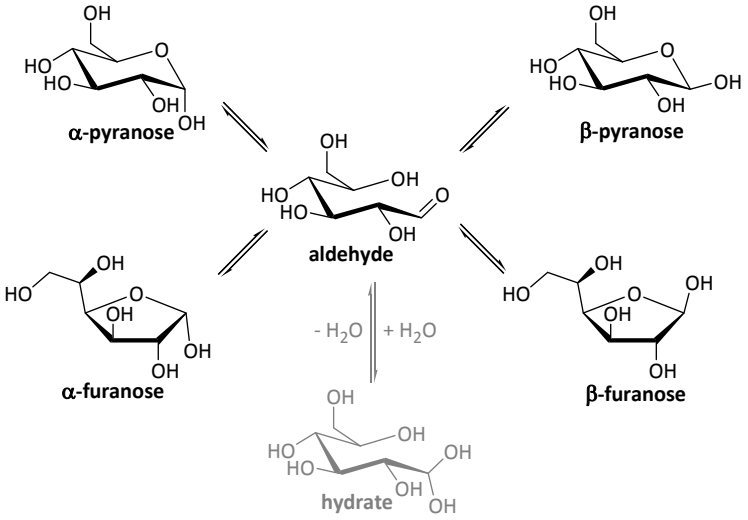
This chapter is based on the original publication:

Saloranta, T.; Müller, C.; Vogt, D.; Leino, R. **Converting Unprotected Monosaccharides into Funtionalised Lactols in Aqueous Media: Metal-Mediated Allylation Combined with Tandem Hydroformylation-Cyclisation**, *Chem. Eur. J.* **2008**, *14*, 10539–10542.

3.1 Introduction

Utilization of biomass and especially carbohydrates for the production of fine chemicals is in accordance with the general principles of sustainable development as agreed in the Rio Declaration.[1] Besides their use in traditional carbohydrate chemistry involving synthetic modification of monosaccharides and synthesis of well-defined oligosaccharides, carbohydrates have likewise been utilized as starting material for the production of synthetically valuable intermediates.[2] Literature examples showing the conversion of unprotected carbohydrates into fine chemicals or precursors thereof with potential biological relevance are, however, scarce.

Reducing carbohydrates generate tautomeric equilibria in aqueous solution. The phenomenon, termed mutarotation, is presented in Scheme 3.1 for D-glucose. The five- or six-membered ring forms, α/β-furanoses and α/β-pyranoses, generally dominate while the ratio between these forms varies for different monosaccharides. The ring forms are converted into each other via the acyclic aldehyde form that may also add water upon forming the acyclic hydrate form. The exact compositions of the tautomeric mixtures for the eight different aldohexoses have been determined by studying the equilibrium of ^{13}C labeled compounds by ^{13}C NMR spectroscopy.[3] The equilibrium composition (%) for D-galactose, D-glucose and D-mannose are presented in Table 3.1.

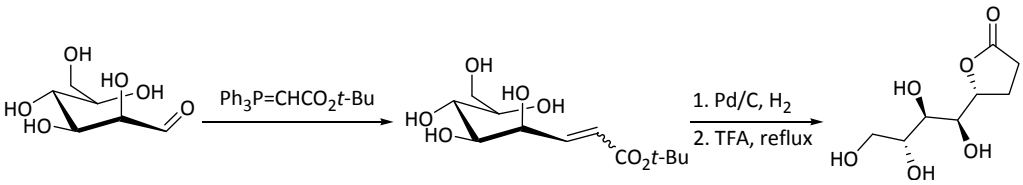


Scheme 3.1. Mutarotation of D-glucose.

Table 3.1. Percentages of cyclic and acyclic forms of common aldohexoses in aqueous solution at 30 °C.[3]

	Furanose		Pyranose			
Aldohexose	α	β	α	β	Aldehyde	Hydrate
D-galactose	2.30	3.68	31.2	62.7	0.046	0.006
D-glucose	0.108	0.28	37.63	61.96	0.0059	0.0040
D-mannose	0.64	0.24	66.23	32.85	0.022	0.0044

The fact that a small fragment of the open chain aldehyde form is present in aqueous solutions of unprotected monosaccharides can be utilized in extension of the carbon chain of unprotected aldoses. One carbon elongation is classically performed by adding hydrogen cyanide to the carbonyl group of an aldose.[4] Wittig reaction has been utilized to extend the carbon chain of unprotected monosaccharides by two carbon atoms.[5] The obtained unsaturated aldonic acid esters have been transformed into higher sugars by dihydroxylation.[5b] Alternatively, hydrogenation of the carbon–carbon double bond in the aldonic acid ester, followed by deprotection of the carboxyl protecting group under acidic conditions yielded a polyhydroxylated lactone as a result of spontaneous intramolecular esterification (Scheme 3.2).[5a]



Scheme 3.2. Synthesis of polyhydroxylated lactone by Wittig reaction/hydrogenation sequence from unprotected D-mannose.

Tin-mediated allylation of unprotected carbohydrates as a method to extend the carbon chain by three carbon atoms was exploited for the first time in 1991 by Schmid and Whitesides.[6] A few years later, indium was likewise reported to be able to act as mediating metal in allylation of unprotected carbohydrates.[7] In addition to allyl bromide, unprotected monosaccharides have also been allylated with functionalized allylating agents such as ethyl α-(bromomethyl)acrylate[8] and 3-bromopropenyl esters.[9] The obtained unsaturated polyols have been transformed into higher sugars by ozonolysis. However, the additional synthetic potential of these highly functionalized structures appears to remain practically unutilized.

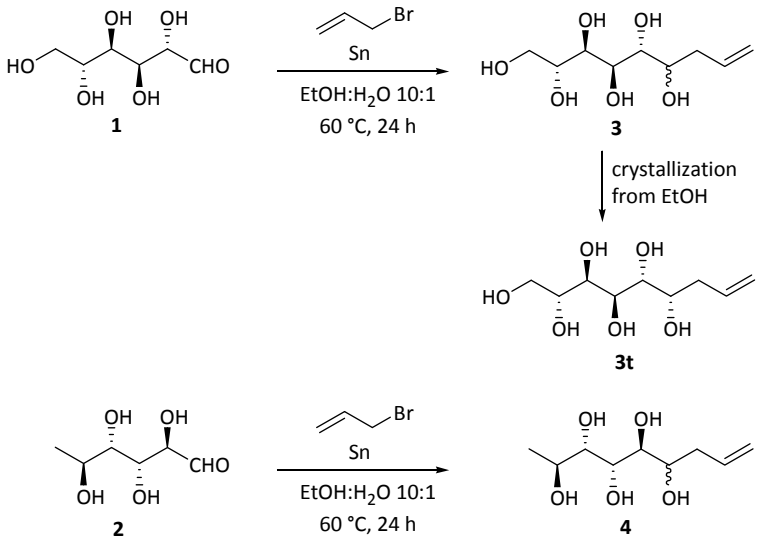
Hydroformylation of olefins into aldehydes and products derived therefrom is one of the most important industrial applications of homogeneous catalysis.[10] The combination of high atom efficiency with highly active and selective catalysts makes this transformation a very attractive tool in organic synthesis with complex natural product targets. Hydroformylation of higher alkenes with negligible solubility in water is generally performed in a monophasic system in organic solvents where the catalyst is situated in the same phase with the substrate. Hydroformylation of such alkenes in an aqueous biphasic system enables recycling of the catalyst but generally requires special arrangements, such as a phase transfer agent to reduce the mass transfer limitations.[11] In turn, hydroformylation of polar substrates with minimal solubility in organic solvents requires non-traditional solvent systems.[12]

In this chapter, the metal-mediated allylation of unprotected monosaccharides has been combined with a subsequent highly regioselective hydroformylation reaction. The functional groups of the multifunctionalized polyol structures were targeted selectively in the absence of any kind of protective groups, giving ultimately rise to the formation of functionalized lactols. Moreover, the reactions were performed in aqueous media thus significantly reducing the need for organic solvents.

3.2 Results and Discussion

3.2.1 Tin-Mediated Allylation of D-Mannose and L-Rhamnose

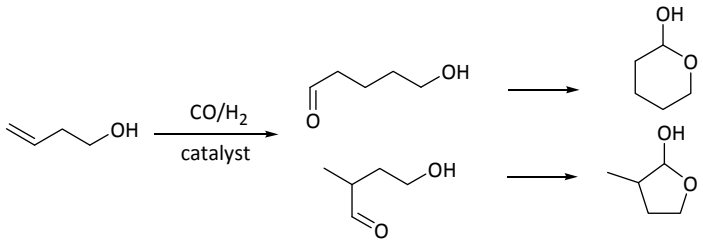
For this work, D-mannose (**1**) and L-rhamnose (**2**) (6-deoxy-L-mannose), the readily available naturally occurring monosaccharides, were chosen as starting materials. Both monosaccharides were successfully allylated in 5 g scale in aqueous ethanol using tin as the mediating metal (Scheme 3.3). Instead of utilizing ultrasound sonication as reported in the original literature procedure,[7a] the reactions were carried out at elevated temperature (+ 60 °C). The monosaccharides were allylated with full conversion giving the corresponding products in a diastereomeric ratio of 3:1 (threo:erythro). The main diastereomer **3t** derived from D-mannose was further isolated by crystallization from ethanol.



Scheme 3.3. Tin-mediated allylation of D-mannose and L-rhamnose.

3.2.2 Rhodium-Catalyzed Hydroformylation of Polyhydroxylated Alkenes

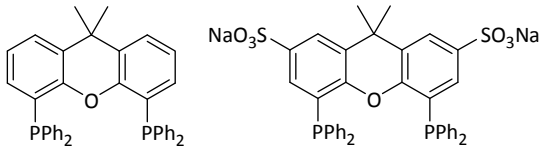
Aldehydes bearing an additional hydroxyl group are expected to undergo an intramolecular acetal formation especially in cases where stable five- or six-membered rings can be formed. Consequently, hydroformylation of homoallylic alcohols generally leads to formation of cyclic lactol products (Scheme 3.4).[13]



Scheme 3.4. Hydroformylation of but-3-en-1-ol yielding cyclic lactol products.

It was therefore considered that compounds **3** and **4** might prove to be optimal substrates for hydroformylation leading to spontaneous formation of lactols by subsequent intramolecular cyclization. For this purpose, the commercially available bidentate Xantphos ligand (Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) as well as its water soluble counterpart, Sulfoxantphos (Figure 3.1), were applied. In hydroformylation reactions, the corresponding Rh-

catalysts are known to promote the formation of the linear aldehydes with high selectivity. Moreover, the highly polar Sulfoxantphos system provides the possibility to perform the hydroformylation reaction of substrates **3** and **4** in water.



Xantphos **Sulfoxantphos**

Figure 3.1. Xantphos and Sulfoxantphos ligands.

The reaction conditions were optimized in small scale experiments in an automated reactor system (AMTEC SPR16). The course of the hydroformylation was followed by on line detection of the gas uptake of CO/H_2 and the reaction was stopped when full conversion was achieved (Figure 3.2). The catalyst was removed by filtration through neutral alumina and the products were analyzed by NMR spectroscopy and HRMS. Interestingly, it was found that the crude product clearly consisted of one major product only. As anticipated from the considerations above, the ring-closed lactol product containing a six-membered ring had indeed been formed selectively from the linear hydroformylation product. This tandem reaction sequence is depicted in Scheme 3.5.

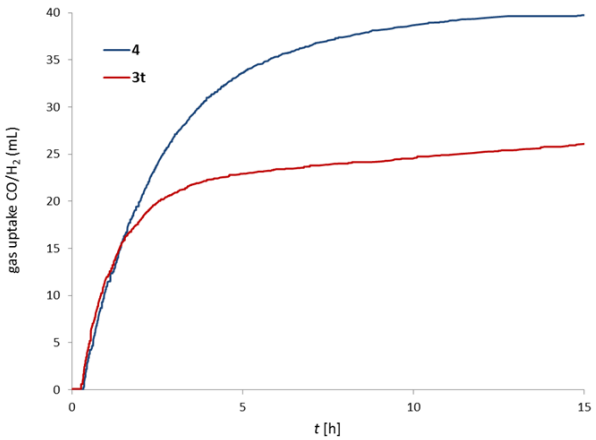
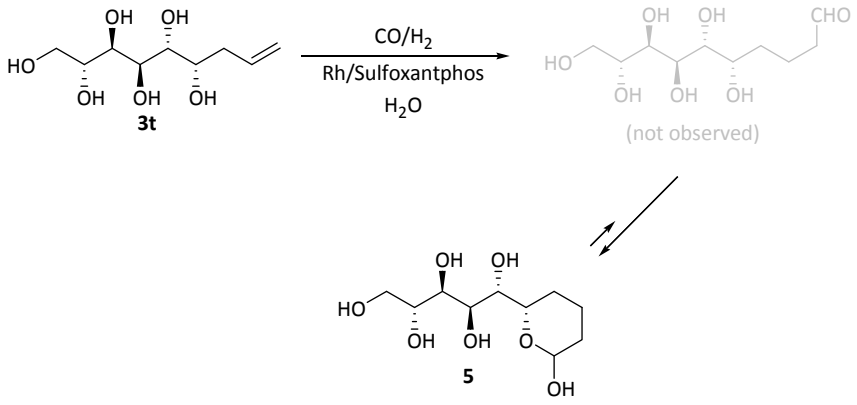


Figure 3.2. Gas uptake of CO/H_2 in the small scale Rh/Sulfoxantphos-catalyzed hydroformylations in water. Hydroformylation of **3t**: $n_{substrate}$ = 0.60 mmol; substrate/Rh = 50; $p(CO/H_2)$ = 20 bar; T = 100 °C. Hydroformylation of **4**: $n_{substrate}$ = 0.90 mmol; substrate/Rh = 75; $p(CO/H_2)$ = 20 bar; T = 100 °C.



Scheme 3.5. Hydroformylation of polyol **3t**.

The hydroformylation was also performed in synthetically preparative scale in 75 or 100 mL autoclaves with either magnetic or mechanical stirring. The scale up with Rh/substrate ratio 1/150-200 was successful and the results comparable with the small scale experiments (Table 3.2, entries 1 and 2).

Encouraged by these results, it became tempting to investigate whether the polyhydroxylated substrate might also be suitable for further functionalizations in inverted biphasic solvent systems. Accordingly, the hydroformylation was performed in a biphasic system water/toluene using the hydrophobic Rh/Xantphos catalyst. The utilization of this type of biphasic systems would enable a simple product separation and recycling of the catalyst as the products of the hydroformylation reaction are water soluble and the hydrophobic catalyst remains in the organic phase.[12a]

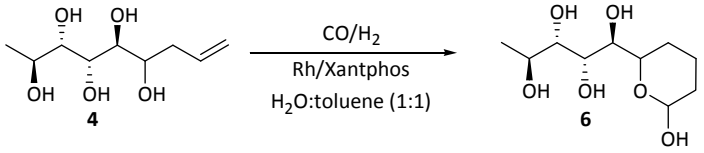
Hydroformylation of the L-rhamnose derived substrate **4** was performed in a 100 mL autoclave with mechanical stirring under the standard reaction conditions (Scheme 3.6). The conversion was monitored by the gas uptake of CO/H_2 and the reaction was stopped after 60 h (Figure 3.3). Gratifyingly, the results were comparable with the hydroformylation in water using the Rh/Sulfoxantphos catalyst (Table 3.2, entries 2 and 3). These results nicely demonstrate that this concept is indeed suitable for efficient catalyst recycling, which is often difficult to achieve in homogeneous catalysis.

Table 3.2. Hydroformylation of the polyhydroxylated substrates **3t** and **4** in synthetically preparative scale.

Entry	Substrate	Ligand	Solvent	Substrate/Rh	Conversion/Yield (%)[a]
1	**3t**	Sulfoxantphos	H_2O	200	>99/>95
2	**4**	Sulfoxantphos	H_2O	150	>99/>95
3[b]	**4**	Xantphos	H_2O:toluene (1:1)	150	>99/>95

[a] Conversion and yield determined by ^{1}H NMR spectroscopy.

[b] [Rh] in the aqueous layer (determined with ICP) below the detection limit 0.05 mg/L.



Scheme 3.6. Hydroformylation of the polyol **4** in inverted biphasic solvent system.

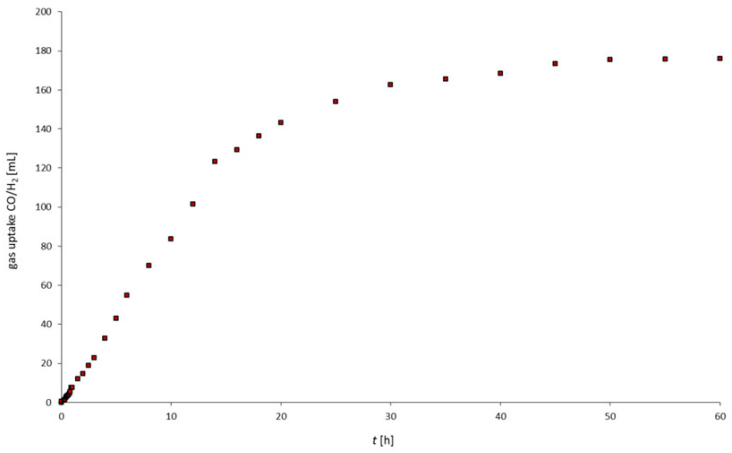
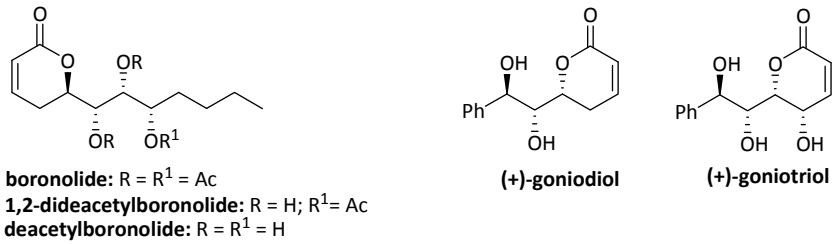


Figure 3.3. Gas uptake of CO/H_2 in the Rh/Xantphos catalysed hydroformylation of **4** in an inverted aqueous biphasic system.

It should be mentioned here that the obtained polyhydroxylated lactols are structural mimics for a number of naturally occurring and biologically active δ-lactones.[14] Representative examples of such

structures, boronolide along with its deacetylated counterparts,[15] as well as goniodiol and goniotriol,[16] are depicted in Figure 3.4.



boronolide: R = R^1 = Ac
1,2-dideacetylboronolide: R = H; R^1= Ac
deacetylboronolide: R = R^1 = H

(+)-goniodiol

(+)-goniotriol

Figure 3.4. Structures of typical polyhydroxylated δ-lactones.

In other words, by converting the obtained lactol product into the corresponding lactone,[17] the single stereocenter formed in the hydroformylation-cyclization sequence would become insignificant. At the same time, the biological relevance of the product potentially increases. The reaction protocol presented herein thus provides an access to valuable intermediates for the synthesis of complex natural product targets or analogues with biological relevance.

3.3 Summary and Conclusions

In conclusion, in this chapter it was shown that readily available starting material (naturally occurring monosaccharides) can efficiently be converted into highly functionalized polyhydroxylated lactols by the combination of two simple transformations: metal-mediated allylation and tandem hydroformylation-cyclization. Moreover, the reaction sequence can be carried out in aqueous medium avoiding the use of organic solvents and resource consuming protection/deprotection strategies. By applying inverted biphasic system for the hydroformylation, the product can easily be separated by phase separation and the catalyst recycled. Finally, the lactol products obtained may potentially be utilized as intermediates in the synthesis of natural products by mimicking the original synthetic strategy of nature with seamless combination of elegant and selective transformations without the need for protective groups.

3.4 Experimental Section

General remarks

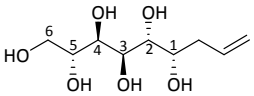
All air- or sensitive operations were performed using standard Schlenk-techniques under a purified argon atmosphere. The deionized water was deoxygenated prior to use. Toluene was purified over alumina column and degassed. 9,9-Dimethyl-2,7-bissulfonato-4,5-bis(diphenylphosphino)xanthene sodium salt was prepared according to a literature procedure.[18] All other reagents were purchased and used as received. The synthesis gas [CO (99.999%)/H_2 (99.999%), 1:1] was purchased from Linde AG. NMR spectra were recorded at room temperature in CD_3OD using Bruker Avance 600 MHz NMR spectrometer. ^{1}H NMR spectra of compounds **3t**, **4**, **5** and **6** were analyzed by PERCH software with spin simulation/iteration techniques.[19] For the sake of uniformity, the atoms are numbered as in the original carbohydrate structure when reporting NMR spectroscopic data, thus contradicting with the systematic nomenclature given in this chapter. Optical rotations were measured with Perkin Elmer 241 polarimeter equipped with a Na-lamp (589 nm). HRMS were recorded using Bruker Micro Q-TOF with ESI (electro spray ionization) operated in positive mode. Melting points were recorded with a Stuart Scientific apparatus. The ICP-OES measurements were performed with a SPECTRO CIROSCCD spectrometer equipped with a free running 27.12 MHz generator at a power of 1400 W. The sample introduction was performed by a cross-flow nebulizer with a double pass Scott type spray chamber and a sample uptake rate of 2 mL/min. The outer gas flow was 12 L/min, the intermediate gas flow was 1 L/min and the nebulizer gas flow was 1.00 L/min.

Allylation of unprotected monosaccharides (details given apply for the allylation of D-mannose)

D-Mannose (5 g, 27.8 mmol) was dissolved in 600 mL of EtOH:H_2O (10:1) at room temperature. Tin powder (6.7 g, 55.5 mmol, 2 equiv) and allyl bromide (7.2 mL, 83.4 mmol, 3 equiv) were added. The reaction mixture was stirred under Ar atmosphere at room temperature for 20 min after which the temperature was gradually raised to 60 °C. A greyish suspension was obtained after stirring for ~2 h. The color of the reaction mixture turned gradually to yellow as the stirring was continued for 24 h. The conversion of the starting material was followed by TLC (MeOH/acetone, 1:1). After cooling to room temperature, the reaction mixture was neutralized by adding 5 M NaOH (18 mL). Dichloromethane (300 mL) and water (300 mL) were added, and the phases were separated. The aqueous phase was washed with dichloromethane (2 x 150 mL). The combined organic layers were washed with water (2 x 200 mL). The combined aqueous layers were filtered through celite. The

colorless filtrate was concentrated under reduced pressure to obtain the crude product as a white solid. ^{1}H NMR spectroscopic analysis of the crude product: conversion 100%, diastereomeric ratio 3:1 (threo:erythro). The crude product was dissolved in EtOH (350 mL) at 60 °C. Upon cooling, the major diastereomer **3t** precipitated as a white crystalline solid. Typically, 2.8 g (45%) of pure diastereomer was obtained.

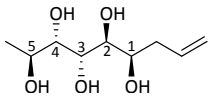
(2*R*,3*R*,4*R*,5*R*,6*S*)-Non-8-ene-1,2,3,4,5,6-hexol (3t)



White solid. mp 186-188 °C. R_f = 0.6 (MeOH/acetone = 1:1). $[\alpha]_D^{20}$ +22.8 (c = 1.0, H_2O). ^{1}H NMR (600.13 MHz, CD_3OD, 25 °C): δ 5.90 (dddd, 1 H, $J_{CH=,CH2b}$ = 6.5 Hz, $J_{CH=,CH2a}$ = 7.5 Hz, $J_{CH=,CH2cis}$ = 10.2 Hz, $J_{CH=,CH2trans}$ = 17.2 Hz, –C*H*=CH_2), 5.14 (dddd, 1 H, $J_{CH2trans,CH2b}$ = −1.4 Hz, $J_{CH2trans,CH2a}$ = −1.5 Hz, $J_{CH2trans,CH2cis}$ = −2.2 Hz, $J_{CHtrans,CH=}$ = 17.2 Hz, –CH=CH_{2trans}), 5.07 (dddd, 1 H, $J_{CH2cis,CH2b}$ = −0.9 Hz, $J_{CH2cis,CH2a}$ = −0.9 Hz, $J_{CH2trans,CH2cis}$ = −2.2 Hz, $J_{CH2cis,CH=}$ = 10.2 Hz, –CH=CH_{2cis}), 3.95 (ddd, 1 H, $J_{1,2}$ = 1.6 Hz, $J_{1,CH2a}$ = 6.2 Hz, $J_{1,CH2b}$ = 7.8 Hz, H-1), 3.91 (dd, 1 H, $J_{3,4}$ = 1.1 Hz, $J_{2,3}$ = 9.2 Hz, H-3), 3.84 (dd, 1 H, $J_{5,6a}$ = 3.5 Hz, $J_{6a,6b}$ = −11.5 Hz, H-6a), 3.81 (dd, 1 H, $J_{3,4}$ = 1.1 Hz, $J_{4,5}$ = 8.5 Hz, H-4), 3.73 (ddd, 1 H, $J_{5,6a}$ = 3.5 Hz, $J_{5,6b}$ = 6.1 Hz, $J_{6a,6b}$ = −11.5 Hz, H-5), 3.66 (dd, 1 H, $J_{5,6a}$ = 6.1 Hz, $J_{6a,6b}$ = −11.5 Hz, H-6b), 3.56 (dd, 1 H, $J_{1,2}$ = 1.6 Hz, $J_{2,3}$ = 9.2 Hz, H-2), 2.39 (dddd, 1 H, $J_{CH2a,CH2cis}$ = −0.9 Hz, $J_{CH2a,\ CH2trans}$ = −1.5 Hz, $J_{CH2a,CH=}$ = 7.5 Hz, $J_{CH2a,CH2b}$ = −14.1 Hz, CH_{2a}), 2.35 (dddd, 1 H, $J_{CH2b,CH2cis}$ = −0.9 Hz, $J_{CH2b,\ CH2trans}$ = −1.4 Hz, $J_{CH2b,CH=}$ = 6.5 Hz, $J_{CH2a,CH2b}$ = −14.1 Hz, CH_{2b}). ^{13}C NMR (150.9 MHz, CD_3OD, 25 °C): δ = 136.6 (-*C*H=CH_2), 117.5 (-CH=*C*H_2), 72.9 (C-5), 72.5 (C-2), 71.1 (C-4), 71.0 (C-1), 70.2 (C-3), 65.0 (C-6), 39.3 (*C*H_2). HRMS calcd for $C_9H_{18}O_6Na$ $[M+Na]^+$ 245.0996, found 245.0984.

4: White solid. R_f = 0.7 (MeOH/acetone = 1:1). HRMS calcd for $C_9H_{18}O_5Na$ $[M+Na]^+$ 229.1046, found 229.1051.

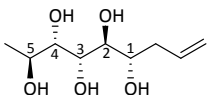
(2*S*,3*S*,4*R*,5*S*,6*R*)-Non-8-ene-2,3,4,5,6-pentol (4t)



^{1}H NMR (600.13 MHz, CD_3OD, 25 °C): δ = 5.90 (dddd, 1 H, $J_{CH=,CH2b}$ = 6.5 Hz, $J_{CH=,CH2a}$ = 7.5 Hz, $J_{CH=,CH2cis}$ = 10.2 Hz, $J_{CH=,CH2trans}$ = 17.2 Hz, –*C*H-CH_2), 5.11 (dddd, 1 H, $J_{CH2trans,CH2b}$ = −1.5 Hz, $J_{CH2trans,CH2a}$ = −1.5 Hz, $J_{CH2trans,CH2cis}$ = −2.2 Hz, $J_{CH2trans,CH=}$ = 17.2 Hz, –CH=CH_{2trans}), 5.04 (dddd, 1 H, $J_{CH2cis,CH2b}$ = −1.0 Hz, $J_{CH2cis,CH2a}$ = −1.1 Hz, $J_{CH2trans,CH2cis}$ = −2.2 Hz, $J_{CH2cis,CH}$ = 10.2 Hz, –CH=CH_{2cis}), 3.92 (ddd, 1 H, $J_{1,2}$ = 1.6 Hz, $J_{1,CH2a}$ = 6.3 Hz, $J_{1,CH2b}$

= 7.7 Hz, H-1), 3.91 (dd, 1 H, $J_{3,4}$ = 1.3 Hz, $J_{2,3}$ = 8.9 Hz, H-3), 3.81 (dq, 1 H, $J_{5,CH3}$ = 6.3 Hz, $J_{4,5}$ = 7.7 Hz, H-5), 3.54 (dd, 1 H, $J_{3,4}$ = 1.3 Hz, $J_{4,5}$ = 7.7 Hz, H-4), 3.52 (dd, 1 H, $J_{1,2}$ = 1.6 Hz, $J_{2,3}$ = 8.9 Hz, H-2), 2.37 (dddd, 1 H, $J_{CH2a,\ CH2cis}$ = −1.1 Hz, $J_{CH2a,\ CH2trans}$ = −1.5 Hz, $J_{CH2a,CH=}$ = 7.5 Hz, $J_{CH2a,CH2b}$ = −14.0 Hz, CH_{2a}), 2.34 (dddd, 1 H, $J_{CH2b,\ CH2cis}$ = −1.0 Hz, $J_{CH2b,\ CH2trans}$ = −1.5 Hz, $J_{CH2b,CH=}$ = 6.5 Hz, $J_{CH2a,CH2b}$ = −14.0 Hz, CH_{2b}), 1.27 (d, 3 H, $J_{5,CH3}$ = 6.3 Hz, CH_3). ^{13}C NMR (150.9 MHz, CD_3OD, 25 °C): δ = 137.0 (-*C*H=CH_2), 117.1 (CH=*C*H_2), 75.1 (C-4), 73.0 (C-2), 71.2 (C-1), 70.5 (C-3), 69.2 (C-5), 39.6 (*C*H_2), 20.6 (*C*H_3).

(2*S*,3*S*,4*R*,5*S*,6*S*)-Non-8-ene-2,3,4,5,6-pentol (4e)



^{1}H NMR (600.13 MHz, CD_3OD, 25 °C): δ = 5.95 (dddd, 1 H, $J_{CH,CH2a}$ = 6.9 Hz, $J_{CH=,CH2b}$ = 7.2 Hz, $J_{CH=,CH2cis}$ = 10.3 Hz, $J_{CH=,CH2trans}$ = 17.1 Hz, –C*H*-CH_2), 5.11 (dddd, 1 H, $J_{CH2trans,CH2a}$ = −1.3 Hz, $J_{CH2trans,CH2b}$ = −1.3 Hz, $J_{CH2trans,CH2cis}$ = −2.3 Hz, $J_{CH2trans,CH=}$ = 17.1 Hz, –CH=CH_{2trans}), 5.05 (dddd, 1 H, $J_{CH2cis,CH2b}$ = −1.2 Hz, $J_{CH2cis,CH2a}$ = −1.9 Hz, $J_{CH2trans,CH2cis}$ = −2.3 Hz, $J_{CH2cis,CH=}$ = 10.3 Hz, –CH=CH_{2cis}), 3.90 (dd, 1 H, $J_{3,4}$ = 1.3 Hz, $J_{2,3}$ = 7.7 Hz, H-3), 3.81 (dq, 1 H, $J_{5,CH3}$ = 6.2 Hz, $J_{4,5}$ = 7.7 Hz, H-5), 3.78 (ddd, 1 H, $J_{1,CH2a}$ = 3.3 Hz, $J_{1,CH2b}$ = 6.2 Hz, $J_{1,2}$ = 6.2 Hz, H-1), 3.61 (dd, 1 H, $J_{1,2}$ = 6.2 Hz, $J_{2,3}$ = 7.7 Hz, H-2), 3.54 (dd, 1 H, $J_{3,4}$ = 1.3 Hz, $J_{4,5}$ = 7.7 Hz, H-4), 2.48 (dddd, 1 H, $J_{CH2a,\ CH2trans}$ = −1.3 Hz, $J_{CH2a,\ CH2cis}$ = −1.9 Hz, $J_{CH2a,CH=}$ = 6.9 Hz, $J_{CH2a,CH2b}$ = −15.2 Hz, CH_{2a}), 2.25 (dddd, 1 H, $J_{CH2b,\ CH2cis}$ = −1.2 Hz, $J_{CH2b,\ CH2trans}$ = −1.3 Hz, $J_{CH2b,CH=}$ = 7.2 Hz, $J_{CH2a,CH2b}$ = −15.2 Hz, CH_{2b}), 1.26 (d, 3 H, $J_{5,CH3}$ = 6.2 Hz, CH_3). ^{13}C NMR (150.9 MHz, CD_3OD, 25 °C): δ = 137.0 (-*C*H=CH_2), 117.1 (CH=*C*H_2), 75.1 (C-4), 75.0 (C-2), 74.1 (C-1), 72.2 (C-3), 68.8 (C-5), 37.9 (*C*H_2), 20.6 (*C*H_3).

Hydroformylation in automated reactor system (AMTEC SPR16)

Catalysis experiments on a small scale were performed in the parallel autoclave system AMTEC SPR16, equipped with pressure sensors and a mass-flow controller and suitable for monitoring and recording gas uptakes throughout the reactions. The stainless steel autoclaves (12 mL) of the AMTEC SPR16 were flushed automatically with argon 6 times to remove oxygen traces. The reactors were charged with a solution of the precatalyst under argon. The atmosphere was further exchanged with a 1:1 mixture of CO/H_2 (gas exchange cycle 1) and the reactors were heated to T = 100 °C and pressurized with CO/H_2 to 20 bar. The preformation of the catalyst under the applied conditions was performed for 2 hours. Subsequently, the substrate dissolved in 3 mL of water was injected and the desired temperature as well as the final pressure was adjusted and kept constant throughout the

experiment. The gas uptake of CO/H_2 was monitored and recorded automatically. At the end of the catalysis experiments, the reactors were cooled to room temperature and the autoclave contents were analyzed by means of NMR spectroscopy.

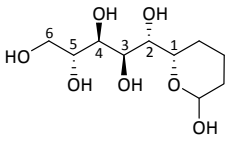
General procedure for the hydroformylation in water

In a typical experiment, the autoclave was charged with a solution of $[Rh(CO)_2(acac)]$ (acac=acetylacetonate) (7.6 mg, 0.030 mmol) and Sulfoxantphos (46.4 mg, 0.060 mmol) in degassed H_2O (10 mL). The catalyst was preformed at 20 bar (CO/H_2) and 80 °C for 2 h at 2000 rpm. Subsequently, the substrate **4** (0.92 g, 4.5 mmol) dissolved in degassed H_2O (15 mL) was added from a dropping funnel and the temperature was raised to 100 °C. Hydroformylation at 20 bar (CO/H_2) and 80 °C for 2 h at 2000 rpm was continued until full conversion was achieved (based on gas uptake). The reaction was stopped by cooling the reactor to room temperature and venting. Catalyst was removed by filtration through neutral alumina, the solvent was evaporated and the product characterized by NMR spectroscopy and HRMS.

General procedure for the hydroformylation in inverted aqueous biphasic system

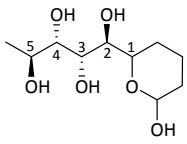
In a typical experiment, the autoclave was charged with a solution of $[Rh(CO)_2(acac)]$ and (7.6 mg, 0.030 mmol) and Xantphos (34.7 mg, 0.060 mmol) in toluene (15 mL). The catalyst was preformed at 20 bar (CO/H_2) and 80 °C for 2 h at 2000 rpm. Subsequently, the substrate **4** (0.92 g, 4.5 mmol) dissolved in degassed H_2O (15 mL) was added from a dropping funnel and the temperature was raised to 100 °C. Hydroformylation at 20 bar (CO/H_2) and 80 °C for 2 h at 2000 rpm was continued until full conversion was achieved (based on gas uptake). The reaction was stopped by cooling the reactor to room temperature and venting. Phase separation was immediate and the aqueous layer was concentrated and the product analyzed as above.

(*1S*,*2S*,*3R*,*4*R)-1-[(2S)-6-Hydroxytetrahydro-2*H*-pyran-2-yl]pentane-1,2,3,4,5-pentol (5)



White solid. R_f = 0.2 (EtOAc/MeOH= 9:1). ^{1}H NMR (600.13 MHz, CD_3OD, 25 °C): δ = 5.43 (br s, 1 H, anom. H), 4.45 (br s, 1 H, H-1), 4.10 (dd, appears as d), 1 H, $J_{2,3}$ = 9.4 Hz, H-2), 3.81 (dd, 1 H, $J_{6a,5}$ = 3.7 Hz, $J_{6a,6b}$ = −11.3 Hz, H-6a), 3.73 (dd, 1 H, $J_{3,4}$ = 1.1 Hz, $J_{4,5}$ = 8.6 Hz, H-4), 3.67 (ddd, 1 H, $J_{6a,5}$ = 3.7 Hz, $J_{6b,5}$ = 6.2 Hz, $J_{4,5}$ = 8.6 Hz, H-5), 3.62 (dd, 1 H, $J_{6b,5}$ = 6.2 Hz, $J_{6a,6b}$ = −11.3 Hz, H-6b), 3.56 (dd, 1 H, $J_{3,4}$ = 1.1 Hz, $J_{2,3}$ = 9.4 Hz, H-3), 1.95-1.87 (m, 2 H, ring-H), 1.66-1.54 (m, 4 H, ring H).^{13}C NMR (150.9 MHz, CD_3OD, 25 °C): δ = 103.9 (C-anom.), 79.0 (C-2) 76.9 (C-1), 72.8 (C-5), 71.2 (C-3), 70.9 (C-4), 65.3 (C-6), 32.2 (C-ring), 29.6 (C-ring), 17.1 (C-ring). HRMS calcd for $C_{10}H_{20}O_7Na$ $[M+Na]^+$ 275.1101, found 275.1096.

(1*R*,2*R*,3*S*,4*S*)-1-(6-Hydroxytetrahydro-2*H*-pyran-2-yl)pentane-1,2,3,4-tetrol (6)



White solid. R_f = 0.5 (EtOAc/MeOH= 9:1). ^{1}H NMR (600.13 MHz, CD_3OD, 25 °C): δ = 5.43 (br s, 1 H, anom. H), 4.45 (br s, 1 H, H-1), 4.08 (dd, appears as d, 1 H, $J_{2,3}$ = 9.4 Hz, H-2), 3.77 (dq, 1 H, $J_{5,CH3}$ = 6.3 Hz, $J_{4,5}$ = 8.1 Hz, H-5), 3.58 (dd, 1 H, $J_{3,4}$ = 1.2 Hz, $J_{2,3}$ = 9.4 Hz, H-3), 3.47 (dd, 1 H, $J_{3,4}$ = 1.2 Hz, $J_{4,5}$ = 8.1 Hz, H-4), 1.95-1.87 (m, 2 H, ring H), 1.66-1.53 (m, 4 H, ring H), 1.26 (d, 3 H, $J_{5,CH3}$ = 6.3 Hz, CH_3). ^{13}C NMR (150.9 MHz, CD_3OD, 25 °C): δ = 103.8 (C-anom), 79.2 (C-2), 76.8 (C-1), 74.6 (C-4), 70.9 (C-3), 68.2 (C-5), 32.1 (C-ring) 29.6 (C-ring), 20.6 (CH_3), 17.0 (C-ring). HRMS calcd for $C_{10}H_{20}O_6Na$ $[M+Na]^+$ 259.1152, found 259.1139.

3.6 References and Notes

[1] For further reading, see for example: Anastas, P.T.; Warner, J.C. *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998.

[2] Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411–2502.

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[4] (a) Kiliani, H. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 767–772. See also (b) Fischer, E. *J. Am. Chem. Soc.* **1890**, *12*, 461–471.

[5] (a) Railton, C. J.; Clive, D. L. J. *Carbohydr. Res.* **1996**, *281*, 69–77. (b) Jørgensen, M.; Iversen, E. H.; Madsen, R. *J. Org. Chem.* **2001**, *66*, 4625–4629.

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[13] See for example: Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329–3365.

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[17] Several literature methods for oxidation of the lactol-ring to the corresponding lactone were explored. Unfortunately, all the methods evaluated were unsuccessful in our hands. However, it seems to be possible to selectively oxidize the secondary hydroxyl groups on C-5 to the corresponding ketone. *Unpublished results.*

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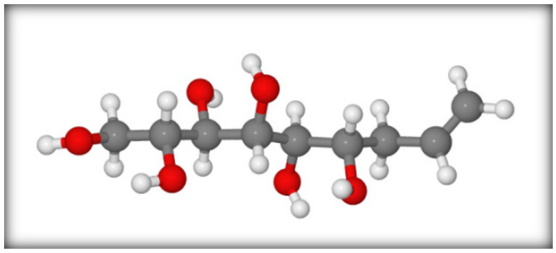
4 CONFORMATIONAL STUDY ON THE HOMOALLYLIC POLYOL DERIVED FROM MANNOSE



In this chapter, conformational analysis of a terminally unsaturated polyol derived from mannose is discussed. This structure is of particular interest due to its spontaneous aggregation behavior in water solution. The conformational analysis discussed herein is based on NMR spectroscopic studies. Moreover, geometry optimization was carried out in the gas phase and using an implicit water solvation through the COSMO solvation model.

This work will be submitted for publication:

Saloranta, T.; Dieterich, J.; Leino, R. et al. **Conformational Study on the Homoallylic Polyol Derived from Mannose and the Aggregation Behavior of the Same**, *manuscript in preparation.*

4.1 Introduction

Acyclic compounds generally adopt a planar zigzag conformation that minimizes the steric interactions between adjacent substituents. The same applies for acyclic carbohydrate derivatives in the absence of bulky substituents, e.g., hydroxyl groups, in 1,3-*syn* relationship. Thus, for example D-mannitol and D-galactitol adapt a linear conformation whereas the corresponding conformation of D-glucitol is distorted due to the *syn*-relationship between O-2 and O-4. The 1,3-*syn* interaction in D-glucitol can be relieved by 120° rotation about the C2-C3 bond leading to a twist in carbon chain (Figure 4.1).[1, 2]

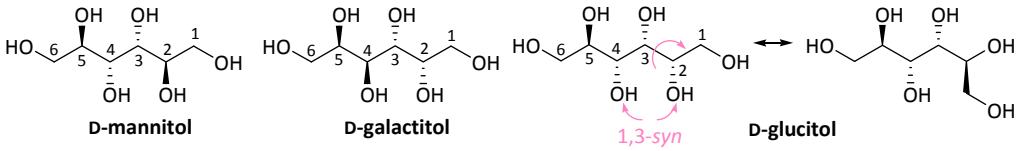
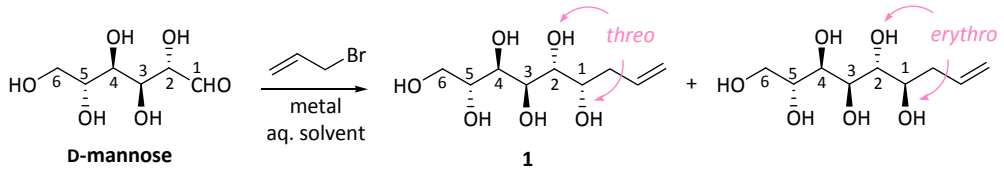


Figure 4.1. Linear zigzag conformations of D-mannitol and D-galactitol (left) and the distorted zigzag conformation of D-glucitol (right).

Other acyclic carbohydrate derivatives can be synthesized from monosaccharide precursors. For instance, metal-mediated allylation of unprotected monosaccharides yields, as shown in the previous chapter, homoallylic polyols containing several stereocenters. However, only one stereocenter (C-1) is formed in the reaction whereas the stereochemistry of the other carbon atoms is determined by the monosaccharide skeleton. That is, the reaction leads to a mixture of diastereoisomers with either *threo* och *erythro*-type configuration (C-1/C-2), where the *threo* form generally dominates (Scheme 4.1).[3] The diastereoisomers can be separated by means of acetylation-chromatography-deacetylation or in some cases by crystallisation.[3,4] The products obtained are thus diastereopure homoallylic polyols with versatile synthetic potential.



Scheme 4.1. Metal-mediated allylation of D-mannose yielding homoallylic polyols.

In the previous chapter, the homoallylic polyols derived from D-mannose and L-rhamnose were subjected to a hydroformylation reaction leading to polyhydroxylated lactols as a result of tandem hydroformylation-cyclization. In the course of the hydroformylation work, it was speculated about

the potential amphiphilic character of the substrate enabling biphasic catalytic processes even in the absence of a phase transfer agent. The approach was successfully challenged in the biphasic hydroformylation (water-toluene) using a catalyst soluble in the organic phase (Rh/Xantphos) while both the starting material and the product were water soluble. The pure experimental approach indicated that the homoallylic polyol truly has some amphiphilic character.

Furthermore, water solution of the *threo* form of the allylated D-mannose **1** showed unexpected, though highly interesting, behavior in our hands. The initially water soluble substrate aggregates spontaneously as the solution is stirred at constant (room) temperature (Figure 4.2). This phenomenon has only been observed with this particular substrate – never with the structural analogs with different configuration at the carbohydrate backbone. This experimental finding supports the hypothesis on the highly ordered structure of this particular compound enabling the formation of agglomerates, potentially as a result of amphiphilic effects.

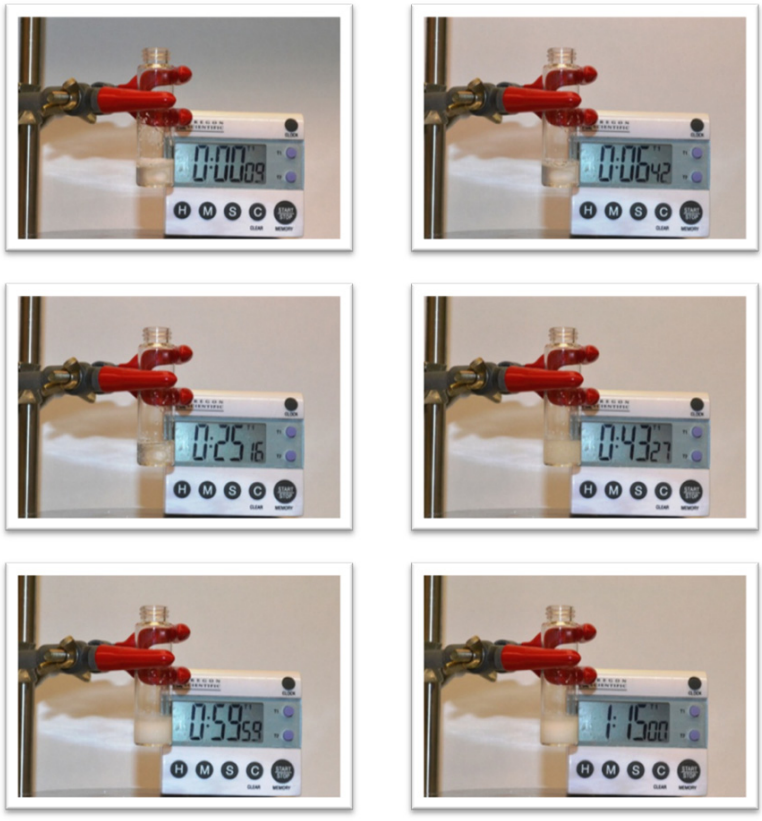


Figure 4.2. Spontaneous aggregation of a water solution of **1** (c = 0.2 M) at room temperature.

However, in order to validate this hypothesis, the structural details of the carbohydrate based homoallylic polyols required more detailed exploration. For this purpose, a detailed conformational study on D-mannose derived homoallylic polyol was pursued. Reference compounds, the corresponding D-glucose and D-galactose derived analogues, were likewise examined. Finally, the most stable conformations were modeled by computational methods.

4.2 Results and Discussion

Conformational studies on a series of carbohydrate based polyols up to heptitols have been reported by Lewis and coworkers.[2,5] The conclusions were mainly based on proton–proton vicinal coupling constants ($^3J_{H,H}$) and a Karplus type equation.[6] The general conformational analysis of acyclic structures based on *J*-couplings was formulated by Murata et al. in 1999.[7,8] In dioxygenated fragments, $^3J_{H,H}$ is less than 3 Hz when two protons are in gauche relationship, whereas $^3J_{H,H}$ varies between 7 and 10 Hz for *anti*-orientation (Figure 4.3). Thus, in an ideal zigzag conformation where the dihedral angles are either 60° (gauche) or 180° (anti), the corresponding values for $^3J_{H,H}$ should be either small or large, respectively. If, however, the coupling constant between two adjacent protons ($^3J_{H,H}$) in such structures is between 3 and 7 Hz (medium sized coupling), the corresponding conformation is twisted (nonlinear). It should be noted that the medium sized coupling cannot be utilized as such to define the conformation. The structures with twisted carbon chain may occur as a conformational mixture and the coupling constant is generally a weighted average of those resulting from each conformer.

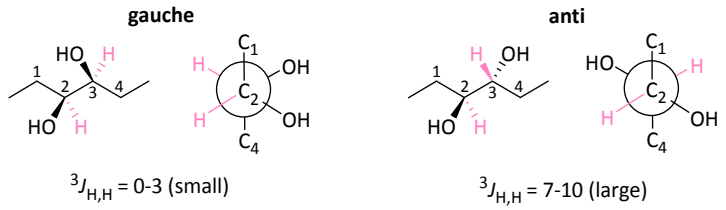
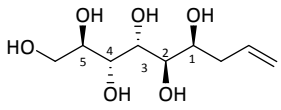
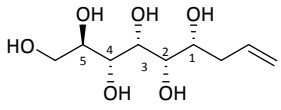
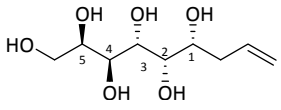


Figure 4.3. $^3J_{H,H}$ coupling constant dependence on dihedral angle.

In this context, the vicinal proton–proton coupling constants of homoallylic derivatives of D-mannose **1**, D-glucose **2**, D-galactose **3** were of interest. In order to obtain the accurate coupling constants of the overlapping signals, the ^{1}H NMR spectra of these compounds were analyzed by PERCH software with spin simulation/iteration techniques.[9] The coupling constants relevant for the conformations of these polyols are shown in Table 4.1.

Table 4.1. $^{3}J_{H,H}$ values for compounds **1**, **2** and **3** (given in Hz).

Entry	Structure	$^{3}J_{H1,H2}$		$^{3}J_{H2,H3}$		$^{3}J_{H3,H4}$		$^{3}J_{H4,H5}$	
1	 **1**	1.5	*threo*	9.4	*erythro*	1.1	*threo*	8.9	*erythro*
2	 **2**	3.5	*threo*	6.1	*threo*	2.3	*threo*	8.2	*erythro*
3	 **3**	6.6	*threo*	1.5	*threo*	9.2	*erythro*	1.6	*threo*

For linear structures with zigzag conformation, the protons in *threo* relationship should occur in *gauche* orientation whereas protons with *erythro* configuration should occur in *anti* orientation. This is perfectly valid for the D-mannose derivative **1** (Table 4.1, entry 1) as expected from the ideal configuration with no 1,3-*syn* OH-groups. For the D-galactose derivative **3**, the configuration is ideal for C2-C5. However, O-1 in the *threo* configuration is in *syn*-relationship to O-3 leading to a twist in the carbon chain as seen from the medium sized coupling constant (6.6 Hz) between protons H-1 and H-2 (entry 3). The effect is even more evident for the D-glucose derivative **2** (entry 2), where the values for three *threo* coupling constants vary between 2.3 Hz and 6.1 Hz indicating total distortion of the zigzag conformation. The reason for this is obvious: the *syn* relationship for both O-1/O-3 and O-2/O-4. Thus, based on the coupling constants, the D-glucose and D-galactose derived structures **2** and **3**, respectively, do not adapt a linear conformation whereas the D-mannose derived structure **1** has an ideal configuration for linear zigzag conformation.

This conclusion is further supported by NOESY experiments. For both D-glucose and D-galactose derivatives **2** and **3**, an NOE correlation between the C*H*$_2$-protons and *H*-3 is observed (Figure 4.5 and Figure 4.6). This is possible only if the carbon chain has lost the linear conformation allowing the olefinic end to come closer to the carbohydrate backbone. The corresponding NOE correlation is

missing for the D-mannose derivative strengthening the assumption about the linear zigzag conformation (Figure 4.4).

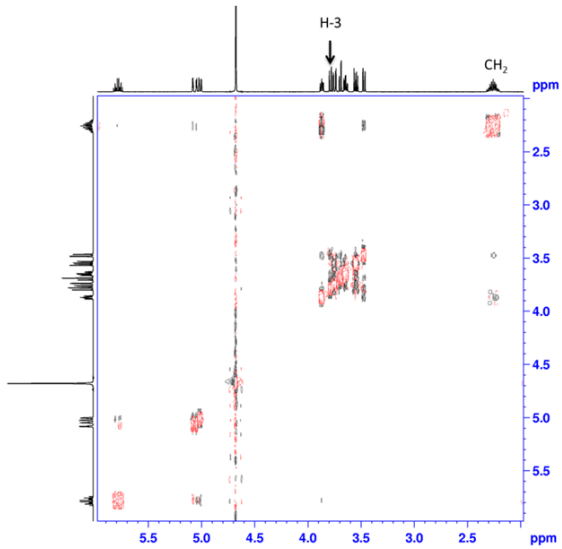


Figure 4.4. NOESY spectrum of compound **1** showing the absence of NOE correlation between CH_2 and *H*-3.

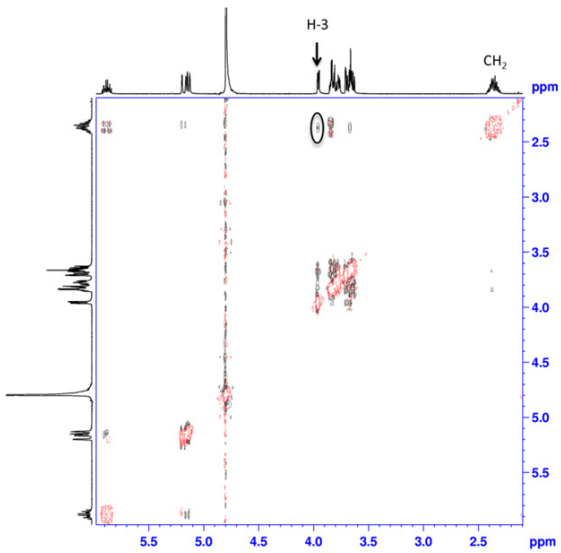


Figure 4.5. NOESY spectrum of compound **2** showing the NOE correlation between CH_2 and *H*-3.

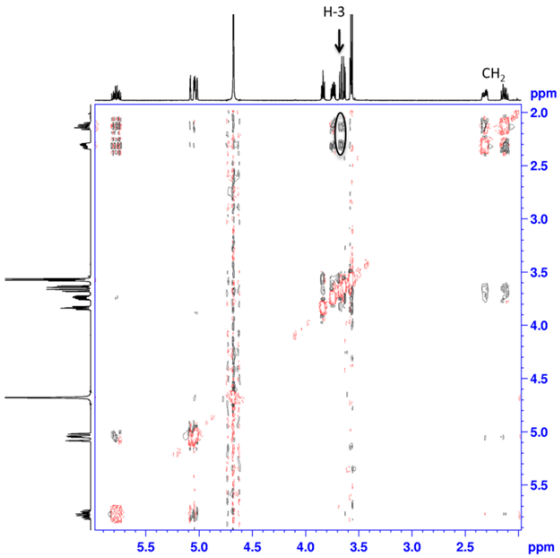


Figure 4.6. NOESY spectrum of compound **3** showing the NOE correlation between C*H*$_2$ and *H*-3.

Noteworthy, the linear conformation strongly influences the melting point as well. For the linear D-mannose derivative **1**, the melting point is 186 – 188 °C, whereas the melting point for non-linear-structures **2** and **3** is significantly lower, being 115 – 117 °C and 99 – 101 °C, respectively. The same phenomenon can be seen with the sugar alcohols, i.e., mannitol, galactitol and glucitol, as well (see Figure 4.1). For mannitol and galactitol uptaking the linear conformation, the corresponding melting points are 166 – 168 °C and 188 – 189 °C, whereas for the non-linear glucitol melts at 110 – 112 °C.[10]

The experimental results clearly indicate that the differences in relative stereochemistry of the OH-groups in the homoallylic polyols studied herein have significant influence on the preferred conformations for these compounds. The original hypothesis was that the conformational differences cause the different aggregation behavior. Therefore, to gain quantitative insight, a geometry optimization was carried out for each monomer structure in the gas phase and by using an implicit water solvation through the COSMO solvation model. In both cases, the ab initio DF-LMP2/aug'-cc-pVTZ level of theory was used for the optimization.[11] As can be visually seen from the optimized gas-phase geometries in Figure 4.7 and the corresponding COSMO-solvated geometries in Figure 4.8, the calculations support the experimental observation of a significant difference in planarity between the different allylated species. The relevant measure of planarity in these systems is the angle between *C5-C3-CH*, (numbering as in original carbohydrate structure, see Table 4.1). The

planarity of the system is proportional to this angle, with an angle of 180° corresponding to perfect planarity. The numeric values of this angle are given in Table 4.2.

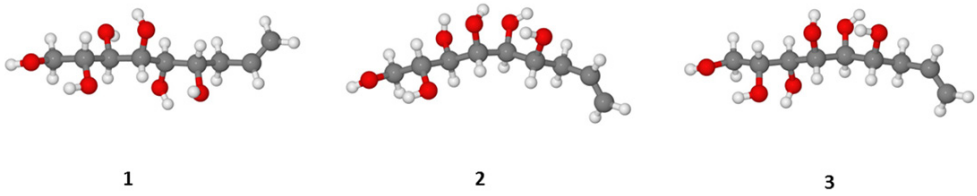


Figure 4.7. Optimized gas-phase geometries of the homoallylic derivatives of D-mannose (left), D-glucose (middle) and D-galactose (right).

Figure 4.8. Optimized COSMO-solvated geometries of the homoallylic derivatives of D-mannose (left), D-glucose (middle) and D-galactose (right).

Table 4.2. Relevant angle for planarity (*C5 – C3 – CH*) in the optimized structures. All values in degrees.

Structure	gas-phase	COSMO-solvated
1	176.6	177.6
2	156.1	168.3
3	169.2	171.0

The D-mannose derivative **1** is clearly close to planar in both gas-phase and with implicit water solvation applied. Both the D-glucose derivative **2** and D-galactose derivative **3** are far from planarity independent of the environment. In general, the implicit solvation reduces the bend of all structures. It should be noted that explicit solvation (atomistic water molecules) could potentially influence the geometry through hydrogen bonds. While the inclusion of a small number of water molecules would

still be computationally feasible on this level of theory, a complete static description would require a complete solvation shell together with a global optimization of the optimal bonding pattern. This in turn is not possible with the high level of theory used for the optimization. As the aggregation of the mannose derivative **1** occurs spontaneously in aqueous solution, the dynamic picture delivered by molecular dynamics (MD) simulations may be helpful in correctly assigning the driving force of the aggregation. Work in this direction is currently in progress.

4.3 Summary and Conclusions

In conclusion, based on the NMR spectroscopic data and geometry optimization presented herein, the homoallylic polyol derived from D-mannose **1** clearly adopts a linear conformation. This high level of structural order has supposedly a major impact on the aggregation behavior of this structure as shown experimentally with a water solution of **1**. The glucose and galactose based counterparts **2** and **3** adapt, in turn, a nonlinear conformation and do not show any aggregation behavior. The highly ordered three-dimensional structure of **1** encourages to seek for applications for this molecule. To exemplify, the terminal carbon–carbon double bond is easily utilized in different coupling reactions enabling synthesis of various hydrophilic functional materials.

4.4 Experimental Section

General remarks

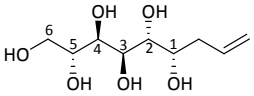
All NMR spectra were recorded with Bruker Avance 500 MHz or 600 MHz NMR spectrometers. ^{1}H NMR spectra were analyzed by PERCH software with spin simulation/iteration techniques.[9] For the sake of uniformity, the atoms are numbered as in the original carbohydrate structure when reporting NMR spectroscopic data, thus contradicting with the systematic nomenclature given in this chapter. Optical rotations were measured with Perkin Elmer 241 polarimeter equipped with a Na-lamp (589 nm). Melting points were recorded with a Stuart Scientific apparatus. HRMS were measured in ESI^{+} mode with Bruker micrOTOF-Q spectrometer.

*Synthesis of homoallylic polyols **1**, **2** and **3***

Compounds **1**, **2** and **3** were prepared according to the literature procedure.[3] Compound **1** was isolated by crystallization from EtOH (see also section 3.4 in this thesis). Compounds **2** and **3** were

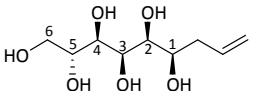
isolated after purification of the diastereomeric mixtures of peracetylated products by flash chromatography (eluent: hexane:acetone) followed by deprotection.

(2*R*,3*R*,4*R*,5*R*,6*S*)-Non-8-ene-1,2,3,4,5,6-hexol (1)



White solid. mp 186–188 °C. $[\alpha]_D^{20}$ = +22.8 (c = 1.0, H_2O). ^{1}H NMR (600.13 MHz, D_2O, 25 °C): δ = 5.89 (dddd, $J_{CH=,CH2b}$ = 6.9 Hz, $J_{CH=,CH2a}$ = 7.1 Hz, $J_{CH=,CH2cis}$ = 10.2 Hz, $J_{CH=,CH2trans}$ = 17.2 Hz, 1 H, –C*H*=CH_2), 5.18 (dddd, $J_{CH2trans,CH2a}$ = –1.4 Hz, $J_{CH2trans,CH2b}$ = –1.5 Hz, $J_{CH2trans,CH2cis}$ = –2.1 Hz, $J_{CH2trans,CH=}$ = 17.2 Hz, 1 H, –C*H*=CH_{2trans}), 5.13 (dddd, $J_{CH2cis,CH2a}$ = –1.1 Hz, $J_{CH2cis,CH2b}$ = –1.1 Hz, $J_{CH2cis,CH2trans}$ = –2.1 Hz, $J_{CH2cis,CH=}$ = 10.2 Hz, 1 H, –C*H*=CH_{2cis}), 3.99 (ddd, $J_{1,2}$ = 1.5 Hz, $J_{1,CH2a}$ = 5.7 Hz, $J_{1,CH2b}$ = 8.3 Hz, 1 H, H-1), 3.91 (dd, $J_{3,4}$ = 1.1 Hz, $J_{3,2}$ = 9.4 Hz, 1 H, H-3), 3.87 (dd, $J_{6a,5}$ = 3.0 Hz, $J_{6a,6b}$ = –11.9 Hz, 1 H, H-6a), 3.81 (dd, $J_{4,3}$ = 1.1 Hz, $J_{4,5}$ = 8.9 Hz, 1 H, H-4), 3.76 (ddd, $J_{5,6a}$ = 3.0 Hz, $J_{5,6b}$ = 6.5 Hz, $J_{5,4}$ = 8.9 Hz, 1 H, H-5), 3.67 (dd, $J_{6b,5}$ = 6.5 Hz, $J_{6b,6a}$ = –11.9 Hz, 1 H, H-6b), 3.59 (dd, $J_{2,1}$ = 1.5 Hz, $J_{2,3}$ = 9.4 Hz, 1 H, H-2), 2.39 (ddddd, $J_{CH2a,CH2cis}$ = -1.1 Hz, $J_{CH2a,CH2trans}$ = –1.4 Hz, $J_{CH2a,CH=}$ = 7.1 Hz, $J_{CH2a,1}$ = 8.3 Hz, $J_{CH2a,CH2b}$ = –14.2 Hz, 1 H, –CH_{2a}-CH=CH_2), 2.35 (ddddd, $J_{CH2b,CH2cis}$ = –1.1 Hz, $J_{CH2b,CH2trans}$ = –1.5 Hz, $J_{CH2b,1}$ = 5.7 Hz, $J_{CH2b,CH=}$ = 6.9 Hz, $J_{CH2b,CH2a}$ = –14.2 Hz, 1 H, –CH_{2b}-CH=CH_2) ppm. ^{13} NMR (150.9 MHz, D_2O, 25 °C): δ = 135.2 (-*C*H=CH_2), 117.3 (-CH=*C*H_2), 71.0 (C-2), 70.9 (C-5), 69.4 (C-5), 69.3 (C-1), 68.5 (C-3), 63.2 (C-6), 37.6 (-*C*H-CH=CH_2) ppm. HRMS calcd for $C_9H_{18}O_6Na$ $[M+Na]^+$ 245.0996, found 245.0984.

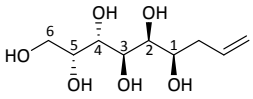
(2*R*,3*R*,4*R*,5*S*,6*R*)-Non-8-ene-1,2,3,4,5,6-hexol (2)



White solid. mp 99–101 °C. $[\alpha]_D^{20}$ = –3.5 (c = 1.0, H_2O). ^{1}H NMR (600.13 MHz, D_2O, 25 °C): δ = 5.88 (dddd, $J_{CH=,CH2a}$ = 6.6 Hz, $J_{CH=,CH2b}$ = 7.5 Hz, $J_{CH=,CH2cis}$ = 10.2 Hz, $J_{CH=,CH2trans}$ = 17.2 Hz, 1 H, –C*H*=CH_2), 5.18 (dddd, $J_{CH2trans,CH2b}$ = –1.4 Hz, $J_{CH2trans,CH2a}$ = –1.6 Hz, $J_{CH2trans,CH2cis}$ = –2.1 Hz, $J_{CH2trans,CH=}$ = 17.2 Hz, 1 H, –C*H*=CH_{2trans}), 5.14 (dddd, $J_{CH2cis,CH2b}$ = –1.0 Hz, $J_{CH2cis,CH2a}$ = –1.2 Hz, $J_{CH2cis,CH2trans}$ = –2.1 Hz, $J_{CH2cis,CH=}$ = 10.2 Hz, 1 H, –C*H*=CH_{2cis}), 3.96 (dd, $J_{3,4}$ = 2.3 Hz, $J_{3,2}$ = 6.1 Hz, 1 H, H-3), 3.84 (ddd, $J_{1,2}$ = 3.5 Hz, $J_{1,CH2a}$ = 5.0 Hz, $J_{1,CH2b}$ = 8.2 Hz, 1 H, H-1), 3.82 (dd, $J_{6a,5}$ = 3.0 Hz, $J_{6a,6b}$ = –11.9 Hz, 1 H, H-6a), 3.78 (ddd, $J_{5,6a}$ = 3.0 Hz, $J_{5,6b}$ = 6.4 Hz, $J_{5,4}$ = 8.2 Hz, 1 H, H-5), 3.70 (dd, $J_{4,3}$ = 2.3 Hz, $J_{4,5}$ = 8.2 Hz, 1 H, H-4), 3.67 (dd, $J_{2,1}$ = 3.5 Hz, $J_{2,3}$ = 6.1 Hz, 1 H, H-2), 3.65 (dd, $J_{6b,5}$ = 6.4 Hz, $J_{6b,6a}$ = –11.9 Hz, 1 H, H-6b), 2.39 (ddddd, $J_{CH2a,CH2cis}$ = –1.2 Hz, $J_{CH2a,CH2trans}$ = –1.6 Hz, $J_{CH2a,1}$ = 5.0 Hz, $J_{CH2a,CH=}$ = 6.6 Hz, $J_{CH2a,CH2b}$ = –14.3 Hz, 1 H, –CH_{2a}-CH=CH_2), 2.34

(ddddd, $J_{CH2b,CH2cis}$ = −1.0 Hz, $J_{CH2b,CH2trans}$ = −1.4 Hz, $J_{CH2b,CH=}$ = 7.5 Hz, $J_{CH2b,1}$ = 8.2 Hz, $J_{CH2b,CH2a}$ = −14.3 Hz, 1 H, −CH_{2b}-CH=CH_2) ppm. ^{13}C NMR (150.9 MHz, D_2O, 25 °C): δ = 134.7 (-*C*H=CH_2), 117.6 (-CH=*C*H_2), 73.8 (C-2), 71.0 (C-4), 71.0 (C-5), 70.3 (C-1), 69.9 (C-3), 62.8 (C-6), 37.4 (-*C*H-CH=CH_2) ppm. HRMS calcd for $C_9H_{18}O_6Na$ $[M+Na]^+$ 245.0996, found 245.1002.

(2*R*,3*S*,4*R*,5*S*,6*R*)-Non-8-ene-1,2,3,4,5,6-hexol (3)



White solid. mp 115–117 °C. $[\alpha]_D^{20}$ = −1.2 (c = 1.0, H_2O). ^{1}H NMR (600.13 MHz, D_2O, 25 °C): δ = 5.89 (dddd, $J_{CH=,CH2a}$ = 6.5 Hz, $J_{CH=,CH2b}$ = 7.7 Hz, $J_{CH=,CH2cis}$ = 10.2 Hz, $J_{CH=,CH2trans}$ = 17.2 Hz, 1 H, −C*H*=CH_2), 5.18 (dddd, $J_{CH2trans,CH2b}$ = −1.3 Hz, $J_{CH2trans,CH2a}$ = −1.6 Hz, $J_{CH2trans,CH2cis}$ = −2.1 Hz, $J_{CH2trans,CH=}$ = 17.2 Hz, 1 H, −C*H*=CH_{2trans}), 5.15 (dddd, $J_{CH2cis,CH2b}$ = −1.0 Hz, $J_{CH2cis,CH2a}$ = −1.2 Hz, $J_{CH2cis,CH2trans}$ = −2.1 Hz, $J_{CH2cis,CH=}$ = 10.2 Hz, 1 H, −C*H*=CH_{2cis}), 3.95 (ddd, $J_{5,4}$ = 1.6 Hz, $J_{5,6a}$ = 4.8 Hz, $J_{5,6b}$ = 8.0 Hz, 1 H, H-5), 3.86 (ddd, $J_{1,CH2a}$ = 4.1 Hz, $J_{1,2}$ = 6.6 Hz, $J_{1,CH2b}$ = 8.3 Hz, 1 H, H-1), 3.78 (dd, $J_{3,2}$ = 1.5 Hz, $J_{3,4}$ = 9.2 Hz, 1 H, H-3), 3.75 (dd, $J_{2,3}$ = 1.5 Hz, $J_{2,1}$ = 6.6 Hz, 1 H, H-2), 3.69 (dd, $J_{4,5}$ = 1.6 Hz, $J_{4,3}$ = 9.2 Hz, 1 H, H-4), 3.69 (dd, $J_{6a,5}$ = 4.8 Hz, $J_{6a,6b}$ = −10.2 Hz, 1 H, H-6a), 3.68 (dd, $J_{6b,5}$ = 8.0 Hz, $J_{6b,6a}$ = −10.2 Hz, 1 H, H-6b), 2.42 (ddddd, $J_{CH2a,CH2cis}$ = −1.2 Hz, $J_{CH2a,CH2trans}$ = −1.6 Hz, $J_{CH2a,1}$ = 4.1 Hz, $J_{CH2a,CH=}$ = 6.5 Hz, $J_{CH2a,CH2b}$ = −14.5 Hz, 1 H, −CH_{2a}-CH=CH_2), 2.25 (ddddd, $J_{CH2b,CH2cis}$ = −1.0 Hz, $J_{CH2b,CH2trans}$ = −1.3 Hz, $J_{CH2b,CH=}$ = 7.7 Hz, $J_{CH2b,1}$ = 8.3 Hz, $J_{CH2b,CH2a}$ = −14.5 Hz, 1 H, −CH_{2b}-CH=CH_2) ppm. ^{13}C NMR (150.9 MHz, D_2O, 25 °C): δ = 134.5 (-*C*H=CH_2), 117.8 (-CH=*C*H_2), 72.2 (C-1), 71.7 (C-2), 70.0 (C-5), 70.0 (C-3), 69.5 (C-4), 63.2 (C-6), 37.0 (-*C*H-CH=CH_2) ppm. HRMS calcd for $C_9H_{18}O_6Na$ $[M+Na]^+$ 245.0996, found 245.1002.

4.5 References and Notes

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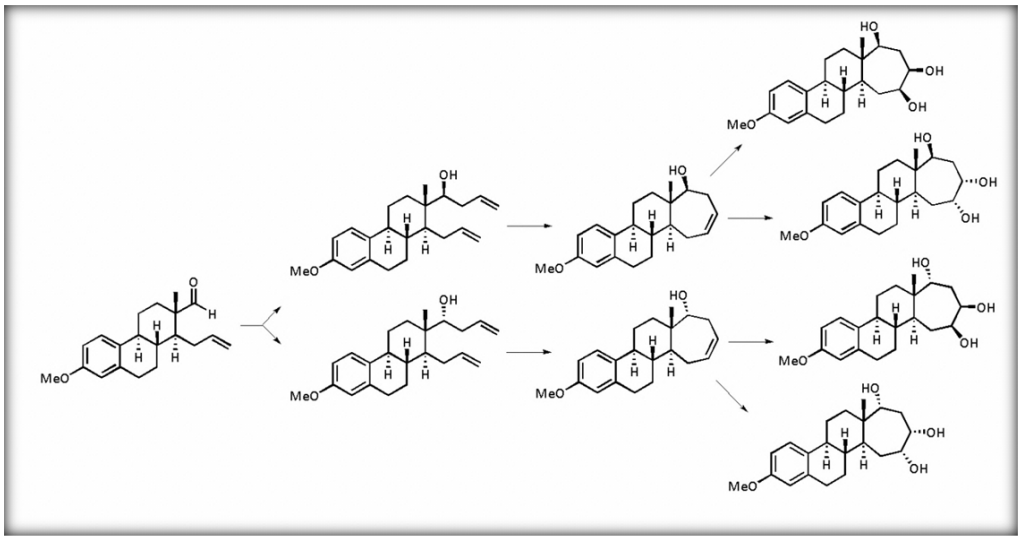
[11] aug-cc-pVTZ basis sets on all non-hydrogen atoms, ss-pVTZ on hydrogen atoms

5 SYNTHESIS OF AMPHIPHILIC ESTRADIOL DERIVATIVES



In this chapter, synthesis of a small library of estradiol derivatives with limited hydrophilicity by Barbier-type allylation – ring-closing metathesis – asymmetric dihydroxylation sequence is presented. All compounds prepared were fully characterized by NMR spectroscopic techniques and completely assigned ^{1}H and ^{13}C NMR spectra are reported herein. Furthermore, the effects of the synthesized amphiphilic steroid derivatives on the proliferation of cancer cells were evaluated.

This chapter is based on the original publication:

Saloranta, T.; Zupkó, I.; Rahkila, J.; Schneider, G.; Wölfling, J.; Leino, R. **Increasing the Amphiphilicity of an Estradiol Based Steroid Structure by Barbier-Allylation - Ring-Closing Metathesis - Dihydroxylation Sequence**, *Steroids* **2012**, *77*, 110–117.

5.1 Introduction

Modification of natural products by chemical methods is an interdisciplinary field of research where the objective is to investigate the influence of structural modifications on both chemical as well as biological properties (structure-activity relationships, SAR). In steroid chemistry, modifications are often aimed at the sterane skeleton or external functional groups with the ultimate goal being to develop new steroid based structures with modified potential in biological and/or pharmaceutical applications.

One possible modification strategy for steroids is to gradually increase the hydrophilicity and, concomitantly, the amphiphilic character of the molecule. Polyhydroxylated steroids, such as brassinosteroids[1,2] and phytoecdysteroids[3] (Figure 5.1) are important compounds possessing interesting pharmacological properties. Glycosteroids, in turn, form a class of molecules that distinctly contain a hydrophobic aglycon part and a hydrophilic glycone part. Such structures result, likewise, in various biologically and pharmaceutically engrossing properties.[4]

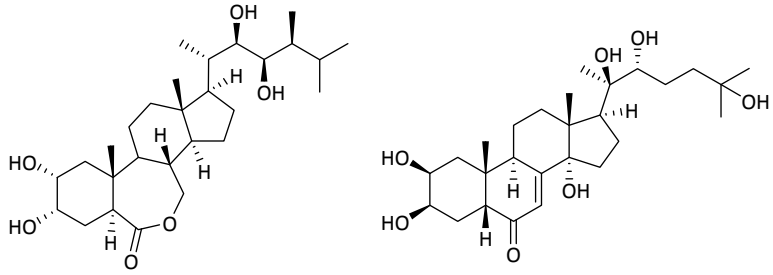
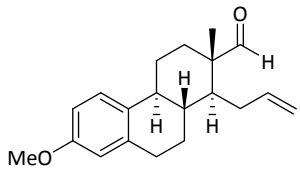


Figure 5.1. The structures of brassinolide and 20-hydroxyecdysone, the most prominent compounds in the families of brassinosteroids and phytoecdysteroids.

It is thus of great interest to develop synthesis routes towards steroid derivatives with limited hydrophilicity and evaluate their potential in biological applications. The obtained molecules with increased hydrophilicity would structurally mimic other hydrophilic steroid based compounds, including the brassinosteroids and phytoecdysteroids, yet retaining the hydrophilic properties between those of unmodified steroids and glycosteroids.

D-Secoestrone derivative **1** (Figure 5.2) has previously been used as a precursor for a number of other modified steroid structures.[5] The aldehyde and allyl functionalities stemming from the D-ring allow for a number of modifications resulting in either acyclic or cyclic substitutes for the D-ring.[6] Herein, the focus was directed on converting the aldehyde functionality into a carbon–carbon double bond

containing moiety, thus creating the possibility to apply ring closing metathesis (RCM) resulting in a medium-sized ring that would mimic the D-ring of steroids. Furthermore, after RCM, the newly constructed ring remains unsaturated allowing for further modifications to be explored.



1

Figure 5.2. Structure of the D-secoestrone derivative **1**.

In this chapter, a straightforward synthetic route towards estradiol based semisynthetic steroids with increased amphiphilicity based on a Barbier-type allylation – ring-closing metathesis – asymmetric dihydroxylation reaction sequence is described. All compounds prepared were fully characterized by 1D and 2D NMR spectroscopic methods and completely assigned ^{1}H and ^{13}C NMR spectra are reported. Finally, the cytotoxic activity of all new compounds was evaluated and is briefly discussed herein.

5.2 Results and Discussion

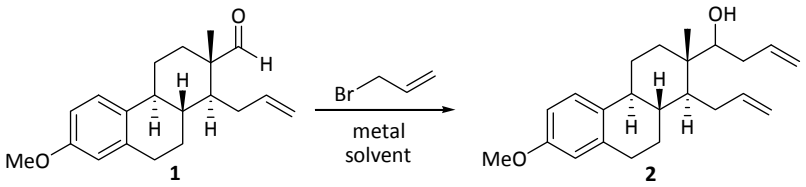
5.2.1 Synthesis and Characterization

While the Barbier-type allylation of carbonyl compounds has been proven as a versatile and reliable synthetic tool, its application for modification of steroid structures has remained relatively unexplored. In the pioneering work of Loh and coworkers, In-mediated allylation of a steroidal aldehyde with various allyl bromides was explored.[7] High chemoselectivities and moderate to high diastereoselectivities were obtained, thus proving the viability of the method for stereoselective construction and modification of steroid side chains.

Here, the metal-mediated allylation of the D-secoestrone derivative **1** was studied in both anhydrous and aqueous media using indium or zinc as the mediating metal. Cyclic ethers THF and 1,4-dioxane and their aqueous mixtures were evaluated as solvents. The results are presented in Table 5.1. The allylation proceeded best in anhydrous solvents (entries 1, 3, 5 and 7) and in THF:H_2O with indium as the mediating metal (entry 2) providing the homoallylic product in nearly quantitative conversion and isolated yield exceeding 90%. In the Zn-mediated reactions in aqueous media (entries 6 and 8)

and the In-mediated allylation in dioxane:H_2O (entry 4), the conversion was, however, remarkably lower than in the reactions carried out under anhydrous conditions. In all reactions, the major product possesses *S*-configuration (**2a**) at the newly formed stereocenter. The configuration was determined and verified in earlier work published by our group.[8] The determination was based on NOESY experiments, the main product being also consistent with the Felkin-Anh model. The diastereomeric ratio slightly depends on the metal and solvent used, with the best selectivity obtained using indium in anhydrous THF.

Table 5.1. Metal-mediated allylation of **1** in different solvents and solvent mixtures.[a]



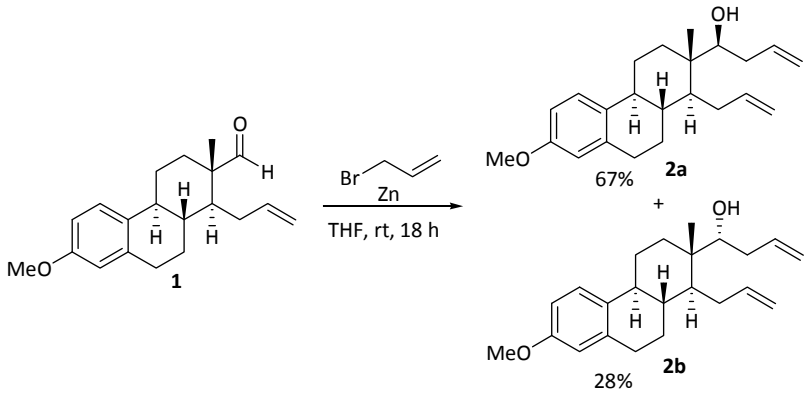
Entry	Metal	Solvent	Conversion (%)[b]		*S*/*R*[b]
1	In	THF	99	99[c]	76:24
2	In	THF:H_2O (1:1)	92	87[c]	69:31
3	In	1,4-dioxane	96	84[c]	69:31
4	In	1,4-dioxane:H_2O (1:1)	51	41[c]	69:31
5	Zn	THF	97	99[c]	69:31
6	Zn	THF:NH_4Cl_{aq} (1:1)	42	32[c]	67:33
7	Zn	1,4-dioxane	98	97[c]	68:32
8	Zn	1,4-dioxane:NH_4Cl_{aq} (1:1)	37	28[c]	68:32

[a] Allylations were performed in 0.1 mmol scale with 3 equivalents of metal and allyl bromide, respectively, at rt for 18 h.

[b] Conversions and *S*/*R*-ratios were determined by ^{1}H NMR spectroscopy.

[c] Reaction performed in the presence of 1 equivalent of BHT.

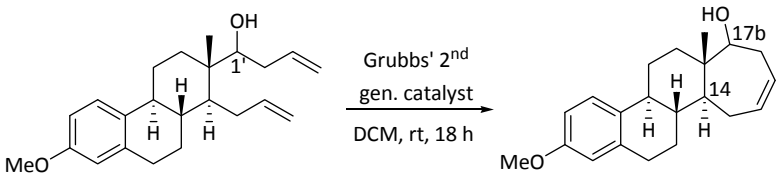
The diastereomers of the homoallylic alcohol can be separated by flash chromatography. For this work, both diastereomers were deemed equally valuable and the allylation was scaled up in THF using Zn as the mediating metal. On 1 g scale, the pure diastereomers were obtained in 67% and 28% yields, respectively, equaling to a total isolated yield of 95% (Scheme 5.1).



Scheme 5.1. Synthesis of homoallylic derivatives of **1**.

In order to study the mechanism of the metal-mediated Barbier-type allylation with this particular substrate, an additional solvent/metal screening in the presence of a radical scavenger (2,6-bis(1,1-dimethylethyl)-4-methylphenol, BHT) was performed. The aim was to evaluate experimentally the possibility for a mechanism involving radical intermediates. The results are summarized in Table 5.1.[9] Based on this data, it seems that the addition of BHT does not significantly change the conversion as compared to the allylations in the absence of any additives. This, in turn, indicate that that the Barbier-type allylation of substrate **1** in THF or 1,4-dioxane or aqueous mixtures of the same using indium or zinc as the mediating metal does not follow a mechanism involving radical species. It is thus more probable that the In- and Zn-mediated allylation proceeds through discrete allylmetal species in both anhydrous and aqueous media. This conclusion is in agreement with the recent study on Barbier-type allylation in aqueous media by Fristrup and Madsen et al., [10] and suggests a similar mechanism for the allylation under anhydrous conditions as well.[11]

With the diallylic steroid derivatives **2a** and **2b** available, it was now possible to investigate the applicability of ring-closing olefin metathesis to these structures. Ring-closing olefin metathesis (RCM) has recently been applied in steroid chemistry for example in the construction of taxosteroids [12] and in the synthesis of furanic-steroid derivatives. [13] In recent work from our laboratories, RCM was successfully applied to the synthesis of a series of glycosteroids containing a modified D-ring.[8] The cyclization required 10 mol-% of the Ru-catalyst at elevated temperature. In the case of the diallylic substrates **2a** and **2b**, the RCM proceeded smoothly at room temperature and the catalyst loading could be decreased to 4 mol-%. The product, steroid derivative containing an unsaturated seven-membered D-ring was obtained in 90% yield (Scheme 5.2).



2a (1'-*S*)
2b (1'-*R*)

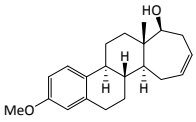
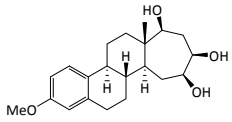
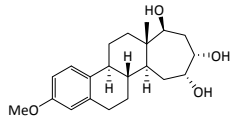
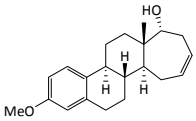
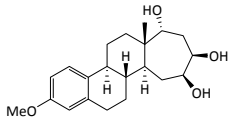
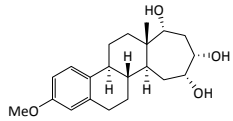
3a (17bβ)
3b (17bα)

Scheme 5.2. Ring closing-olefin metathesis of compounds **2a** and **2b** providing **3a** and **3b**, respectively.

Based on the NMR spectroscopic data of the ring-closed products, the configuration of carbon atom 17b is further supported by the notable difference in the chemical shifts of H-14 in compounds **3a** and **3b**, respectively. In **3b**, the hydroxyl group is on the same side of the ring with H-14 with the chemical shift for H-14 being 1.50 ppm. In **3a** the corresponding chemical shift for H-14 is 1.27 ppm.

The unsaturated modified D-ring allows further modifications to be explored. The original goal was to synthesize steroid derivatives possessing enhanced hydrophilicity. Therefore, the objective was a stereoselective oxidation of the double bond to yield a small library of steroid derivatives containing a functionalized D-ring. For steroid derivatives, epoxide and *syn*-diol functionalities are found in several biologically relevant structures.[14] Here, Sharpless asymmetric dihydroxylation (AD) was explored using the commercially available AD-mix-α and AD-mix-β mixtures for dihydroxylation of the seven-membered D-ring. It was anticipated that the chiral centers close to the double bond, the methyl group in particular, together with the chiral ligands would steer the stereochemical outcome of the reaction. The reactions were performed under standard conditions at +4 °C in the presence of 2 equiv of $MeSO_2NH_2$. The reaction time was 2–6 days depending on the substrate and catalyst mixture used. The selectivity varied from 6:1 (**3a** with AD-mix-α) to fully selective (**3a** with AD-mix-β) with AD-mix-β generally providing higher selectivities, consistent with literature precedence. The diastereomers **5a** and **5b** were separated by flash chromatography whereas **4a** and **4b** could not be separated and thus, **4a** could not be isolated in pure form (Table 5.2).

Table 5.2. Asymmetric dihydroxylation of **3a** and **3b** with AD-mix.

Entry	Substrate	AD-mix-α	yield (%)	AD-mix-β	yield (%)
1	 **3a**	 **4a**	71[a]	 **4b**	78
2	 **3b**	 **5a**	80	 **5b**	82

[a] **4a** not isolated; the yield is calculated as percentage of the total yield.

All isolated products were fully characterized by NMR spectroscopy. The ^{1}H NMR spectra of the modified steroids are, however, generally very complex due to severe overlapping of the signals. Complete assignment of the ^{1}H NMR spectroscopic data is important in determining the structural details, i.e., conformation and configuration of the newly formed stereocenters. For this purpose, the ^{1}H NMR spectra were analyzed by PERCH software with spin simulation/iteration techniques.[15] The original and simulated ^{1}H NMR spectra of **5a** are shown in Figure 5.3.

Configurations of the carbon atoms 16 and 17 in the dihydroxylated structures were determined from the accurate coupling constants. To exemplify, in compound **5a** the coupling constant between H-14 and H-15$_b$ is 8.4 Hz, whereas the coupling constant between H-15$_b$ and H-16 is 10.5 Hz, thus indicating an axial-axial-axial type pattern. The corresponding coupling constants for **5b** are $J_{14,15b}$ = 12.2 Hz and $J_{15b,16}$ = 1.8 Hz indicating an axial-axial-equatorial type relationship between these protons. Similar reasoning applies to **4b** containing OH-groups at C-16 and C-17 in configurations similar to those in **5b.** Since accurate proton–proton coupling constants for **4a** could not be obtained, the proposed structure of **4a** is based on logical reasoning and not on the coupling constants. Further support for this reasoning is obtained from the chemical shifts of H-14. The deshielding effect of the D-ring OH-groups on the chemical shift of the adjacent proton (H-14) increases in the order **4a** < **5a** < **4b** < **5b** and the corresponding chemical shifts for H-14 are 0.90, 1.26, 1.57 and 1.89, respectively. To conclude, the configurations indicate that the diastereomeric induction stems from the methyl group and the chiral ligand used, while the OH-group at C-17$_b$ has no significant effect.

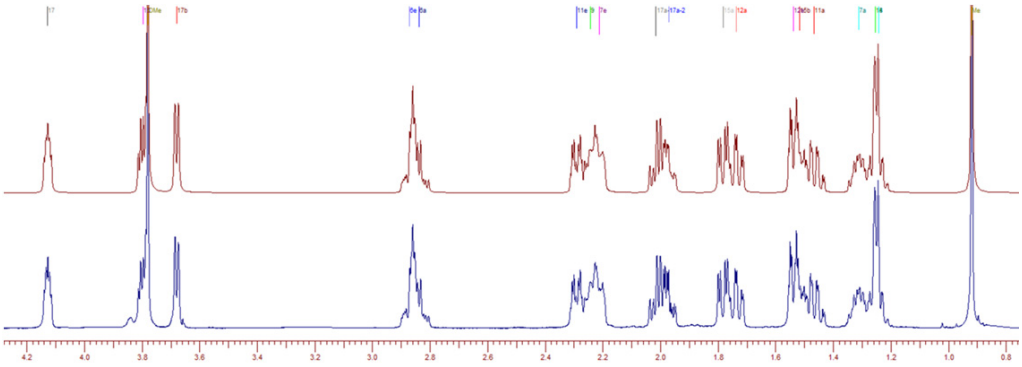


Figure 5.3. Spectral simulation of the ^{1}H NMR spectrum of **5a** (0.8-4.2 ppm range) with the PERCH NMR software: simulated spectrum (top) and observed spectrum (bottom).

5.2.2 Biological Evaluations

The effects of the synthesized compounds on the growth of four human malignant cell lines are presented in Table 5.3. While there are no generally accepted thresholds for antiproliferative efficacies, a growth inhibiting action lower than 20% can not be considered as substantial and have therefore not been specified.

Table 5.3. Effects of the synthesized substances on the proliferation of cancer cells.

			Growth inhibition (%) ± SEM			
Entry	**Compound**	**Concentration**	**HeLa**	**MCF7**	**A2780**	**A431**
1	**2a**	10 μM	-[a]	-	-	-
		30 μM	26.46 ± 2.17	-	31.25 ± 1.17	-
2	**2b**	10 μM	-	-	-	-
		30 μM	-	-	26.86 ± 0.72	-
3	**3a**	10 μM	25.22 ± 0.81	-	42.58 ± 2.14	26.36 ± 1.96
		30 μM	98.01 ± 0.13	61.63 ± 0.69	79.13 ± 0.60	79.02 ± 0.59
4	**3b**	10 μM	-	-	-	-
		30 μM	26.99 ± 1.98	20.02 ± 1.98	37.39 ± 0.70	-
5	**4a**[b]	10 μM	-	-	-	-
		30 μM	-	20.07 ± 2.71	-	-
6	**4b**	10 μM	-	-	-	-
		30 μM	30.74 ± 0.98	30.82 ± 2.33	58.91 ± 0.82	37.29 ± 1.22
7	**5a**	10 μM	-	-	-	-
		30 μM	24.64 ± 2.62	-	46.16 ± 0.65	30.89 ± 2.36
8	**5b**	10 μM	22.59 ± 2.52	20.04 ± 2.23	49.07 ± 1.25	40.12 ± 1.39
		30 μM	93.93 ± 0.46	64.83 ± 1.81	76.44 ± 0.56	72.59 ± 0.85
9	**Cisplatin**	10 μM	42.61 ± 2.33	53.03 ±2.29	83.57 ± 1.21	88.64 ± 0.50
		30 μM	99.93 ± 0.26	86.90 ± 1.24	95.02 ± 0.28	90.18 ± 1.78

[a] Compounds eliciting less than 20% inhibition of proliferation at a given concentration were considered ineffective and the exact results are not presented for simplicity.

[b] Compound **4a** was tested as a 6:1 mixture of **4a** and **4b** (see experimental section).

The diallylic D-secoestrone derivatives **2a** and **2b** did not exert any measurable cytostatic action (entries 1 and 2). In turn, the antiproliferative properties of the steroid derivatives containing seven-membered D-rings (entries 3-8) are strongly dependent on the structural details, i.e., the number and orientation of the OH-groups. In the case of compounds containing a monohydroxylated D-ring, β-configuration at position 17b (structure **3a**, entry 3) is clearly preferred over α-configuration (structure **3b**, entry 4). The pharmacological profile of the trihydroxylated compounds (**4a**, **4b**, **5a** and **5b**, entries 5–8) exhibited, however, a more complex pattern. The efficacy of **3a** is substantially decreased by further hydroxylation of the D-ring, especially by the OH-groups in β-configuration (entry 5), while **3b** can be rendered more potent by creating *syn*-diol functionality in α-configuration (entry 8). Since the activities of **3a** and **5b** are comparable, while both are less effective than the reference agent cisplatin, the optimal degree of hydroxylation can not be established from the

present data. Significant cell type dependent differences were not detected, suggesting nonspecific action on cell growth.

5.3 Summary and Conclusions

To conclude, a three step straightforward sequence consisting of Barbier-type allylation, ring-closing olefin metathesis, and dihydroxylation was evaluated and successfully applied for a D-secoestrone derivative. Eight new amphiphilic steroid structures were obtained in good to excellent yield. Furthermore, the completely characterized NMR spectroscopic data of the synthesized structures was provided. The amphiphilic steroid derivatives were evaluated in biological assays. General correlations between the number or configuration of OH-groups and the pharmacological effect were not found. However, based on the significant pharmacological differences of the presented analogs, in spite of the closely related structure, the synthesis and investigation of further analogs is strongly encouraged.

5.4 Experimental Section

General remarks

The allylation and ring-closing metathesis reactions were performed under dry argon atmosphere using anhydrous solvents. THF and 1,4-dioxane were distilled over Na/benzophenone and DCM was distilled over CaH_2. All anhydrous solvents were stored under argon. All other reagents were purchased and used as received. NMR spectra were recorded with Bruker Avance 600 MHz NMR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in combination with the following 2D-techniques: DQF-COSY, HSQC, and HMBC by using pulse sequences provided by the manufacturer. Chemical shifts are expressed on the δ scale (in ppm) using TMS (tetramethylsilane) as internal standard. Coupling constants are given in Hz. Coupling patterns are given as s, singlet; d, doublet; t, triplet; etc. ^{1}H NMR spectra were analyzed by PERCH software with spin simulation/iteration techniques.[15] Figure 5.4 indicates the numbering system used. Chemical shifts, multiplicities and coupling constants for compounds **2a** and **2b** are collected in Table 5.4, for compounds **3a** and **3b** in Table 5.5 for compounds **4a** and **4b** in Table 5.6 and for compounds **5a** and **5b** in Table 5.7**.** HRMS were measured in ESI^{+} mode using Bruker micrOTOF-Q or Fisons ZABSpecETOF spectrometers. Optical rotations were measured with Perkin Elmer 241 polarimeter equipped with a Na-lamp (589 nm). Flash chromatography was performed using Silica Gel 60 (Fluka, 0.04–0.063 mm).

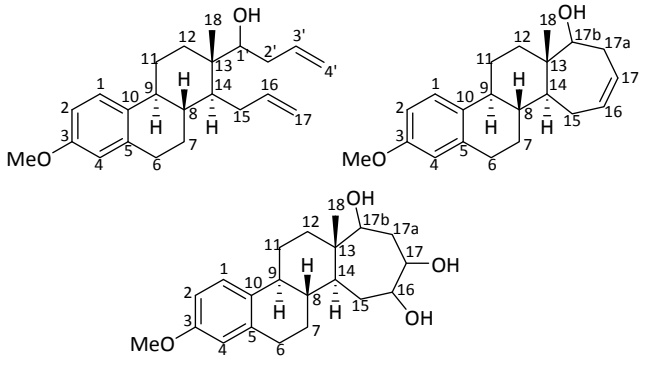
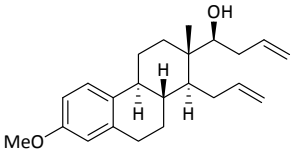


Figure 5.4. Numbering of the steroid backbones.

*Synthesis of **2a** and **2b**: Procedure for metal-mediated allylation*

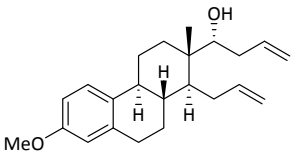
1 (990 mg, 3.3 mmol) was dissolved in anhydrous THF (70 mL). Zinc (660 mg, 10.1 mmol) and allyl bromide (0.87 mL, 10.1 mmol) were added and the mixture was stirred at room temperature for 18 h. The reaction was quenched by adding 1 M HCl until pH ≈ 3 whereafter the mixture was extracted with Et_2O (2 × 100 mL). The organic layers were washed with saturated $NaHCO_3$ solution (2 × 100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (hexane:EtOAc, 4:1) providing the pure diastereomers as colorless oils.

(1'*S*)-13-(1'-Hydroxybut-3'-enyl)-3-methoxy-13,17-secoestra-1,2,5(10),16-tetraene (2a)



(748 mg, 2.2 mmol, 67%). R_f = 0.5 (hexane:EtOAc, 4:1). $[\alpha]_D^{20}$ = +59.3 (c = 0.01, $CHCl_3$). HRMS calcd for $C_{23}H_{32}O_2$ $[M]^+$ 340.2397, found 340.2396.

(1'*R*)-13-(1'-Hydroxybut-3'-enyl)-3-methoxy-13,17-secoestra-1,2,5(10),16-tetraene (2b)



(310 mg, 0.9 mmol, 28%). R_f = 0.4 (hexane:EtOAc, 4:1). $[\alpha]_D^{20}$ = +91.0 (c = 0.01, $CHCl_3$). HRMS calcd for $C_{23}H_{32}O_2$ $[M]^+$ 340.2397, found 340.2403.

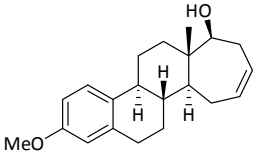
Table 5.4 ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C) and ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C) spectroscopic data for **2a** and **2b.**

	2a			**2b**		
Position	δ ^{13}C	δ ^{1}H	m (*J* [Hz])	δ ^{13}C	δ ^{1}H	m (*J* [Hz])
1	126.4	7.21	d (8.6)	126.4	7.22	d (8.6)
2	111.6	6.72	dd (2.8, 8.6)	111.6	6.72	dd (2.8, 8.6)
3	157.4	-	-	157.5	-	-
4	113.4	6.63	d (2.8)	113.5	6.62	d (2.8)
5	138.0	-	-	138.0	-	-
6	30.5	eq 2.86	ddd (2.4, 6.1, −15.3)	30.5	eq 2.86	ddd (2.0, 5.7, −11.8)
		ax 2.84	ddd (6.1, 11.8, −15.3)		ax 2.85	ddd (6.6, −11.8, 12.1)
7	27.7	eq 2.17	dddd (2.4, 2.4, 6.1, −12.6)	27.7	eq 2.17	dddd (2.0, 2.4, 6.6, −12.8)
		ax 1.36	dddd (6.1, 11.7, 11.8, −12.6)		ax 1.31	dddd (5.7, 11.3, 12.1, −12.8)
8	41.7	1.40	dddd (2.4, 10.4, 10.9, 11.7)	42.0	1.44	dddd (2.4, 10.7, 11.2, 11.3)
9	43.1	2.29	ddd (3.9, 10.4, 12.6)	43.7	2.25	ddd (3.7, 11.2, 11.6)
10	132.9	-	-	132.8		-
11	26.2	eq 2.30	dddd (3.3, 3.9, 4.0, −12.7)	26.0	eq 2.29	dddd (3.3, 3.6, 3.7, −12.9)
		ax 1.37	dddd (3.5, 12.6, −12.7, 13.6)		ax 1.39	dddd (3.3, 11.6, −12.9, 13.4)
12	31.2	ax 1.70	ddd (4.0, −13.0, 13.6)	31.1	eq 1.78	ddd (3.3, 3.3, −13.0)
		eq 1.49	ddd (3.3, 3.5, −13.0)		ax 1.42	ddd (3.6, −13.0, 13.4)
13	40.5	-	-	41.1		-
14	44.1	1.74	ddd (3.4, 4.8, 10.9)	45.7	1.33	ddd (3.0, 5.2, 10.7)
15	32.0	a 2.32	ddddd (−1.7, −1.9, 3.4, 7.0, −16.0)	32.7	a 2.32	ddddd (−1.6, −1.8, 3.0, 7.2, −16.2)
		b 2.03	ddddd (−1.5, −1.7, 4.8, 6.6, −16.0)		b 2.01	ddddd (−1.4, −1.9, 5.2, 6.2, −16.2)
16	140.7	5.95	dddd (6.6, 7.0, 10.2, 17.1)	139.9	5.86	dddd (6.2, 7.2, 10.1, 17.1)
17	114.2	*trans* 5.07	dddd (−1.6, −1.7, −1.9, 17.1)	114.5	*trans* 5.02	dddd (−1.6, −1.6, −1.9, 17.1)
		cis 4.97	dddd (−1.5, −1.6, −1.7, 10.2)		*cis* 4.96	dddd (−1.4, −1.6, −1.8, 10.1)
18	17.3	0.83	s	17.5	1.02	s
1'	74.8	3.61	ddd (1.8, 3.6, 10.5)	76.6	3.67	dd (2.0, 10.8)
2'	35.8	a 2.33	ddddd (−1.5, 1.8, −1.9, 5.7, −13.8)	35.5	a 2.45	ddddd (−1.2, −1.7, 2.0, 5.7, −13.9)
		b 2.08	ddddd (−0.8, −1.1, 8.3, 10.5, −13.8)		b 2.08	ddddd (−0.7, −1.1, 8.4, 10.8, −13.9)
3'	137.1	5.91	dddd (5.7, 8.3, 10.1, 17.1)	136.4	5.86	dddd (5.7, 8.4, 9.7, 17.6)
4'	117.7	*trans* 5.17	dddd (−1.1, −1.5, −1.9, 17.1)	118.0	*trans* 5.16	dddd (−1.1, −1.7, −1.8, 17.6)
		cis 5.15	dddd (−0.8, −1.5, −1.5, 10.1)		*cis* 5.15	dddd (−0.7, −1.2, −1.8, 9.7)
OCH_3	55.2	3.78	s	55.3	3.78	s
OH	-	1.63	d (3.6)	-	n.o.	-

General procedure for ring-closing metathesis

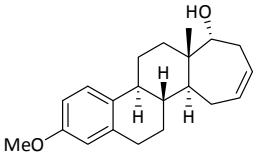
Compound **2a** or **2b** (1 equiv) was dissolved in DCM (0.1 M solution). Grubbs´ second-generation catalyst (NHC)(PCy_3)Cl_2Ru=CHR (4–5 mol-%) was added and the reaction mixture was stirred at room temperature for 18 h. Solvents were evaporated and the crude product was purified by flash chromatography (hexane:EtOAc, 4:1).

3-Methoxy-17a,17b-dihomoestra-1,3,5(10),16-tetraen-17bβ-ol (3a)



Starting from **2a** (340 mg, 1 mmol), 4 mol-% catalyst (34 mg, 0.04 mmol) to yield **3a** (285 mg, 0.91 mmol, 91%) as glassy solid. R_f = 0.2 (hexane:EtOAc, 4:1). $[\alpha]_D^{20}$ = +45.6 (c = 0.01, $CHCl_3$). HRMS calcd for $C_{21}H_{28}O_2$ $[M]^+$ 312.2084, found 312.2098.

3-Methoxy-17a,17b-dihomoestra-1,3,5(10),16-tetraen-17bα-ol (3b)



Starting from **2b** (169 mg, 0.5 mmol), 5 mol-% catalyst (22 mg, 0.026 mmol) to yield **3b** (140 mg, 0.45 mmol, 90%) as glassy solid. R_f = 0.2 (hexane:EtOAc, 4:1). $[\alpha]_D^{20}$ = +31.6 (c = 0.01, $CHCl_3$). HRMS calcd for $C_{21}H_{28}O_2$ $[M]^+$ 312.2084, found 312.2091.

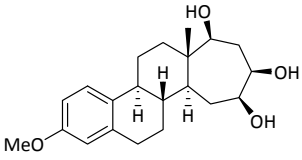
Table 5.5 ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C) and ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C) spectroscopic data for **3a** and **3b**.

	3a			**3b**		
Position	δ ^{13}C	δ ^{1}H	m (*J* [Hz])	δ ^{13}C	δ ^{1}H	m (*J* [Hz])
1	126.0	7.21	d (8.6)	126.0	7.22	d (8.6)
2	111.4	6.72	dd (2.8, 8.6)	111.4	6.72	dd (2.8, 8.6)
3	157.5	-	-	157.5	-	-
4	113.2	6.64	d (2.8)	113.2	6.63	d (2.8)
5	138.1	-	-	138.1	-	
6	30.2	eq 2.85	ddd (3.4, 5.7, −17.3)	30.3	eq 2.85	ddd (3.4, 5.8, −17.3)
		ax 2.82	ddd (6.3, 11.9, −17.3)		ax 2.82	ddd (6.1, 11.8, −17.3)
7	27.7	eq 2.20	dddd (2.9, 3.4, 6.3, −13.2)	27.6	eq 2.21	dddd (3.1, 3.4, 6.1, −12.8)
		ax 1.30	dddd (5.7, 10.7, 11.9, −13.2)		ax 1.31	dddd (5.8, 10.3, 11.8, −12.8)
8	39.6	1.24	dddd (2.9, 9.3, 10.7, 11.3)	39.5	1.27	dddd (3.1, 10.3, 10.6, 11.2)
9	43.3	2.26	ddd (3.3, 9.3, 12.5)	43.2	2.27	ddd (4.1, 10.6, 12.2)
10	133.4	-	-	133.4	-	-
11	26.0	eq 2.29	dddd (3.0, 3.3, 3.6, −13.1)	26.2	eq 2.29	dddd (3.1, 4.0, 4.1, −13.3)
		ax 1.48	dddd (3.5, 12.5, −13.1, 13.5)		ax 1.50	dddd (3.7, 12.2, −13.3, 13.8)
12	37.9	eq 2.01	ddd (3.0, 3.5, −13.0)	36.2	ax 2.03	ddd (4.0, −13.2, 13.8)
		ax 1.39	ddd (3.6, −13.0, 13.5)		eq 1.42	ddd (3.1, 3.7, −13.2)
13	42.5	-	-	41.9	-	-
14	48.4	1.27	dd (10.2, 11.3)	42.5	1.50	ddd (1.8, 10.9, 11.2)
15	26.3	b 2.27	dd (8.5, −16.0)	26.6	b 2.35	ddddd (-2.0, −2.8, 3.9, 10.9, −16.2)
		a 1.99	ddddd (2.3, 3.0, −4.6, 10.2, −16.0)		a 1.95	ddd (1.8, 8.7, −16.2)
16	133.6	5.87	ddd (2.3, 8.5, 10.7)	133.9	5.93	dddd (−2.5, 3.9, 8.7, 10.8)
17	126.1	5.61	dddd (2.7, −4.6, 7.2, 10.7)	126.1	5.57	dddd (−2.8, 4.3, 7.2, 10.8)
17a	33.2	a1 2.60	ddddd (2.7, 3.0, −4.1, 10.1, −15.7)	31.4	a1 2.59	ddddd (1.7, −2.0, −2.5, 4.3, −16.2)
		a2 2.28	ddd (2.5, 7.2, −15.7)		a2 2.43	ddd (6.7, 7.2, −16.2)
17b	79.0	3.34	dd (2.5, 10.1)	76.9	3.39	dd (1.7, 6.7)
18	11.9	0.99	s	17.1	0.96	s
OCH_3	55.3	3.78	s	55.2	3.78	s

General procedure for dihydroxylation

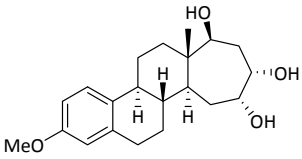
300 mg of AD-mix-α or AD-mix-β was dissolved in a mixture of water (1 mL) and *t*-BuOH (0.5 mL) and the mixture was cooled down using an ice bath. $MeSO_2NH_2$ (39 mg, 0.4 mmol) was added followed by addition of **3a** or **3b** (0.2 mmol) dissolved in *t*-BuOH (0.5 mL). The mixture was stirred at + 4 °C and the conversion was monitored by TLC. Upon completion, Na_2SO_3 (350 mg) was added and the mixture was stirred at r.t. for 45 min. EtOAc (2 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 1.5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The product was purified by flash chromatography (DCM:MeOH, 10:1).

3-Methoxy-17a,17b-dihomoestra-1,3,5(10)-trien-16β,17β,17bβ-triol (4a)



Starting from **3a** (56 mg, 0.18 mmol) with AD-mix-α and reaction time 6 d to yield **4a** and **4b** as 6:1 mixture (white solid) that could not be purified by flash chromatography (53 mg, 0.15 mmol, 85%). HRMS calcd for $C_{21}H_{30}O_4Na$ $[M+Na]^+$ 369.2036, found 369.2031.

3-Methoxy-17a,17b-dihomoestra-1,3,5(10)-trien-16α,17α,17bβ-triol (4b)



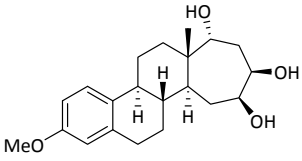
Starting from **3a** (70 mg, 0.23 mmol) with AD-mix-β and reaction time 6 d to yield **4b** (61 mg, 0.18 mmol, 78%) as white solid. R_f = 0.3 (DCM:MeOH, 10:1). $[\alpha]_D^{20}$ = +22.8 (c = 0.005, acetone). HRMS calcd for $C_{21}H_{30}O_4Na$ $[M+Na]^+$ 369.2036, found 369.2041.

Table 5.6 ^{1}H NMR (600.13 MHz, $CDCl_3/CD_3OD$, 25 °C) and ^{13}C NMR (150.9 MHz, $CDCl_3/CD_3OD$, 25 °C) spectroscopic data for **4a**[a] and **4b**.

	4a			**4b**		
Position	δ ^{13}C	δ ^{1}H	m (*J* [Hz])	δ ^{13}C	δ ^{1}H	m (*J* [Hz])
1	125.9	7.20	d (8.6)	126.1	7.21	d (8.6)
2	111.5	6.72	dd (2.7, 8.6)	111.5	6.72	dd (2.7, 8.6)
3	157.4	-	-	157.5	-	-
4	113.4	6.64	d (2.7)	113.3	6.63	d (2.7)
5	138.1	-	-	138.3	-	-
6	30.2	2.91–3.81	m	30.4	eq 2.85 ax 2.81	ddd (3.1, 6.0. –16.8) ddd (6.4, 11.3, –16.8)
7	28.1	eq 2.35–2.16 ax 1.44–1.18	m m	27.8	eq 2.20 ax 1.34	dddd (3.0, 3.1, 6.4, –13.1) dddd (6.0, 11.2, 11.3, –13.1)
8	40.5	1.44–1.18	m	41.0	1.14	dddd (3.0, 10.5, 10.8, 11.2)
9	43.6	2.35–2.16	m	43.2	2.29	ddd (3.5, 10.5, 12.4)
10	133.0	-	-	133.4	-	-
11	25.2	eq 2.35–2.16 ax 1.44–1.18	m m	25.9	eq 2.27 ax 1.40	dddd (3.2, 3.3, 3.5, –13.1) dddd (3.3, 12.4, –13.1, 13.7)
12	39.5	eq 2.12-2.07 ax 1.44–1.18	m m	38.9	eq 2.02 ax 1.37	ddd (3.3, 3.3, –13.1) ddd (3.2, –13.1, 13.7)
13	40.9	-	-	41.1	-	-
14	41.8	0.92–0.88	m	40.9	1.57	ddd (2.7, 9.9, 10.8)
15	31.3	a 1.95–1.91 b 1.55–1.51	m m	33.1	a 1.92 b 1.60	ddd (2.7, 5.3, –15.3) ddd (4.5, 9.9, –15.3)
16	71.2	3.95–3.86	m	71.6	4.00	ddd (4.3, 4.5, 5.3)
17	69.7	3.95–3.86	m	69.8	4.12	ddd (2.9, 4.3, 7.0)
17a	36.6	a1 2.35–2.16 a2 1.71-1.67	m m	37.1	a1 2.10 a2 1.87	ddd (7.0, 3.4, –14.0) ddd (2.9, 10.5-14.0)
17b	81.1	3.46–3.42	m	76.3	3.79	dd (3.4, 10.5)
18	13.86	0.92	s	12.6	0.86	s
OCH_3	55.3	3.78	s	55.3	3.78	s

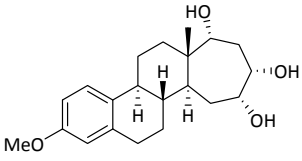
[a] Only selected NMR spectroscopic data is presented for compound **4a** since it could not be purified by chromatography.

3-Methoxy-17a,17b-dihomoestra-1,3,5(10)-trien-16β,17β,17bα-triol (5a)



Starting from **3b** (63 mg, 0.20 mmol) with AD-mix-α and reaction time 6 d to yield **5a** (55 mg, 0.16 mmol, 80%) as white solid. R_f = 0.4 (DCM:MeOH, 10:1). $[\alpha]_D^{20}$ = +14.0 (c = 0.005, acetone). HRMS calcd for $C_{21}H_{30}O_4Na$ $[M+Na]^+$ 369.2036, found 369.2022.

3-Methoxy-17a,17b-dihomoestra-1,3,5(10)-trien-16α,17α,17bα-triol (5b)



Starting from **3b** (63 mg, 0.20 mmol) with AD-mix-β and reaction time 2 d to yield **5b** (57 mg, 0.16 mmol, 82%) as white solid. R_f = 0.5 (DCM:MeOH, 10:1). $[\alpha]_D^{20}$ = +48.8 (c = 0.005, acetone). HRMS calcd for $C_{21}H_{30}O_4Na$ $[M+Na]^+$ 369.2036, found 369.2027.

Table 5.7 ^{1}H NMR (600.13 MHz, $CDCl_3/CD_3OD$, 25 °C) and ^{13}C NMR (150.9 MHz, $CDCl_3/CD_3OD$, 25 °C) spectroscopic data for **5a** and **5b**.

	5a			**5b**		
Position	δ ^{13}C	δ ^{1}H	m (*J* [Hz])	δ ^{13}C	δ ^{1}H	m (*J* [Hz])
1	126.0	7.20	d (8.6)	126.4	7.21	d (8.6)
2	111.5	6.71	dd (2.8, 8.6)	111.6	6.71	dd (2.8, 8.6)
3	157.5	-	-	157.4	-	-
4	113.4	6.64	d (2.8)	113.2	6.62	d (2.8)
5	138.2	-	-	138.0	-	-
6	30.3	eq 2.87	ddd (2.8, 6.0, –16.6)	30.4	eq 2.83	ddd (3.3, 5.9, –15.9)
		ax 2 84	ddd (6.5, 11.6, –16.6)		ax 2.80	ddd (6.2, 11.4, –15.9)
7	27.8	eq 2.21	dddd (2.8, 2.9, 6.5, –13.2)	27.1	eq 2.18	dddd (3.1, 3.3, 6.2, –12.9)
		ax 1.31	dddd (6.0, 10.6, 11.6, –13.2)		ax 1.32	dddd (5.9, 11.3, 11.4, –12.9)
8	39.9	1.24	dddd (2.9, 10.2, 10.4, 10.6)	40.4	1.25	dddd (3.1, 10.4, 10.6, 11.3)
9	43.7	2.24	ddd (4.3, 10.2,12.1)	43.0	2.30	ddd (3.9, 10.4, 12.2)
10	133.4	-	-	133.3	-	-
11	25.6	eq 2.29	dddd (3.1, 3.9, 4.3, –13.2)	26.8	eq 2 27	dddd (3.0, 3.9, 4.0, –13.2)
		ax 1.47	dddd (3.5, 12.1, –13.2, 13.6)		ax 1.47	dddd (3.6, 12.2, –13.2, 14.1)
12	29.7	ax 1.74	ddd (3.9, –13.0, 13.6)	38.2	ax 2.10	ddd (4.0, –13.1, 14.1)
		eq 1.54	ddd (3.1, 3.5, –13.0)		eq 1.34	ddd (3.0, 3.6, –13.1)
13	40.6	-	-	41.4	-	-
14	41.7	1.26	dd (8.4, 10.4)	37.3	1.89	ddd (3.7, 10.6, 12.2)
15	34.1	a 1.78	dd (5.0, –14.4)	32.1	a 2.27	ddd (3.7, 7.1, –14.7)
		b 1.52	ddd (8.4, 10.5, –14.4)		b 1.26	ddd (1.8, 12.2, –14.7)
16	72.7	3.80	ddd (5.0, 5.0, 10.5)	74.4	4.07	ddd (1.8, 2.4, 7.1)
17	67.7	4.13	ddd (2.9, 5.0, 7.8)	73.3	3.96	ddd (2.4, 7.0 8.5)
17a	34.6	a1 2.02	ddd (1.3, 7.8, –14.9)	38.7	a1 2.51	ddd (4.8, 8.5, –15.8)
		a2 1.97	ddd (2.9, 7.7, –14.9)		a2 1.85	ddd (2.9, 7.0, –15.8)
17b	74.8	3.68	dd (1.3, 7.7)	77.3	3.36	dd (2.9, 4.8)
18	18.8	0.92	s	16.1	0.83	s
OCH_3	55.3	3.78	s	55.3	3.78	s

Determination of antiproliferative activities

Growth inhibiting effects were measured *in vitro* on four malignant human cell lines (ECACC, Salisbury, UK): HeLa (cervix adenocarcinoma), MCF7 (breast adenocarcinoma), A2780 (ovarian carcinoma) and A431 (skin epidermoid carcinoma). The cells were cultivated in minimal essential medium supplemented with 10% fetal bovine serum, 1% non-essential amino acids and an antibiotic-antimycotic mixture. All media and supplements were obtained from PAA Laboratories GmbH, Pasching, Austria. Near-confluent cancer cells were seeded onto a 96-well microplate at the density of 5000 cells/well and, after standing overnight, new medium (200 µL) containing the tested compound was added. The final concentrations of the tested agents were 10 and 30 µM. After incubation for 72 h at 37 °C in humidified air containing 5% CO_2, the living cells were assayed by the addition of 5 mg/mL MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) solution (20 µL). MTT was converted by intact mitochondrial reductase and precipitated as blue crystals during a 4-h contact period. The medium was then removed and the precipitated formazan crystals were dissolved in 100 µL dimethyl sulfoxide (DMSO) during a 60 min period of shaking at 25 °C. Finally, the reduced MTT was assayed at 545 nm, using a microplate reader; wells with untreated cells were utilized as controls. All *in vitro* experiments were carried out on two microplates with at least five parallel wells. Cisplatin[16] was used as positive control. Stock solutions of the tested substances (10 mM) were prepared with DMSO. The DMSO content of the medium did not have any significant effect on the cell proliferation.

5.5 References and Notes

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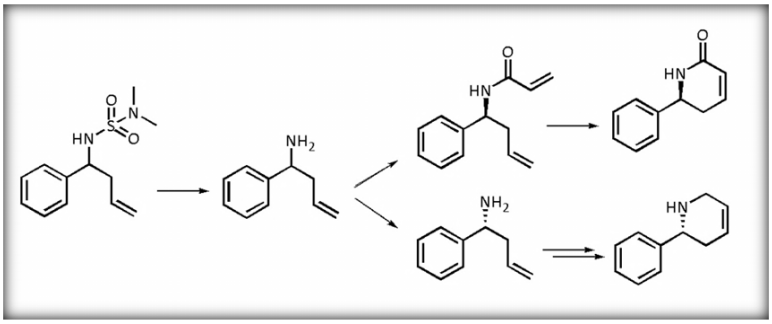
6 SYNTHESIS OF HOMOALLYLIC AMINES AND THEIR ENANTIOPURE HETEROCYCLIC DERIVATIVES



In this chapter, synthesis of a series of homoallylic amines by Barbier-type allylation of *N*,*N*-dimethylsulfamoyl-protected aldimines followed by deprotection by transamination is described. Separation of the amine enantiomers by enzymatic kinetic resolution to obtain the corresponding (*S*)-amines and (*R*)-amides is likewise discussed. Finally, further derivatization of the enantiopure amine and the functionalized amide by applying ring-closing metathesis as a key step is presented herein.

This chapter is based on the original publications:

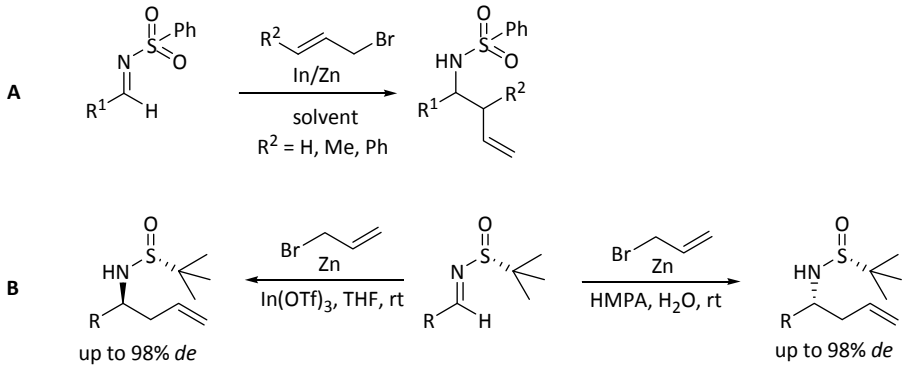
Källström, S.; Saloranta, T.; Minnaard, A. J.; Leino, R. **Indium- and Zinc-Mediated Barbier-Type Allylations of an *N*,*N*-(Dimethylsulfamoyl)-Protected Aldimine and Subsequent Deprotection**, *Tetrahedron Lett*. **2007**, *48*, 6958–6961.

Hietanen, A.; Saloranta, T.; Rosenberg, S.; Laitinen, E.; Leino, R.; Kanerva, L. T. **Synthesis of Enantiopure Benzyl Homoallylamines by Indium-Mediated Barbier-Type Allylation Combined with Enzymatic Kinetic Resolution: Towards Chemoenzymatic Synthesis of N-Containing Heterocycles**, *Eur. J. Org. Chem.* **2010**, 909–919.

6.1 Introduction

Barbier-type allylation of aldehydes and ketones is a straightforward synthetic procedure being applicable for a wide range of substrates bearing the corresponding carbonyl functionality. On the contrary, the nitrogen counterparts, such as primary aldimines, are not sufficiently electrophilic to be directly allylated under Barbier-type conditions. However, the electrophilicity of the carbon atom at C=N bond can be increased by introducing different activating groups on the nitrogen atom.[1] The obtained N-substituted aldimines are generally more reactive and can be allylated in a similar fashion as the corresponding aldehydes. The drawback of this approach is, however, that the activating group needs to be removed in a separate step after the allylation reaction. The increased number of synthesis steps in turn leads to decreased overall yield and increased production costs.

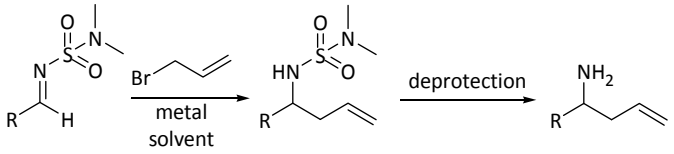
In the literature, different activating/protective groups have been successfully applied for metal mediated allylation of aldimines. One of the first literature examples includes N-alkyl and N-aryl aldimines that were successfully allylated using indium as the mediating metal under mild and simple conditions.[2] Zinc-mediated allylation of substituted oximes has likewise been reported in the literature.[3] Sulfonimines, introduced by Lu and Chan, were shown to be applicable in both Zn- and In-mediated allylation in aqueous media. The aromatic and aliphatic sulfonimines are generally stable towards hydrolysis and the homoallylic amines were obtained in good to excellent yield (**A**, Scheme 6.1).[4] Noteworthy, for less reactive aliphatic sulfonimines and for less reactive bulky bromides, zinc in aqueous media was reported to be more efficient than indium. Sulfinylaldimines, in turn, have proved to be highly valuable substrates in Barbier-type allylations since the chiral sulfur atom can be utilized to induce stereoselectivity in the addition of the allyl group.[5a] Remarkably, Xu and Lin have reported a diastereoselective allylation protocol of chiral (*R*)-*N*-*tert*-butanesulfinyl imines that allows the preparation of both stereoisomers by simply varying the reaction conditions (**B**, Scheme 6.1).[5b]



Scheme 6.1. Barbier-type allylation of a sulfonimine (**A**) and enantiopure sulfinylimine (**B**).

However, the choice of protective/activating group should not only be dependent on the reaction where the substrate is applied. In order to develop a synthetically useful method even the deprotection should be trivial. Moreover, for unsaturated products, such as homoallylic amines, the deprotection method should leave the double bond intact.

In this chapter, an alternative protective/activating group for aldimines, *N*,*N*-dimethylsulfamoyl,[6] is presented and evaluated in Barbier-type allylation reactions. *N*,*N*-Dimethylsulfamoyl protected aldimines have earlier been applied in Rh/phosphoramidite catalyzed asymmetric arylations.[7] In addition to being suitable protective group for aldimines in the Rh-catalyzed arylations, the *N*,*N*-dimethylsulfamoyl as protective group was also favored owing to its facile removal by transamination under mild conditions. It was, thus, anticipated that *N*,*N*-dimethylssulfamoyl-group would also serve as a suitable activating group for Barbier-type allylations to produce homoallylic amines that could be readily deprotected yielding the corresponding unprotected amines (Scheme 6.2).



Scheme 6.2. Illustration of Barbier-type allylation of *N*,*N*-dimethylsulfamoyl-protected aldimine and subsequent deprotection by transamination.

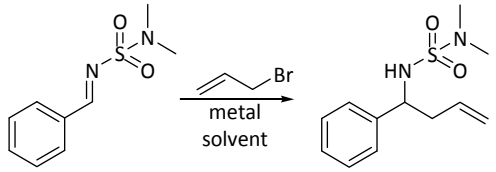
Barbier-type allylation of *N*,*N*-dimethylsulfamoyl-protected aldimines produces homoallylic amines as a racemic mixture. However, for pharmaceutical purposes, a common prerequisite is to obtain enantiopure building blocks. Previously, homoallylic amines have been synthesized in an enantioselective manner by utilizing chiral induction from the protective group,[5] enantiodifferentiation by addition of cinchona alkaloids,[8] or in the presence of a chiral ligand in catalytic allylations.[9] In this chapter, a methodology to separate the enantiomers using enzymatic kinetic resolution is discussed. By applying this method, it becomes possible to produce both amine enantiomers in enantiopure form from their racemic mixture. The enantiopure functionalized amines in turn are suitable building blocks for synthesis of pharmaceutically relevant targets. Furthermore, by choosing an appropriate acyl donor for the enzymatic kinetic resolution, the product amide serves likewise as building block for further synthesis.

6.2 Results and Discussion

6.2.1 Metal-Mediated Allylation of *N,N*-Dimethylsulfamoyl-Protected Aldimines

For the initial studies, the simplest aromatic aldimine, *N,N*-(dimethylsulfamoyl)benzaldimine (**1a**), was selected as a model compound. The allylation of **1a** was first studied in anhydrous THF, in aqueous mixtures (THF:H_2O, THF:NH_4Cl_{aq}) and in pure aqueous media using indium or zinc as the mediating metal. The results are summarized in Table 6.1. The In- and Zn-mediated allylations in anhydrous THF gave full conversions and high yields when either indium or zinc was employed as the mediating metal (Table 6.1, Entries 1 and 4). The use of aqueous media for the allylation reaction resulted in partial hydrolysis of the aldimine, leading to the corresponding homoallylic alcohol as side product and consequently decreased the yield of the amine product **2a**. (Table 6.1, entries 2, 3, 5 and 6). Nevertheless, a comparison of the reactions performed with In and Zn in aqueous media alone (entries 3 and 6) demonstrates the substrate and metal surface activation in the Zn-mediated reaction by NH_4Cl_{aq}. This then, supposedly, leads to the more efficient formation of the allylating reagent as well as the product **2a**.

Table 6.1. Metal-mediated allylation **1a**.



1a **2a**

Entry	Metal	Solvent	Conversion[b] (%)	Yield[d] (%)
1	In	THF	100	90
2	In	THF:H_2O 1:1	89[c]	81
3	In	H_2O	19[c]	13
4	Zn	THF	100	81
5	Zn	THF:NH_4Cl_{aq} 1:1	74[c]	50
6	Zn	NH_4Cl_{aq}	84[c]	54

[a] Allylations were performed at rt on a 0.10–0.30 mmol scale with 3 equiv of metal and allyl bromide, respectively.

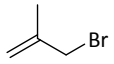
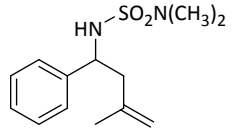
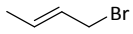
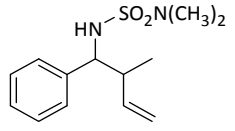
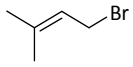
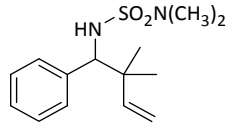
[b] Conversions were determined by ^{1}H NMR spectroscopy.

[c] Lower conversions are due to formation of 1-phenyl-3-buten-1-ol as a result of hydrolysis of **1** in the aqueous solvent and subsequent allylation.

[d] Isolated yield.

Encouraged by these results, the allylation was studied further with substituted allylating agents. The reactions were performed in anhydrous THF, being the optimal solvent of choice based on the initial experiments, using either zinc or indium as the mediating metal. The results are presented in Table 6.2. Good to excellent conversions and isolated yields were observed in all reactions with methallyl, crotyl and prenyl bromides with either Zn or In as mediating metal. Conversions lower than 100% were obtained with the bulkier prenyl bromide reagent only (Table 6.2, entries 5 and 6) and moderate yields of **2d** were obtained (In = 63%, Zn = 46%), most likely due to the steric constraints induced by the bulkier allylating agent.

Table 6.2. Metal-mediated allylation of *N*,*N*-(dimethylsulfamoyl)-benzaldimine (**1a**) with different allylating agents.[a]

Entry	Metal	Allylating agent	Product	Conversion (%)[b]	Yield (%)[c]
1	In		 **2b**	100	87
2	Zn			100	72
3	In		 **2c**	100	89[d]
4	Zn			100	68[d]
5	In		 **2d**	75	63
6	Zn			89	46

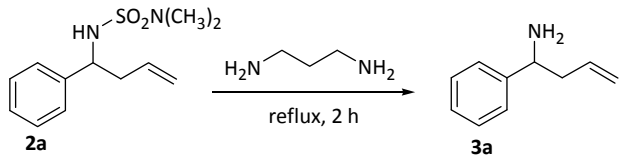
[a] Allylations were performed at r.t. on a 0.10–0.30 mmol scale with 3 equiv of metal and allylating agent, respectively.

[b] Conversions were determined by ^{1}H NMR spectroscopy.

[c] Isolated yield.

[d] The crotylated product appears as a mixture of the *syn*/*anti* diastereoisomers (entries 3 and 4) as determined by ^{1}H NMR spectroscopy of the crude product.

The removal of *N*,*N*-dimethylsulfamoyl-group from a diarylmethylamine by microwave-assisted transamination was recently reported by de Vries, Feringa, Minnaard and coworkers.[7] Under these mild reaction conditions, the deprotected amine was obtained in excellent (96%) yield. Deprotection of the *N*,*N*-dimethylsulfamoyl-protected homoallylic amine **2a** was thus investigated in a similar fashion. Conventional heating with oil bath was used instead of microwave irradiation. Under these conditions, **2a** was successfully deprotected in small scale (0.20 mmol) by transamination with 1,3-diaminopropane yielding the deprotected homoallylic amine in 92% yield (Scheme 6.3).



Scheme 6.3. Deprotection of **2a** by transamination to yield **3a**.

With this two-step procedure available, it was possible to proceed with the development of the enzymatic kinetic resolution for a series of racemic benzylhomoallylamines including the model substrate **3a** and the corresponding deprotected amines **3b** and **3d** derived from **2b** and **2d,** respectively. The crotylated amine **2c** was excluded from this study due to its occurrence as a mixture of two diastereomers (*syn*/*anti*) that would unnecessarily complicate the enzymatic resolution. Additionally, the substrate scope was further expanded to include even structures with varying electronic properties, i.e., *para* fluoro and *para* methoxy-susbtituted benzyl homoallylamines **3e** and **3f** (Figure 6.1). In order to produce a sufficient amount of the homoallylic amines, the allylation and the deprotection were scaled up to 4 – 11 mmol scale. For these reactions, indium was used as the mediating metal and anhydrous THF as solvent. The results are summarized in Table 6.3.

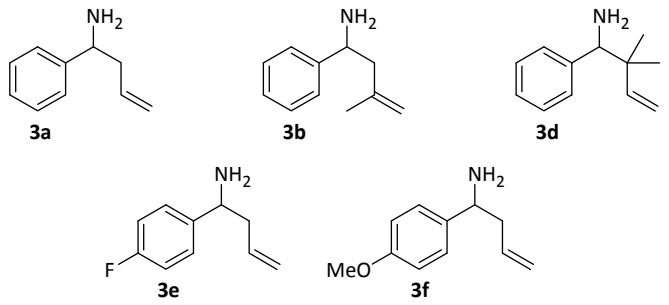
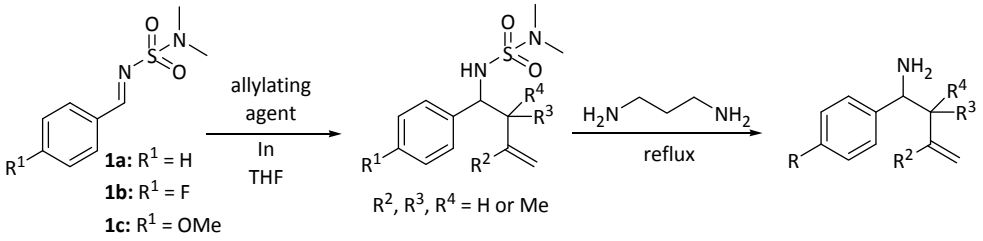


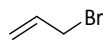
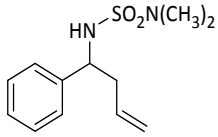
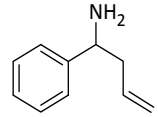
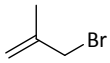
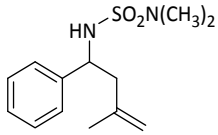
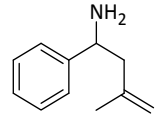
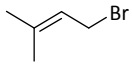
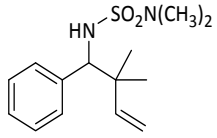
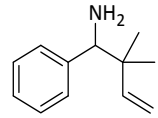
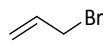
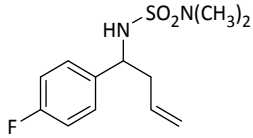
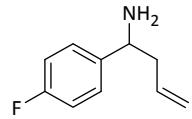
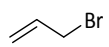
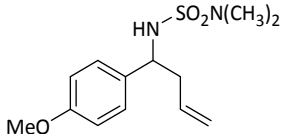
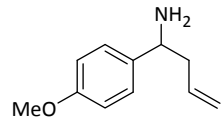
Figure 6.1. Structures of deprotected benzylhomoallylamines included in this chapter.

Table 6.3. Barbier-type metal-mediated allylation of homoallylic amines from *N*,*N*-dimethylsulfamoyl-protected aldimines and subsequent deprotection.



1a: R^1 = H
1b: R^1 = F
1c: R^1 = OMe

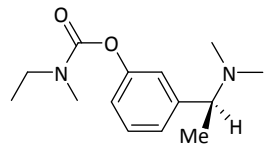
R^2, R^3, R^4 = H or Me

Entry	1	Allylating agent	Allylation		Deprotection	
			Product	Yield (%)	Product	Yield (%)
1	**1a**		 **2a**	71	 **3a**	91
2	**1a**		 **2b**	65	 **3b**	76
3	**1a**		 **2d**	27	 **3d**	83
4	**1b**		 **2e**	68	 **3e**	68
5	**1c**		 **2f**	68	 **3f**	90

The allylation proceeded with full conversion in all cases except with the bulkier prenyl bromide as the allylating agent (Table 6.3, entry 3) whereby the product **2d** was obtained in 27% yield only (see also Table 6.2, entries 5 and 6). The isolated yield of the protected homoallylic amines in all other cases was good varying between 65% and 71%. As shown already with the model substrate **2a** in small scale, the *N,N*-dimethylsulfamoyl group can be smoothly removed by transamination with 1,3-diaminopropane under conventional reflux conditions. Herein, the same protocol was utilized to deprotect all modified substrates **2(b, d–f)**. The method proved its feasibility and the desired allylic amines **3a**, **3b**, **3d**, **3e** and **3f** were obtained in good to excellent yields (Table 6.3).

6.2.2 Enzymatic Kinetic Resolution of Homoallylic Amines

The racemic homoallylic amines synthesized are, however, not sufficiently attractive for pharmaceutical applications. However, their enantiopure counterparts are highly important intermediates in the synthesis of number of biologically and pharmaceutically relevant targets. Thus, the development of synthetic strategies towards such moieties is of considerable academic as well as industrial importance in both fine chemical and pharmaceutical industries. In particular, chiral benzylamines have emerged as fragments in some neuroactive pharmaceutical ingredients. For example, the parasympathomimetic (*S*)-rivastigmine (Figure 6.2) has been adopted in the clinical treatment of dementia associated with Alzheimer's disease.[10]



(*S*)-rivastigmine

Figure 6.2. Example of chiral benzylamines.

Enzymatic kinetic resolution of racemic amines, as a method for preparing enantiopure amines, can be regarded as inefficient when considering the maximum yield of 50% (see also Section 2.5 in this thesis). If, however, both amine enantiomers are valued equally, enzymatic kinetic resolution is a very useful method for accessing both enantiomers from their racemic mixture. The resolution is typically based on reactions between a primary amine and a suitable acyl donor in organic solvents in the presence of an enzyme.[11] Lipases (E.C. 3.1.1.3), in general, are useful biocatalysts for the enantioselective N-acylation of amino groups since they only rarely can split an amide bond and, accordingly, induce the transformation of the amide back into the amine.[12] Furthermore, the intrinsic reactivity of the acyl donor is of great importance. Sufficient reactivity is pivotal to enable reasonable

reaction rates while too high reactivity can lead to chemical N-acylation parallel with the enzymatic one.

For developing a procedure for the enzymatic kinetic resolution, *rac*-**3a** was first subjected to enzyme screening using commercial lipase preparations (25 mg mL^{-1}) and ethyl methoxyacetate as acyl donor in *tert*-butyl methyl ether (TBME) dried over molecular sieves (4 Å). CAL-A was by far the most reactive but virtually a non-enantioselective catalyst while lipase PS-D (ee_{amide} = 95% at 30% conversion) and CAL-B (ee_{amide} = 92% at 35% conversion) both showed reactivity with relatively good enantioselectivity. Based on this initial screening, lipase PS-D proved to be the enzyme of choice for further experiments. At this point it was noticed, however, that the hydrolysis product of the acyl donor, methoxyacetic acid, forms an ammonium salt precipitate with the substrate lowering the rate and selectivity of the resolution. By changing the solvent from TBME to toluene (dried over molecular sieves), the water content of the solvent was decreased from 90 ppm to about 40 ppm and formation of the ammonium salt could be diminished considerably.

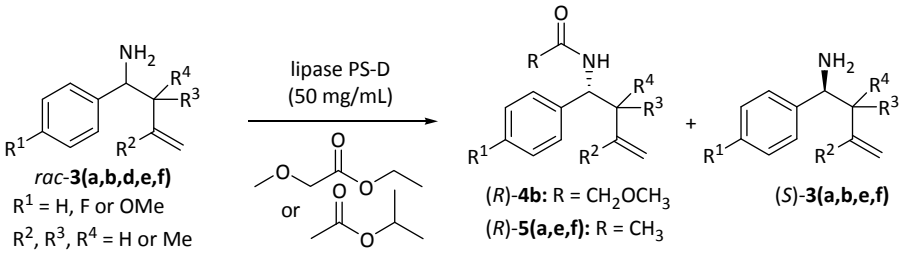
In order to further increase the reactivity and enantioselectivity, the acyl donor and the other reaction conditions were likewise optimized. Best results were obtained with isopropyl acetate or ethyl methoxyacetate as acyl donors. The water content of the reaction mixture during the resolution was controlled by the molecular sieves (4 Å) present. Excellent *E* values (>200) could be obtained when the reaction proceeded in neat isopropyl acetate (water content 60 ppm) or with ethyl methoxyacetate in lower content (6 vol-% equaling to 5 equivalents) in toluene (water content 40 ppm). In order to further increase the reactivity, the enzyme content was increased from 25 mg mL^{-1} to 50 mg mL^{-1}.

With this data available, the preparative-scale kinetic resolution of the homoallylic amines *rac*-**3a**, *rac*-**3e** and *rac*-**3f** were successfully performed in isopropyl acetate in the presence of lipase PS-D (50 mg mL^{-1}) and molecular sieves (4 Å) at room temperature (Table 6.4, entries 1, 4 and 5). The corresponding (*R*)-amides [(*R*)-**5a**, (*R*)-**5e** and (*R*)-**5f**], were obtained with excellent enantiopurity. However, all the tested lipases (PS-D, CAL-B and CAL-A) were unable to acylate the sterically more demanding amines *rac*-**3b** and *rac*-**3d** in neat isopropyl acetate. When the acyl donor was changed to ethyl methoxyacetate (20 vol-% was required) in toluene, acylation of **3b** slowly proceeded in the presence of CAL-B, and after 7 days, (*R*)-**4b** was obtained with high enantiopurity (*ee* > 99%) at 31% conversion (Table 6.4, entry 2). Under all evaluated conditions, *rac*-**3d** remained unreacted. The enantiomerically enriched unreacted amines (*S*)-**3a** (*ee* = 84%), (*S*)-**3b** (*ee* = 44%) and (*S*)-**3e** (*ee* = 48%) were further purified by subjecting them for repeated kinetic resolution, yielding 99%, 72% and

95% *ee*, respectively. In general, the isolated yields of the unreacted (*S*)-amines remained somewhat low and the need to repeat the enzymatic acylation further lowered the yields.

According to the Kazlauskas rule, the (*R*)-enantiopreference was expected for the lipase PS-D in the present *N*-acylations.[13] This conclusion was supported when $[\alpha]_D$ values of (*S*)-**3a** and (*S*)-**3f** obtained after the kinetic resolution were compared with the corresponding $[\alpha]_D$ values for the (*S*)-enantiomers reported in the literature.[14,15]

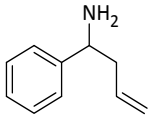
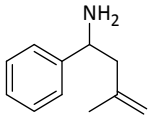
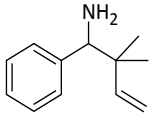
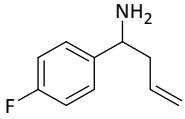
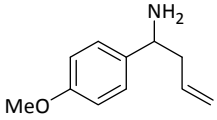
Table 6.4. Preparative scale kinetic resolution of racemic homoallylic amines (0.1 M) in isopropyl acetate (neat) at r.t. or with ethyl methoxyacetate in toluene in the presence of molecular sieves (4 Å).



rac-**3(a,b,d,e,f)**
R^1 = H, F or OMe
R^2, R^3, R^4 = H or Me

(*R*)-**4b:** R = CH_2OCH_3
(*R*)-**5(a,e,f):** R = CH_3

(*S*)-**3(a,b,e,f)**

Entry	Substrate	Time (d)	Conv. (%)	(*R*)-amide		(*S*)-amine	
				Yield (%)[a]	*ee* (%)	Yield (%)[a]	*ee* (%)
1	 **3a**	3	46	92	99	66	84/99[d]
2	 **3b**[b]	7	31	quant	>99	35	44/72[d]
3	 **3d**	-[c]	-	-	-	-	-
4	 **3e**	4	33	75	>99	75	48/95[d]
5	 **3f**	4	49	65	>99	93	94

[a] Isolated yields based on conversion.

[b] CAL-B (50 mg mL^{-1}) in the place of lipase PS-D.

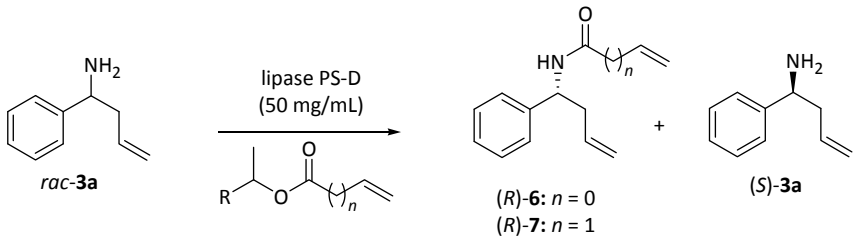
[c] No reaction with any applied method.

[d] *ee* after enantiomeric enrichments.

The enantioenriched amide produced by enzymatic kinetic resolution is not always the final product of interest but it generally needs to be hydrolyzed in order to obtain the enantiopure amine for further synthesis. The hydrolysis of amides is unfortunately not always a straightforward process leading to decreased yield and/or enantiopurity. However, by applying functionalized acyl donors, the amide itself becomes a more interesting target. To exemplify, by applying acyl donors with a terminal double bond, the product amide would serve as precursor for the corresponding cyclic lactams.

With this in mind, the scope of the resolution was extended by evaluating ethyl and isopropyl acrylates and isopropyl 3-butenoate as functionalized acyl donors in the kinetic resolution of *rac*-**3a** in toluene (Table 6.5). The resolution with isopropyl acrylate was completely non-enantioselective (data not shown) while excellent enantioselectivities were observed with ethyl acrylate (entries 1-3) and with isopropyl 3-butenoate (entries 4-6). The reactions with ethyl acrylate remained very slow, and it was not possible to affect the reactivity by increasing the content of the acyl donor from 5 to 20 vol-% (entries 1-3). Finally, preparative-scale kinetic resolution produced (*R*)-**6** in 65% isolated yield (calculated from conversion) when 19% of the racemate had reacted. Resolution of **3a** using isopropyl 3-butenoate as the acyl donor (10 vol-%) successfully afforded the amide (*R*)-**7** at 48% conversion in 85% isolated yield and *ee* > 99%.

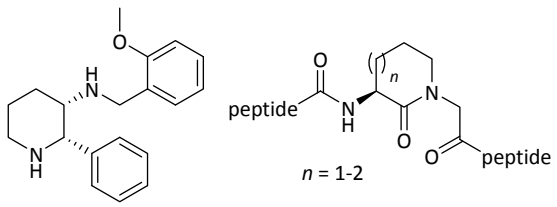
Table 6.5. Kinetic resolution of *rac*-**3a** (0.1 M) with ethyl acrylate and isopropyl 3-butenoate (toluene as the cosolvent) in the presence of lipase PS-D (50 mg mL^{-1}) and molecular sieves (4 Å) at room temperature.



Entry	R	*n*	Acyl donor (vol-%)	Conv (%)	$ee_{(R)\text{-amide}}$	$ee_{(S)\text{-amine}}$	*E*
1	H	0	5	17	98	21	>100
2	H	0	10	16	98	19	>100
3	H	0	20	18	98	21	>100
4	CH_3	1	5	40	>99	67	>200
5	CH_3	1	10	45	>99	83	>200
6	CH_3	1	20	48	>99	91	>200

6.2.3 Synthesis of N-Containing Heterocycles

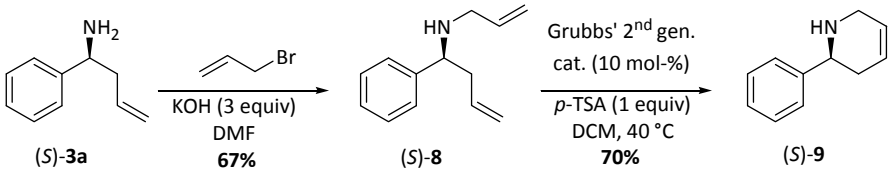
Synthesis of N-containing heterocycles such as piperidines,[16] lactams[17] and their derivatives is of topical interest due to the frequent occurrence of such moieties in biologically active small molecules, whether of natural or synthetic origin, and peptidomimetics. Figure 6.3 illustrates representative examples of these compound classes.[18]



CP-99,994 STAT3 peptidomimetics

Figure 6.3. Examples of chiral piperidines and lactams.

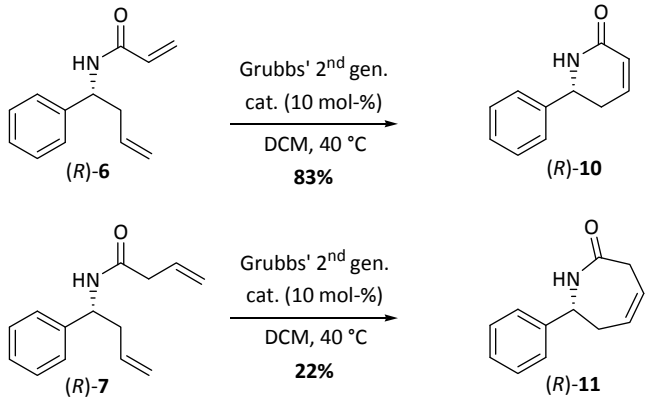
In previous work from our group, the *N*,*N*-dimethylsulfamoyl-protected crotylated amine was converted into the corresponding diallylic sulfamide that was then ring-closed using Grubbs' 2nd generation catalyst to yield a substituted dehydropiperidine in excellent overall yield.[19] Unfortunately, removal of the *N*,*N*-dimethylsulfamoyl protective group from this tertiary amine proved unsuccessful. At this point, having the enantiopure amines available, the synthesis strategy was redesigned for preparation of enantiopure dehydropiperidines in a similar fashion. Accordingly, the unprotected amine (*S*)-**3a** was converted into the corresponding diallylic amine (*S*)-**8** by deprotonation with KOH and subsequent reaction with one equivalent of allyl bromide in 67% yield. The diallylic amine obtained was then subjected to ring-closing metathesis. As known from the literature, free amines are detrimental to the Grubbs-type ruthenium catalysts.[20] When, however, the diallylic amine was converted to the corresponding salt by adding one equivalent of *p*-toluenesulfonic acid (*p*-TSA) the ring-closure proceeded smoothly affording the enantiopure dehydropiperidine (*S*)-**9** in 70% isolated yield (Scheme 6.4).



(*S*)-**3a** (*S*)-**8** (*S*)-**9**

Scheme 6.4. Synthesis of enantiopure dehydropiperidine (*S*)-**9**.

Finally, the diallylic resolution products (*R*)-**6** and (*R*)-**7** were likewise subjected to ring-closing metathesis using Grubbs' 2nd generation catalyst. A similar type of approach, although based on a longer synthetic route for preparation of the enantiopure diallyl precursors, has been described by Fiorelli and Savoia.[21] In their work, a number of substituted diallylic amides were successfully ring-closed to yield the corresponding α,β-unsaturated δ-lactams in good to excellent yields. In accordance with this published procedure, the δ-lactam (*R*)-**10** was synthesized from (*R*)-**6** in 83% isolated yield. In our hands, however, the corresponding seven-membered lactam (*R*)-**11** was formed in low yield only (22%) when starting from the diallylic amide (*R*)-**7** (Scheme 6.5).



Scheme 6.5. Synthesis of the lactams (*R*)-**10** and (*R*)-**11** by ring-closing metathesis.

6.3 Summary and Conclusions

In summary, metal-mediated allylation of *N*,*N*-dimethylsulfamoyl-protected aldimines and the subsequent deprotection by transamination was shown to be a reliable procedure for production of homoallylic amines with different electronic and sterical properties. Moreover, this study has shown that the enzymatic kinetic resolution of the sterically demanding benzyl homoallylamines (allyl as the medium-sized group) is possible by carefully adjusting the most critical reaction parameters. As the steric crowding is transferred closer to the reaction center the resolution becomes more challenging.

Furthermore, by utilizing acyl donors with a terminal double bond, the N-acylation has been used as a synthetic step as the resolution product can be directly subjected to ring-closing metathesis yielding unsaturated lactam products as exemplified by the straightforward synthesis of an enantiopure α,β-unsaturated δ-lactam. Finally, an enantiopure amine has been transferred into its diallylic counterpart which has been subjected to ring-closing metathesis producing a substituted enantiopure dehydropiperidine product. The obtained N-containing heterocycles represent an

attractive class of moieties found in a number of biologically and pharmaceutically relevant targets. In conclusion, the work presented in this chapter has shown that a number of biologically relevant N-containing heterocycles can be produced by combining the elegancy of enzymatic and metal catalyzed reactions.

6.4 Experimental Section

General remarks

The allylation and ring-closing reactions were performed under a dry argon atmosphere using anhydrous solvents. THF was distilled over Na/benzophenone and DCM was distilled over CaH_2. The anhydrous solvents were then stored under argon. *N*,*N*-dimethylsulfamide was readily prepared from commercial dimethylsulfamoyl chloride and 30% aqueous ammonia.[22] All other reagents were purchased and used as received. Solvents and acyl donors for enzymatic reactions were obtained from commercial sources and stored over molecular sieves unless stated otherwise. Enantiomeric excesses of the amines (as corresponding amide derivatives) were determined with a HP1090 gas chromatograph equipped with a Varian CP Chirasil-Dex CP chiral column. Enzymatic reactions were performed at room temperature unless indicated otherwise. The determination of E was based on equation $E = \ln[(1-c)(1-ee_S)]/\ln[(1-c)(1+ee_S)]$ with $c = ee_S/(ee_S+ee_P)$ using linear regression (E as the slope of the line $\ln[(1-c)(1-ee_S)]$ versus $\ln[(1-c)(1+ee_S)]$). NMR spectra were recorded with Bruker Avance 500 MHz or 600 MHz NMR spectrometers. ^{1}H NMR spectra were analysed by PERCH software with spin simulation/iteration techniques.[23] HRMS were measured in ESI+ mode with Bruker micrOTOF-Q quadrupole-TOF or Fisons ZABSpec-oaTOF spectrometers. Melting points were recorded with a Gallenkamp apparatus. Optical rotations were determined with a PerkinElmer 241 or 341 polarimeter. Flash chromatography was performed using silica gel 60 Å (Merck, 230–400 mesh, enriched with 0.1% Ca).

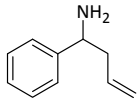
Synthesis of N,N-(dimethylsulfamoyl)benzaldimines

Compounds **1(a–c)** were synthesized according to a literature procedure.[6] The corresponding benzaldehyde (20 mmol) and *N*,*N*-dimethylsulfamide (2.54 g, 20.5 mmol) were dissolved in toluene (80 mL) and water was azeotropically distilled for 16 h using a Dean-Stark apparatus. After removal of the solvent under reduced pressure, the residue was dissolved in DCM and filtered. Solvents were evaporated under reduced pressure and the crude product was used as such in the allylation step.

Synthesis of homoallylic amines

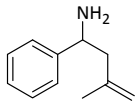
Standard procedure for Table 6.3: In a Schlenk tube flushed with argon, substrate **1(a–c)** was dissolved in anhydrous THF. Indium (3 equiv) and allylating agent (3 equiv) were added and the resulting mixture was stirred overnight at room temperature. The reaction was quenched by adding 1 M HCl and extracted with ether. The combined organic phase was washed with saturated $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. After evaporation of ether, the crude product was subjected to analysis and purified by flash chromatography (hexane:EtOAc, 4:1) affording **2(a, b, d–f)** as a white solid. Compound **2(a, b, d–f)** was then dissolved in 1,3-diaminopropane, the mixture was heated to 140 °C and refluxed for 2 h. After cooling to room temperature, the mixture was diluted with DCM and washed with water. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to yield **3(a, b, d–f)** as light yellow oil.

1-Phenylbut-3-en-1-amine (3a)



Step 1: starting from **1a** (1.95 g, 9.18 mmol) to yield **2a** (1.67 g, 6.56 mmol, 71%). Step 2: starting from **2a** (2.14 g, 8.41 mmol) to yield **3a** (1.13 g, 7.68 mmol, 91%) as light yellow oil. ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 7.38-7.33 (m, 4 H, arom. H), 7.28-7.23 (m, 1 H, arom. H), 5.75 (dddd, $J_{CH=, CH2a}$ = 6.3 Hz, $J_{CH=, CH2b}$ = 8.0 Hz, $J_{CH=, CH2cis}$ = 10.2 Hz, $J_{CH=, CH2trans}$ = 17.1 Hz, 1 H, CH_2-C*H*=CH_2), 5.12 (dddd, $J_{CH2trans, CH2b}$ = −1.2 Hz, $J_{CH2trans, CH2a}$ = −1.6 Hz, $J_{CH2trans, CH2cis}$ = −2.0 Hz, $J_{CH2trans, CH=}$ = 17.1 Hz, 1 H, CH_2-CH=C*H*$_{2trans}$), 5.08 (dddd, $J_{CH2cis, CH2b}$ = −0.8 Hz, $J_{CH2cis, CH2a}$ = −1.2 Hz, $J_{CH2cis, CH2trans}$ = −2.0 Hz, $J_{CHcis, CH=}$ = 10.2 Hz, 1 H, CH_2-CH=C*H*$_{2cis}$), 3.99 (dd, $J_{CH, CH2a}$ = 5.2 Hz, $J_{CH, CH2b}$ = 8.2 Hz, 1 H, C*H*NH_2), 2.46 (ddddd, $J_{CH2a, CH2cis}$ = −1.2 Hz, $J_{CH2a, CH2trans}$ = −1.6 Hz, $J_{CH2a, CH}$ = 5.2 Hz, $J_{CH2a, CH=}$ = 6.2 Hz, $J_{CH2a, CH2b}$ = −13.8 Hz, 1 H, C*H*$_{2a}$-CH=CH_2), 2.36 (ddddd, $J_{CH2b, CH2cis}$ = −0.8 Hz, $J_{CH2b, CH2trans}$ = −1.2 Hz, $J_{CH2b, CH=}$ = 8.0 Hz, $J_{CH2b, CH}$ = 8.2 Hz, $J_{CH2b, CH2a}$ = −13.8 Hz, 1 H, C*H*$_{2b}$-CH=CH_2), 1.53 (br. s., 2 H, NH_2) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 145.9 (arom. C), 135.5 (*C*H=CH_2), 128.4 (2 arom. C), 126.9 (arom. C), 126.4 (2 arom. C), 117.6 (CH=*C*H_2), 55.4 (*C*HNH_2), 44.1 (*C*H_2-CH=CH_2) ppm. HRMS calcd for $C_{10}H_{13}N$ $[M]^+$ 147.1042, found 147.1048.

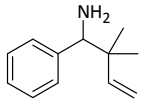
3-Methyl-1-phenylbut-3-en-1-amine (3b)



Step 1: starting from **1a** (2.42 g, 11.4 mmol) to yield **2b** (1.92 g, 7.15 mmol, 65%). Step 2: starting from **2b** (1.60 g, 5.86 mmol) to yield **3b** (0.72 g, 4.44 mmol, 76%) as light yellow oil. ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 7.38-7.35 (m, 2 H, arom. H),

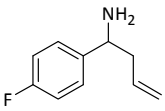
7.35-7.31 (m, 2H, arom. H), 7.26-7.22 (m, 1 H, arom. H), 4.85 (ddq, $J_{CHtrans,\ CHa}$ = –0.5 Hz, $J_{CH2trans,\ CH3}$ = 1.5 Hz, $J_{CHtrans,\ CHcis}$ = –2.2 Hz, 1 H, CH_2-C(CH_3)=CH_{2trans}), 4.80 (dddq, $J_{CH2cis,\ CH3}$ = 0.9 Hz, $J_{CHcis,\ CHb}$ = –0.9 Hz, $J_{CHcis,\ CHa}$ = –1.4, $J_{CHcis,\ CHtrans}$ = –2.2 Hz, 1 H, CH_2-C(CH_3)=CH_{2cis}), 4.10 (dd, $J_{CH,\ CH2a}$ = 4.5 Hz, $J_{CH,\ CH2b}$ = 9.5 Hz, 1 H, CHNH_2), 2.36 (dddd, $J_{CH2a,\ CH2trans}$ = –0.5 Hz, $J_{CH2a,\ CH2cis}$ = –1.4 Hz, $J_{H2a,\ CH}$ = 4.5 Hz, $J_{CH2a,\ CH2b}$ = –13.6 Hz, 1 H, CH_{2a}-CH=CH_2), 2.31 (ddd, $J_{CH2b,\ CH2cis}$ = –0.9 Hz, $J_{H2b,\ CH}$ = 9.5 Hz, $J_{CH2a,\ CH2b}$ = –13.7 Hz, 1 H, CH_{2b}-CH=CH_2), 1.76 (dd, $J_{CH3,\ CH2cis}$ = 0.9 Hz, $J_{CH3,\ CH2trans}$ =1.5 Hz, 3 H, CH_3), 1.48 (br. s, 2 H NH_2) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 146.2 (arom. C), 142.9 (*C*(CH_3)=CH_2), 128.4 (2 arom. C), 126.9 (arom. C), 126.3 (2 arom. C), 113.3 (CH(CH_3)=*C*H_2), 53.4 (*C*HNH_2), 48.6 (*C*H_2-C(CH_3)=CH_2), 22.2 (*C*H_3) ppm. HRMS calcd for $C_{11}H_{15}N$ $[M]^+$ 161.1199, found 161.1223.

2,2-Dimethyl-1-phenylbut-3-en-1-amine (3d)



Step 1: starting from **1a** (2.12 g, 9.99 mmol) to yield **2d** (0.76 g, 2.69 mmol, 27%) after repeated purification by column chromatography. Step 2: starting from **2d** (1.25 g, 4.42 mmol) to yield **3d** (0.64 g, 3.67 mmol, 83%) as yellow oil. ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 7.30 – 7.27 (m, 4 H, arom. H), 7.25 – 7.22 (m, 1 H arom. H), 5.87 (dd, $J_{CH=,\ CH2cis}$ = 10.8 Hz, $J_{CH=,\ CH2trans}$= 17.5 Hz, 1 H, C*H*=CH_2), 5.09 (dd, $J_{CH2cis,\ CH2trans}$ = – 1.4, Hz, $J_{CHcis,\ CH=s}$ = 10.8 Hz, 1 H, CH=CH_{2cis}), 5.03 (dd, $J_{CH2trans,\ CH2cis}$ = –1.4 Hz, $J_{CH2trans,\ CH=}$ = 17.5 Hz, 1 H, CH=CH_{2trans}), 3.75 (s, 1 H, C*H*NH_2), 1.43 (br. s, 2 H, NH_2), 0.99 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 145.8 (*C*H=CH_2), 142.9 (arom C), 128.5 (2 arom C), 127.5 (2 arom. C), 126.9 (arom C), 113.0 (CH=*C*H_2), 64.1 (*C*HNH_2), 41.5 (*C*(CH_3)$_2$), 25.5 (*C*H_3), 21.7 (*C*H_3) ppm. HRMS calcd for $C_{12}H_{17}N$ $[M]^+$ 175.1355, found 175.1311.

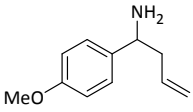
1-(4-Fluorophenyl)-but-3-en-1-amine (3e)



Step 1: starting from **1b** (1.59 g, 6.91 mmol) to yield **2e** (1.28 g, 4.69 mmol, 68%). Step 2: starting from **2e** (1.28 g, 4.69 mmol) to yield **3e** (0.53 g, 3.21 mmol, 68%) as yellow oil. ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 7.33-7.29 (m, 2 H, arom. H), 7.04-6.99 (m, 2 H, arom. H), 5.73 (dddd, $J_{CH=,\ CH2a}$ = 6.2 Hz, $J_{CH=,\ CH2b}$ = 8.0 Hz, $J_{CH=,\ CH2cis}$ = 10.1 Hz, $J_{CH=,\ CH2trans}$ = 17.1 Hz, 1 H, CH_2-C*H*=CH_2), 5.11 (dddd, $J_{CH2trans,\ CH2b}$ = –1.2 Hz, $J_{CH2trans,\ CH2a}$ = –1.6 Hz, $J_{CH2trans,\ CH2cis}$ = –2.0 Hz, $J_{CH2trans,\ CH=}$ = 17.1 Hz, 1 H, CH_2-CH=CH_{2trans}), 5.08 (dddd, $J_{CH2cis,\ CH2b}$ = –0.9 Hz, $J_{CH2cis,\ CH2a}$ = –1.2 Hz, $J_{CH2cis,\ CH2trans}$ = –2.0 Hz, $J_{CHcis,\ CH2=}$ = 10.1 Hz, 1 H, CH_2-CH=CH_{2cis}), 3.99 (dd, $J_{CH,\ CH2a}$ = 5.3 Hz, $J_{CH,\ CH2b}$ = 8.1 Hz, 1 H, C*H*NH_2), 2.42 (ddddd, $J_{CH2a,\ CH2cis}$ = –1.2 Hz, $J_{CH2a,\ CH2trans}$ = –1.6 Hz, $J_{CH2a,\ CH}$ = 5.3 Hz,

$J_{CH2a,\ CH=}$ = 6.2 Hz, $J_{CH2a,\ CH2b}$ = −13.8 Hz, 1 H, CH_{2a}-CH=CH_2), 2.33 (ddddd, $J_{CH2b,\ CH2cis}$ = −0.9 Hz, $J_{CH2b,\ CH2trans}$ = −1.2 Hz, $J_{CH2b,\ CH=}$ = 8.0 Hz, $J_{CH2b,\ CH}$ = 8.1 Hz, $J_{CH2b,\ CH2a}$ = −13.8 Hz, 1 H, CH_{2b}-CH=CH_2), 1.47 (br. s, 2 H NH_2) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 161.8 (d, $^1J_{C,F}$ = 244.7 Hz, arom. *C*-F), 141.5 (d, $^4J_{C,F}$ = 3.3 Hz, arom. C), 135.2 (*C*H=CH_2), 127.8 (d, $^3J_{C,F}$ = 7.7 Hz, 2 arom. C), 117.8 (CH=*C*H_2), 115.1 (d, $^2Jc_{,F}$ = 20.9 Hz, 2 arom. C), 54.7 (*C*HNH_2), 44.3 (*C*H_2-CH=CH_2) ppm. HRMS calcd for $C_{10}H_{12}NF$ $[M]^+$ 165.0949, found 165.0929.

1-(4-Methoxyphenyl)-but-3-en-1-amine (3f)



Step 1: starting from **1c** (0.93 g, 4.42 mmol) to yield **2f** (0.85 g, 3.00 mmol, 68%). Step 2: starting from **2f** (0.85 g, 3.00 mmol) to yield **3f** (0.48 g, 2.70 mmol, 90%) as colorless oil. ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 7.28-7.24 (m, 2 H, arom. H), 6.89-6.85 (m, 2 H, arom. H), 5.75 (dddd, $J_{CH=,\ CH2a}$ = 6.2 Hz, $J_{CH=,\ CH2b}$ = 8.0 Hz, $J_{CH=,\ CH2cis}$ = 10.2 Hz, $J_{CH=,\ CH2trans}$ = 17.1 Hz, 1 H, CH_2-C*H*=CH_2), 5.11 (dddd, $J_{CH2trans,\ CH2b}$ = −1.3 Hz, $J_{CH2trans,\ CH2a}$ = −1.6 Hz, $J_{CH2trans,\ CH2cis}$ = −2.1 Hz, $J_{CH2trans,\ CH=}$ = 17.1 Hz, 1 H, CH_2-CH=CH_{2trans}), 5.07 (dddd, $J_{CH2cis,\ CH2b}$ = −0.9 Hz, $J_{CH2cis,\ CH2a}$ = −1.1 Hz, $J_{CH2cis,\ CH2trans}$ = −2.1 Hz, $J_{CH2cis,\ CH2=}$ = 10.2 Hz, 1 H, CH_2-CH=CH_{2cis}), 3.95 (dd, $J_{CH,\ CH2a}$ = 5.3 Hz, $J_{CH,\ CH2b}$ = 8.1 Hz, 1 H, C*H*NH_2), 3.80 (s, 3 H, OCH_3), 2.43 (ddddd, $J_{CH2a,\ CH2cis}$ = −1.1 Hz, $J_{CH2a,\ CH2trans}$ = −1.6 Hz, $J_{CH2a,\ CH}$ = 5.3 Hz, $J_{CH2a,\ CH=}$ = 6.2 Hz, $J_{CH2a,\ CH2b}$ = −13.8 Hz, 1 H, CH_{2a}-CH=CH_2), 2.34 (ddddd, $J_{CH2b,\ CH2cis}$ = −0.9 Hz, $J_{CH2b,\ CH2trans}$ = −1.2 Hz, $J_{CH2b,\ CH=}$ = 8.0 Hz, $J_{CH2b,\ CH}$ = 8.1 Hz, $J_{CH2b,\ CH2a}$ = −13.8 Hz, 1 H, CH_{2b}-CH=CH_2), 1.46 (br. s, 2 H NH_2) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 158.5 (arom. C), 138.0 (arom. C), 135.6 (*C*H=CH_2), 127.3 (2 arom. C), 117.5 (CH=*C*H_2), 113.7 (2 arom. C), 55.3 (O*C*H_3), 54.8 (*C*HNH_2), 44.3 (*C*H_2-CH=CH_2) ppm. HRMS calcd for $C_{11}H_{15}NO$ $[M]^+$ 177.1154, found 177.1112.

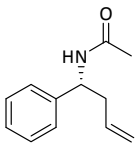
Standard procedure for the small-scale enzymatic kinetic resolution

Lipase PS-D and molecular sieves (4 Å) were weighed in a reaction vial before *rac*-**3a** (0.1 M, 1.0 mL) in dry isopropyl acetate (or an acyl donor in an organic solvent) was added. Reactions proceeded under shaking at 170 rpm. The progress was followed by taking samples (100 µL) at intervals, filtering off the enzyme and analyzing the samples (diluted with hexane after derivatization of the amine with an appropriate acid anhydride) by GC.

Procedures for the preparative-scale enzymatic kinetic resolutions

1-Phenylbut-3-en-1-amine (3a) with isopropyl acetate: Lipase PS-D (1.00 g, 50 mg mL^{-1}) and molecular sieves (4 Å, 1.00 g) were weighed in the reaction vessel before *rac*-**3a** (300 mg, 2.04 mmol) in neat isopropyl acetate (20 mL) was added. After 3 days the reaction was stopped at 46% conversion. The crude product was purified by silica gel chromatography (EtOAc) to yield (*S*)-**3a** as a colorless oil (108 mg, 0.73 mmol, 66%, *ee* = 84%) and (*R*)-**5a** as white solid [163 mg, 0.86 mmol, 92%, *ee* = 99%, $[\alpha]_D^{25}$ = +115 (c = 1.0, $CHCl_3$), mp (74 ± 1) °C]. A fraction of the enantiomerically enriched (*S*)-**3a** (86 mg, 0.59 mmol) was purified under kinetic resolution conditions, yielding (*S*)-**3a** as a colorless oil [38 mg, 0.26 mmol, 44%, *ee* = 99%, $[\alpha]_D^{25}$ = −51 (c = 1.0, $CHCl_3$)].

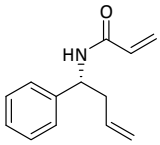
***N*-[(1*R*)-1-Phenylbut-3-enyl]ethanamide [(*R*)-5a]**



^{1}H NMR ($CDCl_3$, 500.13 MHz, 25 °C): δ = 7.39-7.23 (m, 5 H, arom. H), 5.99 (d, $J_{NH,\,CH}$ = 8.2 Hz, 1 H, NH), 5.68 (dddd, $J_{CH=,\,CH2b}$ = 6.7 Hz, $J_{CH=,\,CH2a}$ = 7.3 Hz, $J_{CH=,\,CH2cis}$ = 10.1 Hz, $J_{CH=,\,CH2trans}$ = 17.2 Hz, 1 H, CH_2-C*H*=CH_2), 5.10 (dddd, $J_{CH2trans,\,CHa}$ = −1.4 Hz, $J_{CH2trans,\,CH2b}$ = −1.4 Hz, $J_{CH2trans,\,CH2cis}$ = −1.9 Hz, $J_{CH2trans,\,CH=}$ = 17.2 Hz, 1 H, CH_2-CH=CH_{2trans}), 5.07 (dddd, $J_{CH2cis,\,CHa}$ = −1.1 Hz, $J_{CH2cis,\,CH2b}$ = −1.1 Hz, $J_{CH2cis,\,CH2trans}$ = −1.9 Hz, $J_{CH2cis,\,CH=}$ = 10.1 Hz, 1 H, CH_2-CH=CH_{2cis}), 5.07 (ddd, $J_{CH,\,CH2b}$ = 5.9 Hz, $J_{CH,\,CH2a}$ = 7.9 Hz, $J_{CH,\,NH}$ = 8.2 Hz, 1 H, C*H*NH), 2.57 (ddddd, $J_{CH2a,\,CH2cis}$ = −1.1 Hz, $J_{CH2a,\,CH2trans}$ = −1.4 Hz, $J_{CH2a,\,CH=}$ = 7.3 Hz, $J_{CH2a,\,CH}$ = 7.9 Hz, $J_{CH2a,\,CH2b}$ = −13.8 Hz, 1 H, CH_{2a}-CH=CH_2), 2.56 (ddddd, $J_{CH2b,\,CH2cis}$ = −1.1 Hz, $J_{CH2b,\,CH2trans}$ = −1.4 Hz, $J_{CH2b,\,CH}$ = 5.9 Hz, $J_{CH2b,\,CH=}$ = 6.7 Hz, $J_{CH2b,\,CH2a}$ = −13.8 Hz, 1 H, CH_{2b}-CH=CH_2), 1.99 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz, 25°C): δ = 169.3 (*C*O), 141.6 (arom. C), 134.0 (*C*H=CH_2), 128.6 (2 arom. C), 127.4 (arom. C), 126.5 (2 arom. C), 125.9 (C_{arom}), 118.2 (CH=*C*H_2), 52.5 (*C*HNH), 40.5 (CH_2-CH=CH_2), 23.4 (CO*C*H_3) ppm. HRMS calcd for $C_{12}H_{15}NONa$ $[M+Na]^+$ 212.1046, found 212.1039.

1-Phenylbut-3-en-1-amine (3a) with ethyl acrylate: *rac*-**3a** (296 mg, 2.01 mmol) in 1:9 (v/v) mixture of ethyl acrylate in toluene was added on lipase PS-D (1.00 g, 50 mg mL^{-1}) and molecular sieves (4Å, 1.00 g). After 5 days the reaction was stopped at 19% conversion. The crude product was dissolved in H_2O (5 mL) and the solution was acidified with 2 M HCl (5 mL) and by silica pad filtration (EtOAc) to yield (*R*)-**6** as a white solid [50 mg, 0.25 mmol, 65%, *ee* = 95%, $[\alpha]_D^{25}$ = +133 (c = 1.0, $CHCl_3$), mp (83 ± 1) °C].

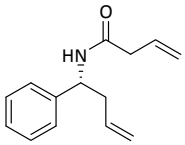
_N_-[(1_R_)-1-Phenylbut-3-enyl]prop-2-enamide [(_R_)-6]



^{1}H NMR ($CDCl_3$, 600.13 MHz, 25 °C): δ = 7.36-7.24 (m, 5 H, arom. H), 6.28 (dd, $J_{CH2trans', CH2cis'}$ = –1.5 Hz, $J_{CH2trans', CH=}$ = 17.0 Hz, 1 H, CO-CH=CH_{2trans}), 6.11 (dd, $J_{CH=, CH2cis'}$ = 10.4 Hz, $J_{CH=, CH2trans'}$ = 17.0 Hz, 1 H, CO-CH=CH_2), 5.87 (d, $J_{NH, CH}$ = 8.1 Hz, 1 H, NH), 5.70 (dddd, $J_{CH=, CH2b}$ = 6.9 Hz, $J_{CH=, CH2a}$ = 7.1 Hz, $J_{CH=, CH2cis}$ = 10.2 Hz, $J_{CH=, CH2trans}$ = 17.1 Hz, 1 H, CH_2-CH=CH_2), 5.64 (dd, $J_{CH2cis', CH2trans'}$ = –1.5 Hz, $J_{CH2cis', CH=}$ = 10.4 Hz, 1 H, CO-CH=CH_{2cis}), 5.17 (dd, $J_{CH, CH2b}$ = 6.4 Hz, $J_{CH, CH2a}$ = 7.3 Hz, 1 H, CHNH), 5.12 (dddd, $J_{CH2trans, CH2a}$ = –1.4 Hz, $J_{CH2trans, CH2b}$ = –1.5 Hz, $J_{CH2trans, CH2cis}$ = –1.9 Hz, $J_{CH2trans, CH=}$ = 17.1 Hz, 1 H, CH_2-CH=CH_{2trans}), 5.09 (dddd, $J_{CH2cis, CH2a}$ = –1.0 Hz, $J_{CH2cis, CH2b}$ = –1.2 Hz, $J_{CH2cis, CH2trans}$ = –1.9 Hz, $J_{CH2cis, CH=}$ = 10.2 Hz, 1 H, CH_2-CH=CH_{2cis}), 2.62 (ddddd, $J_{CH2a, CH2cis}$ = –1.0 Hz, $J_{CH2a, CH2trans}$ = –1.4 Hz, $J_{CH2a, CH=}$ = 7.1 Hz, $J_{CH2a, CH}$ = 7.3 Hz, $J_{CH2a, CH2b}$ = –13.7 Hz, 1 H, CH_{2a}-CH=CH_2), 2.61 (ddddd, $J_{CH2b, CH2cis}$ = –1.2 Hz, $J_{CH2b, CH2trans}$ = –1.5 Hz, $J_{CH2b, CH}$ = 6.4 Hz, $J_{CH2b, CH=}$ = 6.9, $J_{CH2b, CH2a}$ = –13.7 Hz, 1 H, CH_{2b}-CH=CH_2) ppm. ^{13}C NMR ($CDCl_3$, 150.9 MHz, 25 °C): δ = 164.7 (*C*O), 141.4 (arom. C), 133.9 (*C*H=CH_2), 130.7 (CO-*C*H=CH_2), 128.7 (2 arom. C), 127.4 (arom. C), 126.8 (CO-CH=*C*H_2), 126.5 (2 arom. C), 118.3 (CH=*C*H_2), 52.5 (*C*HNH), 40.4 (*C*H_2-CH=CH_2) ppm. HRMS calcd for $C_{13}H_{15}NONa$ $[M+Na]^+$ 224.1046, found 224.1144.

1-Phenylbut-3-en-1-amine (3a) with isopropyl 3-butenoate: *rac*-**3a** (693 mg, 4.71 mmol) in the 1:9 (v/v) mixture of isopropyl 3-butenoate in toluene was added on lipase PS-D (2.36 g, 50 mg mL^{-1}) and molecular sieves (4 Å, 2.40 g). After 5 days the reaction was stopped at 47% conversion. The crude product was dissolved in H_2O (10 mL) and the solution was acidified with 4 M HCl (4 mL) and extracted with EtOAc (3 × 20 mL). Purification as above yielded (*R*)-**7** as a white solid [504 mg, 1.88 mmol, 85%, *ee* > 99%, $[\alpha]_D^{25}$ = +63 (c = 1.0, $CHCl_3$), mp (55 ± 1)°C].

_N_-[(1_R_)-1-Phenylbut-3-enyl]but-3-enamide [(_R_)-7]

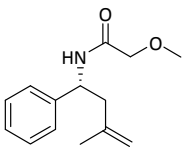


^{1}H NMR ($CDCl_3$, 500.13 MHz, 25 °C): δ = 7.35-7.31 (m, 2 H, arom. H), 7.27-7.23 (m, 3 H, arom. H), 5.94 (dddd, $J_{CH=', CH2a'}$ = 7.1 Hz, $J_{CH=', CH2b'}$ = 7.2 Hz, $J_{CH=', CH2cis'}$ = 10.1 Hz, $J_{CH=', CH2trans'}$ = 17.1 Hz, 1 H, CO- CH_2'-CH'=CH_2'), 5.92 (d, $J_{NH, CH}$ = 8.2 Hz, 1 H, NH), 5.67 ($J_{CH=, CH2a}$ = 6.9 Hz, $J_{CH=, CH2b}$ = 7.3 Hz, $J_{CH=, CH2cis}$ = 10.1 Hz, $J_{CH=, CH2trans}$ = 17.1 Hz, 1 H, CH_2-CH=CH_2), 5.25 (dddd, $J_{CH2cis', CH2b'}$ = –1.0 Hz, $J_{CH2cis', CH2a'}$ = –1.1 Hz, $J_{CH2cis', CH2trans'}$ = –1.6 Hz, $J_{CH2cis', CH='}$ = 10.1 Hz, 1 H, CO-CH_2'-CH'=CH_{2cis}'), 5.23 (dddd, $J_{CH2trans', CH2b'}$ = –1.4 Hz, $J_{CH2trans', CH2a'}$ = –1.4 Hz, $J_{CH2trans', CH2cis'}$ = –1.6 Hz, $J_{CH2trans', CH='}$ = 17.1 Hz, 1 H, CO-CH_2'-CH'=CH_{2trans}'), 5.10 (dddd, $J_{CH2trans, CH2b}$ = –

1.4 Hz, $J_{CH2trans,\ CH2a}$ = −1.4 Hz, $J_{CH2trans,\ CH2cis}$ = −1.9 Hz, $J_{CH2trans,\ CH=}$ = 17.1 Hz, 1 H, CH_2-CH=CH_{2trans}), 5.09 (ddd, $J_{CH,\ CH2a}$ = 5.9 Hz, $J_{CH,\ CH2b}$ = 7.6 Hz, $J_{CH,\ NH}$ = 8.2 Hz, 1 H, C*H*NH), 5.08 (dddd, $J_{CH2cis,\ CH2b}$ = −0.9 Hz, $J_{CH2cis,\ CH2a}$ = −1.2 Hz, $J_{CH2cis,\ CH2trans}$ = −1.9 Hz, $J_{CH2cis',\ CH='}$ = 10.1 Hz, 1 H, CH_2-CH=CH_{2cis}), 3.03 (dddd, $J_{CH2a',\ CH2cis'}$ = −1.1 Hz, $J_{CH2a',\ CH2trans'}$ = −1.4 Hz, $J_{CH2a',\ CH='}$ = 7.1 Hz, $J_{CH2a',\ CH2b'}$ = −14.1 Hz, 1 H, CO-CH_{2a}'-CH'=CH_2'), 3.02 (dddd, $J_{CH2b',\ CH2cis'}$ = −1.0 Hz, $J_{CH2b',\ CH2trans'}$ = −1.4 Hz, $J_{CH2b',\ CH='}$ = 7.2 Hz, $J_{CH2b,\ CH2a'}$ = −14.1 Hz, 1 H, CO-CH_{2b}'-CH'=CH_2'), 2.56 (ddddd, $J_{CH2a,\ CH2cis}$ = −1.2 Hz, $J_{CH2a,\ CH2trans}$ = −1.4 Hz, $J_{CH2a,\ CH}$ = 5.9 Hz, $J_{CH2a,\ CH=}$ = 6.9 Hz, $J_{CH2a,\ CH2b}$ = −14.2 Hz, 1 H, CH_{2a}-CH=CH_2), 2.55 (ddddd, $J_{CH2b,\ CH2cis}$ = −0.9 Hz, $J_{CH2b,\ CH2trans}$ = −1.4 Hz, $J_{CH2b,\ CH=}$ = 7.3, $J_{CH2b,\ CH}$ = 7.6 Hz, $J_{CH2b,\ CH2a}$ = −14.2 Hz, 1 H, CH_{2b}-CH=CH_2) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz, 25 °C): δ = 169.6 (CO), 141.5 (arom. C), 133.9 (*C*H=CH_2), 131.3 (*C*'H=C'H_2), 128.6 (2 arom. C), 127.4 (arom. C), 126.4 (2 arom. C), 120.0 (C'H=*C*'H_2), 118.3 (CH=CH_2), 52.2 (*C*HNH), 41.7 (*C*'H_2-C'H=C'H_2), 40.5 (CH_2-CH=CH_2) ppm. HRMS calcd for $C_{14}H_{17}NONa$ $[M+Na]^+$ 238.1202, found 238.1187.

3-Methyl-1-phenylbut-3-en-1-amine (3b) with ethyl methoxyacetate: *rac*-**3b** (380 mg, 2.36 mmol) was resolved as above except that CAL-B (Novozym 435, 1.22 g, 50 mg mL^{-1}) was used in the place of lipase PS-D. After 7 days the reaction was stopped at 31% conversion. The crude product was dissolved in H_2O (10 mL) and the solution was acidified with 4 M HCl (4 mL) and extracted with EtOAc (3 × 20 mL). The aqueous phase was alkalized with 4 N NaOH (4 mL) and extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried with Na_2SO_4 and concentrated to yield (*S*)-**3b** as a colorless oil (93 mg, 0.57 mmol, 35%, *ee* = 44%). The enantiomerically enriched (*S*)-**3b** was purified under kinetic resolution conditions, yielding *(S)*-**3b** as a colorless oil [20 mg, 0.12 mmol, 21%, *ee* = 72%, $[\alpha]_D^{25}$ = −31 (c = 1.0, $CHCl_3$)]. The combined organic phases containing (*R*)-**4b** was treated in the same way and purified by silica pad filtration (EtOAc) to yield (*R*)-**4b** as a white solid [184 mg, 0.79 mmol, quant. yield, *ee* > 99%, $[\alpha]_D^{25}$ = +45 (c = 1.0, $CHCl_3$), mp (53 ± 1) °C].

2-Methoxy-*N*-[(1*R*)-3-methyl-1-phenylbut-3-enyl]ethanamide [(*R*)-4b]

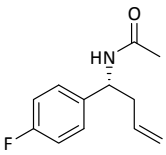


^{1}H NMR ($CDCl_3$, 500.13 MHz, 25 °C): δ = 7.35-7.23 (m, 5 H, arom. H), 6.78 (d, $J_{NH,\ CH}$ = 8.4 Hz, 1 H, NH), 5.20 (ddd, $J_{CH,\ CH2a}$ = 5.8 Hz, $J_{CH,\ NH}$ = 8.4 Hz, $J_{CH,\ CH2b}$ = 9.4 Hz, 1 H, C*H*NH), 4.82 (ddq, $J_{CH2trans,\ CHa}$ = −0.6 Hz, $J_{CH2trans,\ CH3}$ = 1.4 Hz, $J_{CH2trans,\ CH2cis}$ = −2.0 Hz, 1 H, CH_2-CH=CH_{2trans}), 4.74 (dddq, $J_{CH2cis,\ CH3}$ = 0.9 Hz, $J_{CH2cis,\ CH2b}$ = −1.0 Hz, $J_{CH2cis,\ CHa}$ = −1.3 Hz, $J_{CH2cis,\ CH2trans}$ = −2.0 Hz, 1 H, CH_2-CH=CH_{2cis}), 3.88 (s, 2 H, CH_2OCH_3), 3.40 (s, 3H, CH_2OCH_3), 2.54 (dddd, $J_{CH2a,\ CH2trans}$ = −0.6 Hz, $J_{CH2a,\ CH2cis}$ = −1.3 Hz, $J_{CH2a,\ CH}$ = 5.8 Hz, $J_{CH2a,\ CH2b}$ = −14.2 Hz, 1 H, CH_{2a}-CH=CH_2), 2.50 (ddd, $J_{CH2b,\ CH2cis}$ = −1.0 Hz, $J_{CH2b,\ CH}$ = 9.4 Hz, $J_{CH2b,\ CH2a}$ = −14.1 Hz, 1 H, CH_{2b}-CH=CH_2), 1.74

(s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz, 25 °C):): δ = 168.8 (*C*O), 142.1 (arom. C), 141.8 (*C*(CH_3)=CH_2), 128.6 (2 arom. C), 127.3 (arom. C), 126.3 (2 arom. C), 113.8 (C(CH_3)=*C*H_2), 72.0 (*C*H_2OCH_3), 59.3 (CH_2O*C*H_3), 50.5 (*C*HNH), 45.1 (*C*H_2-C(CH_3)=CH_2), 22.1 (*C*H_3) ppm. HRMS calcd for $C_{14}H_{19}NO_2Na$ $[M+Na]^+$ 256.1308, found 256.1396.

1-(4-Fluorophenyl)but-3-en-1-amine (3e) with isopropyl acetate: *rac*-**3e** (429 mg, 2.60 mmol) was resolved as above. After 4 days the reaction was stopped at 33% conversion. The work-up gave (*S*)-**3e** as a pale yellow oil (216 mg, 1.31 mmol, 75%, *ee* = 48%). The enzymatic purification gave (*S*)-**3e** as a pale yellow oil [71 mg, 0.43 mmol, 33%, *ee* = 95%, $[\alpha]_D^{25}$ = −35 (c = 1.0, $CHCl_3$)]. (*R*)-**5e** was a white solid [133 mg, 0.64 mmol, 75%, *ee* > 99%, $[\alpha]_D^{25}$ = +109.0 (c = 1.0, $CHCl_3$), mp (120 ± 1) °C].

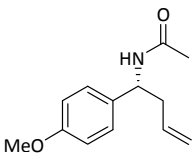
***N*-[(1*R*)-1-(4-Fluorophenyl)but-3-enyl]ethanamide [(*R*)-5e]**



^{1}H NMR ($CDCl_3$, 500.13 MHz, 25 °C): δ = 7.26-7.22 (m, 2 H, arom. H), 7.04-6.99 (m, 2 H, arom. H), 5.75 (d, $J_{NH,\ CH}$ = 8.0 Hz, 1 H, NH), 5.66 (dddd, $J_{CH=,\ CH2b}$ = 6.8 Hz, $J_{CH=,\ CH2a}$ = 7.2 Hz, $J_{CH=,\ CH2cis}$ = 10.1 Hz, $J_{CH=,\ CH2trans}$ = 17.2 Hz, 1 H, CH_2-C*H*=CH_2), 5.11 (dddd, $J_{CH2trans,\ CHa}$ = −1.4 Hz, $J_{CH2trans,\ CH2b}$ = −1.5 Hz, $J_{CH2trans,\ CH2cis}$ = −1.9 Hz, $J_{CH2trans,\ CH=}$ = 17.2 Hz, 1 H, CH_2-CH=CH_{2trans}), 5.09 (dddd, $J_{CH2cis,\ CHa}$ = −1.1 Hz, $J_{CH2cis,\ CH2b}$ = −1.1 Hz, $J_{CH2cis,\ CH2trans}$ = −1.9 Hz, $J_{CH2cis,\ CH=}$ = 10.1 Hz, 1 H, CH_2-CH=CH_{2cis}), 5.05 (ddd, $J_{CH,\ CH2b}$ = 6.6 Hz, $J_{CH,\ CH2a}$ = 7.2 Hz, $J_{CH,\ NH}$ = 8.0 Hz, 1 H, C*H*NH), 2.54 (ddddd, $J_{CH2a,\ CH2cis}$ = −1.1 Hz, $J_{CH2a,\ CH2trans}$ = −1.4 Hz, $J_{CH2a,\ CH}$ = 7.2 Hz, $J_{CH2a,\ CH=}$ = 7.2 Hz, $J_{CH2a,\ CH2b}$ = −13.9 Hz, 1 H, CH_{2a}-CH=CH_2), 2.54 (ddddd, $J_{CH2b,\ CH2cis}$ = −1.1 Hz, $J_{CH2b,\ CH2trans}$ = −1.5 Hz, $J_{CH2b,\ CH}$ = 6.6 Hz, $J_{CH2b,\ CH=}$ = 6.8 Hz, $J_{CH2b,\ CH2a}$ = −13.9 Hz, 1 H, CH_{2b}-CH=CH_2), 1.99 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz, 25 °C): δ = 169.3 (*C*O), 162.0 (d, $^1J_{C,F}$ = 245.8 Hz, arom. C), 137.5 (d, $^4J_{C,F}$ = 2.8 Hz, arom. C), 133.7 (*C*H=CH_2), 128.0 (d, $^3J_{C,F}$ = 8.3 Hz, 2 arom. C), 118.5 (CH=*C*H_2), 115.4 (d, $^2J_{C,F}$ = 21.1 Hz, 2 arom. C), 51.9 (*C*HNH), 40.5 (*C*H_2-CH=CH_2), 23.4 (CO*C*H_3) ppm. HRMS calcd for $C_{12}H_{14}FNONa$ $[M+Na]^+$ 230.0952, found 230.0949.

1-(4-Methoxyphenyl)but-3-en-1-amine (3f) with isopropyl acetate: *rac*-**3f** (227 mg, 1.28 mmol) was resolved as above. After 4 days the reaction was stopped at 49% conversion. The work-up gave (*S*)-**3f** as a colorless oil (0.108 mg, 0.61 mmol, 93%, *ee* = 94%, $[\alpha]_D^{25}$ = −34 (c = 1.0, $CHCl_3$), and (*R*)-**5f** as a white solid [91 mg, 0.41 mmol, 65%, *ee* >99%, $[\alpha]_D^{25}$ = +110 (c = 1.0, $CHCl_3$), mp (122 ± 1) °C].

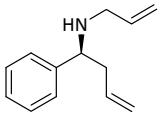
_N_-[(1_R_)-1-(4-Methoxyphenyl)but-3-enyl]ethanamide [(_R_)-5f]



^{1}H NMR ($CDCl_3$, 500.13 MHz, 25 °C): δ = 7.22-7.18 (m, 2 H, arom. H), 6.88-6.84 (m, 2 H, arom. H), 5.84 (d, $J_{NH,\ CH}$ = 8.1 Hz, 1 H, NH), 5.68 (dddd, $J_{CH=,\ CH2b}$ = 6.9 Hz, $J_{CH=,\ CH2a}$ = 7.1 Hz, $J_{CH=,\ CH2cis}$ = 10.2 Hz, $J_{CH=,\ CH2trans}$ = 17.2 Hz, 1 H, CH_2-C*H*=CH_2), 5.09 (dddd, $J_{CH2trans,\ CHa}$ = −1.4 Hz, $J_{CH2trans,\ CH2b}$ = −1.5 Hz, $J_{CH2trans,\ CH2cis}$ = −1.9 Hz, $J_{CH2trans,\ CH=}$ = 17.2 Hz, 1 H, CH_2-CH=CH_{2trans}), 5.06 (dddd, $J_{CH2cis,\ CHa}$ = −1.1 Hz, $J_{CH2cis,\ CH2b}$ = −1.1 Hz, $J_{CH2cis,\ CH2trans}$ = −1.9 Hz, $J_{CH2cis,\ CH=}$ = 10.2 Hz, 1 H, CH_2-CH=CH_{2cis}), 5.03 (ddd, $J_{CH,\ CH2b}$ = 6.7 Hz, $J_{CH,\ CH2a}$ = 7.3 Hz, $J_{CH,\ NH}$ = 8.1 Hz, 1 H, C*H*NH), 2.56 (ddddd, $J_{CH2a,\ CH2cis}$ = −1.1 Hz, $J_{CH2a,\ CH2trans}$ = −1.4 Hz, $J_{CH2a,\ CH=}$ = 7.1 Hz, $J_{CH2a,\ CH}$ = 7.3 Hz, $J_{CH2a,\ CH2b}$ = −14.2 Hz, 1 H, CH_{2a}-CH=CH_2), 2.53 (ddddd, $J_{CH2b,\ CH2cis}$ = −1.1 Hz, $J_{CH2b,\ CH2trans}$ = −1.5 Hz, $J_{CH2b,\ CH}$ = 6.7 Hz, $J_{CH2b,\ CH=}$ = 6.9 Hz, $J_{CH2b,\ CH2a}$ = −14.2 Hz, 1 H, CH_{2b}-CH=CH_2), 1.97 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 125.8 MHz, 25 °C): δ = 169.2 (*C*O), 158.8 (arom. C), 134.2 (*C*H=CH_2), 133.7 (arom. C), 127.7 (2 arom. C), 118.0 (CH=*C*H_2), 114.0 (2 arom. C), 55.3 (O*C*H_3), 52.0 (*C*HNH), 40.4 (*C*H_2-CH=CH_2), 23.4 (CO*C*H_3) ppm. HRMS calcd for $C_{13}H_{17}NO_2Na$ $[M+Na]^+$ 242.1152, found 242.1257.

Synthesis of N-containing heterocycles

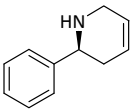
Synthesis of (1*S*)-1-phenyl-*N*-(prop-2-enyl)but-3-en-1-amine [(*S*)-8]



In a Schlenk tube flushed with argon, (*S*)-**3a** (60 mg, 0.41 mmol, *ee* 99%) was dissolved in anhydrous DMF (1.5 mL). KOH (70.2 mg, 1.25 mmol, 3 equiv.) was added and the mixture was stirred for 15 min. Allyl bromide (35 µl, 0.40 mmol, 1 equiv.) was added and the mixture was stirred at room temperature for 3 h. The reaction was quenched by adding H_2O (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to yield the crude product that was purified by flash chromatography (eluent hexane:EtOAc 1:1 + 1% Et_3N; silica enriched with ~0.1% Ca) yielding of (1*S*)-1-phenyl-*N*-(prop-2-en-1-yl)but-3-en-1-amine (51.5 mg, 0.27 mmol, 67%) as a colorless oil. $[\alpha]_D^{20}$ = −27 (c = 0.01, $CHCl_3$). R_f = 0.7 (hexane:EtOAc 1:1). ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): *δ* = 7.35-7.29 (m, 4 H, arom. H), 7.26-7.22 (m, 1 H, arom. H), 5.86 (dddd, $J_{CH=',\ CH2a'}$ = 5.4 Hz, $J_{CH=',\ CH2b'}$ = 6.7 Hz, $J_{CH=',\ CH2cis'}$ = 10.2 Hz, $J_{CH=',\ CH2trans'}$ = 17.2 Hz, 1 H, CH_2'-C*H*'=CH_2'), 5.72 (dddd, $J_{CH=,\ CH2a}$ = 5.9 Hz, $J_{CH=,\ CH2b}$ = 8.3 Hz, $J_{CH=,\ CH2cis}$ = 10.1 Hz, $J_{CH=,\ CH2trans}$ = 17.1 Hz, 1 H, CH_2-C*H*=CH_2), 5.10 (dddd, $J_{CH2trans',\ CH2b'}$ = −1.4 Hz, $J_{CH2trans',\ CH2a'}$ = −1.7 Hz, $J_{CH2trans',\ CH2cis'}$ = −1.9 Hz, $J_{CH2trans',\ CH='}$ = 17.2 Hz, 1 H, $CH_2^{'}$-CH'=C$H_{2trans}^{'}$), 5.09 (dddd, $J_{CH2trans,\ CH2b}$ = −1.2 Hz, $J_{CH2trans,\ CH2a}$ = −1.7 Hz, $J_{CH2trans,\ CH2cis}$ = −2.0 Hz, $J_{CH2trans,\ CH=}$ = 17.1 Hz, 1 H, CH_2-CH=CH_{2trans}), 5.06 (dddd, $J_{CH2cis',\ CH2b'}$ = −1.2 Hz, $J_{CH2cis',\ CH2a'}$ = −1.4 Hz, $J_{CH2cis',\ CH2trans'}$ = −1.9 Hz, $J_{CH2cis',\ CH='}$ = 10.2 Hz, 1 H, $CH_2^{'}$-CH'=CH_{2cis}'), 5.05 (dddd, $J_{CH2cis,\ CH2b}$ = −0.9 Hz, $J_{CH2cis,\ CH2a}$ = −1.3

Hz, $J_{CH2cis,\ CH2trans}$ = −2.0 Hz, $J_{CH2cis,\ CH=}$ = 10.1 Hz, 1 H, CH_2-CH=CH_{2cis}), 3.70 (dd, $J_{CH,\ CH2a}$ = 5.8 Hz, $J_{CH,\ CH2b}$ = 7.9 Hz, 1 H, C*H*NH), 3.11 (dddd, $J_{CH2a',\ CH2cis'}$ = −1.4 Hz, $J_{CH2a',\ CH2trans'}$ = −1.7 Hz, $J_{CH2a',\ CH='}$ = 5.4 Hz, $J_{CH2a',\ CH2b'}$ = −14.2 Hz, 1 H , C*H*2a'-CH'=CH2'), 3.02 (dddd, $J_{CH2b',\ CH2cis'}$ = −1.2 Hz, $J_{CH2b',\ CH2trans'}$ = −1.4 Hz, $J_{CH2b',\ CH='}$ = 6.7 Hz, $J_{CH2b',\ CH2a'}$ = −14.2 Hz, 1 H , CH_{2b}'-CH'=CH_2'), 2.43 (ddddd, $J_{CH2a,\ CH2cis}$ = −1.3 Hz, $J_{CH2a,\ CH2trans}$ = −1.7 Hz, $J_{CH2a,\ CH}$ = 5.8 Hz, $J_{CH2a,\ CH=}$ = 5.9 Hz, $J_{CH2a,\ CH2b}$ = −13.9 Hz, 1 H , CH_{2a}-CH=CH_2), 2.40 (ddddd, $J_{CH2b,\ CH2cis}$ = −0.9 Hz, $J_{CH2b,\ CH2trans}$ = −1.2 Hz, $J_{CH2b,\ CH}$ = 7.9 Hz, $J_{CH2a,\ CH=}$ = 8.3 Hz, $J_{CH2a,\ CH2b}$ = −13.9 Hz, 1 H , CH_{2a}-CH=CH_2) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 143.7 (arom. C), 136.9 (*C*'H=C'H_2) 135.4 (*C*H=CH_2), 128.3 (2 arom. C) 127.2 (2 arom. C.), 127.0 (arom. C), 117.5 (CH=*C*H_2), 115.7 (CH'=*C*H_2'), 61.7 (*C*HNH), 50.0 (*C*'H_2-C'H=C'H_2), 43.0 (*C*H_2-CH=CH_2) ppm. HRMS calcd for $C_{13}H_{17}N$ $[M]^+$ 187.1356, found 187.1350.

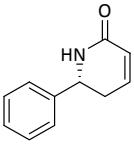
Synthesis of (2*S*)-2-phenyl-1,2,3,6-tetrahydropyridine [(*S*)-9]



In a Schlenk tube flushed with argon, (1*S*)-1-phenyl-*N*-(prop-2-en-1-yl)but-3-en-1-amine [(*S*)-**8**] (22.0 mg, 0.12 mmol) was dissolved in anhydrous DCM (1.2 mL). *p*-toluenesulfonic acid monohydrate (23.4 mg, 0.12 mmol) of was added and the mixture was stirred for 10 min. Grubbs´ second-generation catalyst (NHC)$(PCy_3)Cl_2$Ru=CHR (10.2 mg, 0.012 mmol, 10 mol-%) was added and the resulting mixture was stirred at room temperature for 17 h. The solvent was evaporated and the residue dissolved in EtOAc (15 mL). The organic layer was extracted with 1 M HCl (4 × 5 mL). The combined aqueous layers were alkalized (pH = 14) by adding NaOH (s). The basic solution was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated to yield the crude product that was purified by flash chromatography (eluent hexane:EtOAc 1:1 + 1% Et_3N; silica enriched with ~0.1% Ca) yielding of (2*S*)-2-phenyl-1,2,3,6-tetrahydropyridine (13.4 mg, 0.084 mmol, 70%) as yellowish oil. $[\alpha]_D^{20}$ = −88 (c = 0.01, $CHCl_3$). R_f = 0.2 (hexane:EtOAc 1:1). ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 7.40-7.37 (m, 2 H arom. H), 7.36-7.32 (m, 2 H, arom. H), 7.28-7.25 (m, 1 H, arom. H), 5.87 (ddddd, $J_{CH=,\ CH2a'}$ = −1.8 Hz, $J_{CH=,\ CH2a}$ = 1.8 Hz, $J_{CH=,\ CH2b}$ = 2.5 Hz, $J_{CH=,\ CH2b'}$ = −5.3 Hz, $J_{CH=,\ CH='}$ = 10.1 Hz, 1 H, C*H*'=CH'), 5.79 (ddddd, $J_{CH=',\ CH2b'}$ = 1.5 Hz, $J_{CH=',\ CH2b}$ = −1.9 Hz, $J_{CH=',\ CH2a'}$ = 2.7 Hz, $J_{CH=',\ CH2a}$ = −4.4 Hz, $J_{CH=',\ CH=}$ = 10.1 Hz, 1 H, CH'=C*H*'), 3.85 (dd, $J_{CH,\ CH2b'}$ = 3.8 Hz, $J_{CH,\ CH2a'}$ = 10.3 Hz, 1 H, C*H*), 3.62 (ddddd, $J_{CH2a,\ CH=}$ = 1.8 Hz, $J_{CH2a,\ CH2a'}$ = −2.5 Hz, $J_{CH2a,\ CH2b'}$ = −3.4 Hz, $J_{CH2a,\ CH='}$ = −4.4 Hz, $J_{CH2a,\ CH2b}$ = −16.9 Hz, 1 H, C*H*2a-CH=CH'), 3.50 (ddddd, $J_{CH2b,\ CH2b'}$ = −0.9 Hz, $J_{CH2b,\ CH='}$ = −1.9 Hz, $J_{CH2b,\ CH=}$ = 2.5 Hz, $J_{CH2b,\ CH2a'}$ = −4.7 Hz, $J_{CH2b,\ CH2a}$ = −16.9 Hz, 1 H, C*H*2b-CH=CH'), 2.29 (dddddd, $J_{CH2a',\ CH=}$ = −1.8 Hz, $J_{CH2a',\ CH2a}$ = −2.5 Hz, $J_{CH2a',\ CH='}$ = 2.7 Hz, $J_{CH2a',\ CH2b}$ = −4.7 Hz, $J_{CH2a',\ CH}$ = 10.3 Hz, $J_{CH2a',\ CH2b'}$ = −17.3 Hz, 1 H, C*H*2a'-CH'=CH'), 2.25 (dddddd, , $J_{CH2b',\ CH2b}$ = −0.9 Hz, $J_{CH2b',\ CH='}$ = 1.5 Hz, $J_{CH2b',\ CH2a}$ = −3.4 Hz, $J_{CH2b',\ CH}$ = 3.8 Hz, $J_{CH2b',\ CH=}$ = −5.3 Hz, $J_{CH2b',\ CH2a'}$ = −

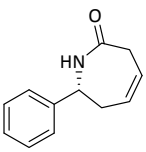
17.3 Hz, 1 H, C*H*2b'-CH'=CH') ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 144.4 (arom C), 128.6 (2 arom. C), 127.2 (arom. C), 126.6 (2 arom. C) 125.9 (CH=*C*H'), 125.6 (*C*H=CH'), 57.7 (*C*H), 46.1 (CH_2), 34.1 (CH_2') ppm. HRMS calcd for $C_{11}H_{13}N$ $[M]^+$ 159.1043, found 159.1046.

Synthesis of (6*R*)-6-phenyl-5,6-dihydropyridin-2(1*H*)-one [(*R*)-10]



In a Schlenk tube flushed with argon, *(R)-N*-(1-phenylbut-3-enyl)acrylamide [(*R*)-**6**] (20.2 mg, 0.10 mmol, *ee* 95%) was dissolved in anhydrous DCM (1.5 mL). Grubbs´ second-generation catalyst (NHC)(PCy_3)Cl_2Ru=CHR (3.6 mg, 0.0042 mmol) dissolved in anhydrous DCM (0.5 mL) was added and the resulting mixture was stirred at room temperature for 30 min and then refluxed (+40 °C) for 4 h after which Grubbs´ second-generation catalyst (3.9 mg, 0.0046 mmol) dissolved in anhydrous DCM (0.5 mL) was added and stirring at reflux was continued for 18.5 h. The crude product was purified by flash chromatography (eluent hexane:EtOAc 1:1 + 1% Et_3N; silica enriched with ~0.1% Ca) yielding (6*R*)-6-phenyl-5,6-dihydropyridin-2(1*H*)-one (14.4.mg , 0.083 mmol, 83%) as an off-white solid. $[\alpha]_D^{20}$ = +210 (c = 0.01, $CHCl_3$). R_f = 0.1 (hexane:EtOAc 1:1). ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 7.41-7.33 (m, 5 H, arom. H), 6.65 (ddd $J_{CH=, CH2b}$ = –2.8 Hz, $J_{CH=, CH2a}$ = –5.5 Hz, $J_{CH=, CH='}$ = 10.0 Hz, 1 H, CO-C*H*=CH), 6.03 (dddd, $J_{CH=', CH}$ = –1.1 Hz, $J_{CH=', CH2a}$ = 1.4 Hz, $J_{CH=', CH2b}$ = 2.6 Hz, $J_{CH=', CH=}$ = 10.0 Hz, 1 H, CO-CH=C*H*), 5.58 (br. s., 1 H, N*H*), 4.75 (dd, $J_{CH, CH2a}$= 5.5 Hz, $J_{CH, CH2b}$=11.8 Hz, 1 H, C*H*), 2.59 (dddd, $J_{CH2a, CH='}$ = 1.4 Hz, $J_{CH2a, CH}$ = 5.5 Hz, $J_{CH2a, CH=}$= –5.5 Hz, $J_{CH2a, CH2b}$ = –17.8 Hz, 1 H, CH_{2a}), 2.52 (dddd, $J_{CH2b, CH='}$ = 2.6 Hz, $J_{CH2b, CH=}$ = –2.8 Hz, $J_{CH2b, CH}$ = 11.8 Hz, $J_{CH2b, CH2b}$ = –17.8 Hz, 1 H, CH_{2b})ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 166.5 (CO), 141.0 (arom. C), 140.3 (CO-*C*H=CH'), 129.0 (2 arom. C), 128.4 (arom. C), 126.4 (2 arom. C), 124.5 (CO-CH=*C*H'), 56.0 (*C*H), 33.1 (CH_2) ppm. HRMS calcd for $C_{11}H_{11}NONa$ $[M+Na]^+$ 196.0733, found 196.0750.

Synthesis (7*R*)-7-phenyl-1,3,6,7-tetrahydro-2*H*-azepin-2-one [(*R*)-11)]



Procedure as above starting from [(*R*)-**7**] (16.6 mg, 0.08 mmol, *ee* > 99%). Yield (3.2 mg, 0.017 mmol, 22%). The amount of purified material was not sufficient for reliable measurement of the optical rotation. R_f = 0.2 (hexane:EtOAc 1:1), ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 7.42-7.38 (m, 2 H, arom. H), 7.37-7.33 (m, 3 H, arom. H), 5.76 (dd, $J_{NH=, CH2b'}$ = –2.3 Hz, $J_{NH=, CH}$ = 5.8 Hz, 1 H, N*H*), 5.74 (dddd, $J_{CH=, CH2a'}$ = 2.9 Hz, $J_{CH=, CH2a}$ = 3.1 Hz, $J_{CH=, CH2b'}$ = 5.1 Hz, $J_{CH=, CH='}$ = 11.6 Hz, 1 H, $COCH_2$C*H*=CH'), 5.66 (ddddd, $J_{CH=', CH2b'}$ = 1.8 Hz, $J_{CH=', CH2a'}$ = 2.4 Hz, $J_{CH=', CH2a}$ = 2.8 Hz, $J_{CH=', CH2b}$ = 8.6 Hz, $J_{CH=', CH=}$ = 11.6 Hz, 1 H, $COCH_2$CH=C*H*'), 4.95 (ddd, $J_{CH, CH2b'}$ = 2.4 Hz, $J_{CH, NH}$ = 5.8 Hz, $J_{CH, CH2a'}$ = 12.1 Hz, 1 H, C*H*), 3.66 (ddddd, $J_{CH2a, CH='}$ = 2.8 Hz, $J_{CH2a, CH=}$ = 3.1 Hz,

$J_{CH2a, CH2b'}$ = −3.6 Hz, $J_{CH2a, CH2a'}$ = −4.3 Hz, $J_{CH2a, CH2b}$ = −16.7 Hz, 1 H, CO-CH_{2a}), 2,92 (dddd, $J_{CH2b, CH2a'}$ = −1.0 Hz, $J_{CH2b, CH2b'}$ = −1.9 Hz, $J_{CH2b, CH='}$ = 8.6 Hz, $J_{CH2b, CH2a}$ = −16.7 Hz, 1 H, CO-CH_{2b}), 2.71 (dddddd, $J_{CH2a', CH2b}$ = −1.0 Hz, $J_{CH2a', CH='}$ = 2.4 Hz, $J_{CH2a', CH=}$ = 2.9 Hz, $J_{CH2a', CH2a}$ = −4.3 Hz, $J_{CH2a', CH}$ = 12.1 Hz, $J_{CH2a', CH2b'}$ = −18.2 Hz, 1 H, CH-$CH_{2a'}$), 2.48 (ddddddd, $J_{CH2b', CH='}$ = 1.8 Hz, $J_{CH2b', CH2b}$ = −1.9 Hz, $J_{CH2b', NH}$ = −2.3 Hz, $J_{CH2b', CH}$ = 2.4 Hz, $J_{CH2b', CH2a}$ = −3.6 Hz, $J_{CH2b', CH=}$ = 5.1 Hz, $J_{CH2b', CH2a'}$ = −18.2 Hz. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 174.2 (CO), 140.4 (arom. C), 129.2 (2 arom. C), 128.7 (*C*H=CH'), 128.4 (arom. C), 126.3 (2 arom. C), 120.3 (CH=*C*H'), 55.0 (*C*H), 37.1 (CH_2'), 35.4 (CH_2) ppm. HRMS calcd for $C_{12}H_{13}NO$ $[M]^+$ 187.0992, found 187.0993.

6.5 References and Notes

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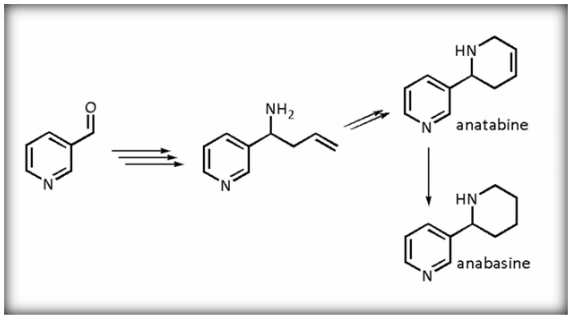
7 FROM A BUILDING BLOCK TO A NATURAL PRODUCT – A SHORT SYNTHESIS OF (±)-ANATABINE AND (±)-ANABASINE



In this chapter, a short and straightforward synthesis of the racemic tobacco alkaloids anatabine and anabasine in five and six steps, respectively, from 3-pyridinecarboxaldehyde utilizing Barbier-type Zn-mediated allylation and ring closing olefin metathesis as the key steps is described. Additionally, a complete NMR spectroscopic analysis of the final products was carried out and full assignment of the ^{1}H and ^{13}C NMR spectra of anatabine and anabasine with accurate proton–proton coupling constants was accomplished and is reported here.

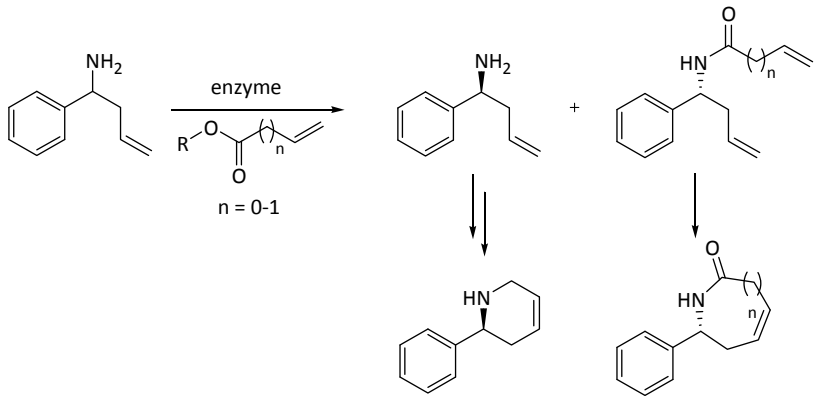
This chapter is based on the original publication:

Saloranta, T.; Leino, R. **From Building Block to Natural Products: A Short Synthesis and Complete NMR Spectroscopic Characterization of (±)-Anatabine and (±)-Anabasine**, *Tetrahedron Lett.* **2011**, *52*, 4619–4621.

7.1 Introduction

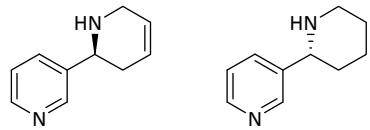
The development of methods for constructing versatile building blocks for the synthesis of more complicated target molecules is a recurring theme in synthetic organic chemistry. Of particular interest are building blocks containing functionalities that can be readily converted to a variety of other functional groups or alternatively can be utilized in carbon–carbon bond forming reactions. The carbon–carbon double bond is a functional group commonly fulfilling both of the aforementioned prerequisites. In this context, homoallylic primary amines are of particular importance being used as precursors for the synthesis of several nitrogen-containing molecules.

In the previous chapter, a simple synthetic route to homoallylic amines by use of Barbier-type allylation of *N*,*N*-dimethylsulfamoyl-protected aldimines followed by efficient deprotection by transamination was described.[1] This methodology was successfully applied to the preparation of benzylic aldimines with variable electronic properties using either unsubstituted or substituted allylating agents and indium or zinc as the mediating metals. The racemic amines were then subjected to lipase catalyzed enzymatic kinetic resolution using terminally unsaturated acyl donors. The enantiopure building blocks so obtained could be transformed further by ring-closing metathesis to provide N-heterocyclic model structures with potential biological and pharmaceutical relevance (Scheme 7.1).



Scheme 7.1. Chemoenzymatic synthesis of N-containing heterocycles.

One of the earlier prepared compounds was a benzylic analogue of the minor tobacco alkaloid (*S*)-anatabine. This inspired us to investigate the utilization of the same methodology for the synthesis of anatabine as well as its hydrogenated congener, anabasine (Figure 7.1).



(*S*)-anatabine (*R*)-anabasine

Figure 7.1 The minor tobacco alkaloids (*S*)-anatabine and (*R*)-anabasine.

In recent years, several enantioselective syntheses of the minor tobacco alkaloids have been reported.[2] In the cases of anatabine and anabasine, the majority of the stereospecific syntheses have targeted the corresponding (*S*)-enantiomers. It should be noted, however, that the naturally occurring minor tobacco alkaloids anatabine and anabasine exist as mixtures of enantiomers in tobacco leafs with the exact enantiomeric composition depending on the species of *Nicotiana* from which they are isolated. For anatabine, the relative percentage of (*R*)-enantiomer ranges from 14.1 to 17.6%, whereas anabasine is found in nature as a nearly racemic mixture (Table 7.1).[3]

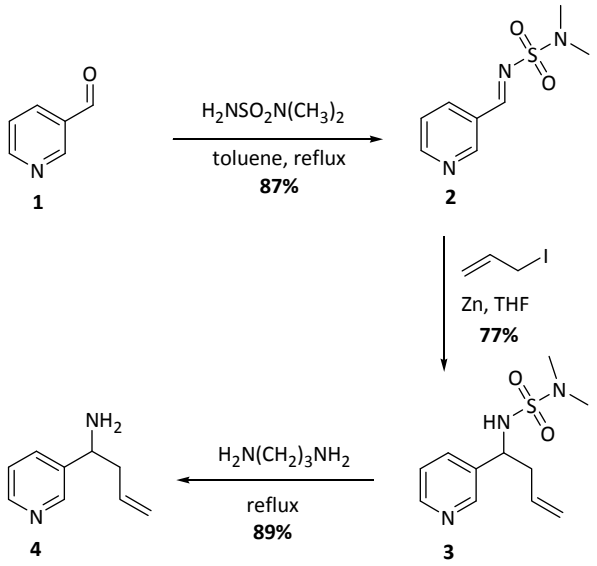
Table 7.1. Enantiomeric composition of anatabine and anabasine in tobaccco leaf.[3]

		Enantiomeric ratio [(*S*)/(*R*)]	
Sample	Type	Anatabine	Anabasine
Tobacco leaf	Burley	85.9/14.1	58.7/41.3
	Turkish	83.7/16.3	59.4/40.6
	Virginia	82.4/17.6	59.2/40.8

However, the pharmacological evaluations of these compounds are often performed with either the racemic alkaloids or with the pure (*S*)-enantiomers.[4] Thus, it is of relevance to develop new synthetic approaches to the preparation of either the pure anatabine and anabasine enantiomers for detailed evaluations of their individual biological and pharmaceutical properties, or to efficient preparations of the racemic mixtures and methods for their resolution. In the former case, a chemoenzymatic route based on kinetic resolution of a racemic precursor or intermediate at suitable stage would be optimal.

7.2 Results and Discussion

The *N*,*N*-dimethylsulfamoyl protected 3-pyridylaldimine **2** was prepared from 3-pyridinecarboxaldehyde (**1**) according to a slightly modified literature procedure utilized earlier for preparation of *N*,*N*-dimethylsulfamoyl aldimines from the corresponding aldehydes.[5] Allylation of compound **2** in anhydrous THF under Barbier-type conditions using zinc as the mediating metal afforded the homoallylic protected amine **3**. In order to increase the reactivity of the allylating agent, allyl iodide was used instead of allyl bromide. The *N*,*N*-dimethylsulfamoyl-protected amine **3** was subsequently deprotected to yield the unprotected amine **4** utilizing the efficient transamination procedure applied previously for deprotection of the benzylic analogues (Scheme 7.2).[1]



Scheme 7.2 Three-step synthesis of the pyridinyl homoallylic amine **4** from 3-pyridinecarboxaldehyde (nicotinealdehyde).

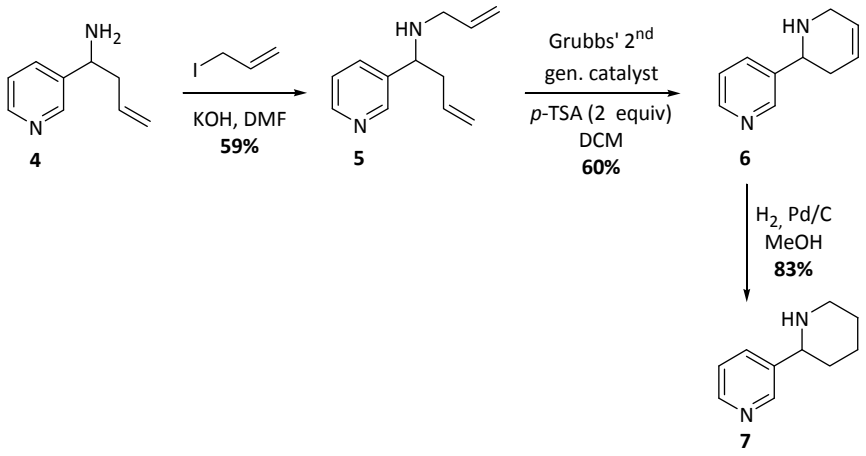
In accordance with the chemoenzymatic work described in previous chapter, the racemic homoallylic amine **4** was likewise subjected to enzymatic kinetic resolution. The lipase PS-D catalyzed resolution using isopropyl acetate as acyl donor seemed promising. Unfortunately, the attempts to purify the amide/amine mixture proved problematic.[6] However, with the key intermediate **4** available, it was possible to complete the total synthesis of racemic anatabine and anabasine.

In the previous chapter, a straightforward, two-step sequence for conversion of the enantiopure benzylic homoallylic amines to the corresponding dehydropiperidines by N-allylation/ring-closing

olefin metathesis was described. In this chapter, a similar strategy was applied for conversion of the homoallylic amine **4** to racemic anatabine. In the N-allylation step, modified reaction conditions were required using 1 equiv of the homoallylic amine, 1.5 equiv of allyl iodide and 3 equiv of KOH in anhydrous DMF with quenching of the reaction after 30 min (Scheme 7.3). Longer reaction times resulted in decomposition with the N-monoallylated product being isolated in only a 20–25% yield.

During the course of the present investigation, it was repeatedly observed that the nitrogen atom in the pyridine ring significantly changes the reactivity and solubility properties of the amines as compared to their benzylic analogues. Thus, reoptimization of the reaction and modified purification procedures for all synthetic steps were needed. In the N-allylation step, application of the optimized work-up procedure and extraction with Et_2O provided the diallylic product **5** in 59% isolated yield without chromatographic purification. By further extraction of the aqueous phase with DCM, only unreacted starting material and byproducts were recovered. The present approach with facile isolation and good yields compares favorably with the recently reported synthesis of anatabine, anabasine and the N-methylated analogs by Lebreton and coworkers, where the route based on N-monoallylation was deemed unsuccessful and the primary amine temporarily protected as the benzyl carbamate followed by NaH promoted N-allylation.[2b] This earlier approach adds a protection-deprotection sequence in the reaction path towards the tobacco alkaloids, thus prolonging the overall synthesis by two steps without adding desired functionality.

The diallylic amine obtained was then subjected to ring-closing metathesis. As reported in prior literature, free amines are detrimental to Grubbs-type ruthenium catalysts. In our previous work, the diallylic amine was converted to the corresponding salt by adding one equivalent of *p*-toluenesulfonic acid (*p*-TSA) with the subsequent ring-closure then proceeding smoothly to afford the enantiopure dehydropiperidine in 70% isolated yield. In the present work, the diallylic amine **5** contains one additional nitrogen atom in the pyridinyl ring being equally detrimental to the Ru-catalyst. Consequently, two equivalents of *p*-TSA were required for successful masking of this compound. Under these conditions, the desired product, racemic anatabine **6** was obtained in a 60% yield. Hydrogenation of **6** using Pd/C as the catalyst (5 mol-%) proceeded smoothly affording racemic anabasine **7** in 83% yield.



Scheme 7.3. Synthesis of racemic anatabine (**6**) and anabasine (**7**) from precursor **4**.

The racemic minor tobacco alkaloids anatabine and anabasine together with their intermediates were characterized by complete NMR spectroscopic analyses. Furthermore, the ^{1}H NMR spectra were analyzed by PERCH software with spin simulation/iteration techniques. By use of this software and the information gained from the 1D and 2D NMR spectroscopic measurements, a complete assignment of the ^{1}H and ^{13}C NMR spectra of anatabine and anabasine with accurate proton–proton coupling constants was accomplished. The original and simulated spectra for anatabine are illustrated in Figure 7.2 and for anabasine in Figure 7.3, respectively. From the spectral analysis it is evident that the piperidine ring in anabasine prefers the chair conformation in which the pyridine ring takes an equatorial orientation. To our knowledge, this is the first report of the fully assigned NMR spectra of these natural products.

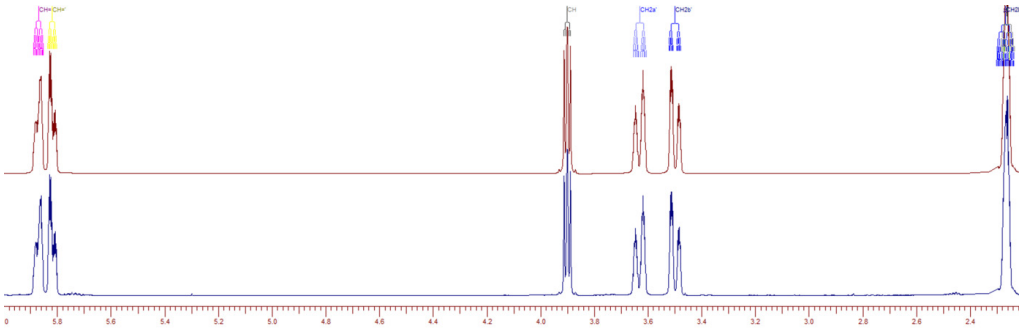


Figure 7.2. Spectral simulation of the ^{1}H NMR spectrum of anatabine (2.2-5.9 ppm range) with the PERCH NMR software: simulated spectrum (top) and observed spectrum (bottom).

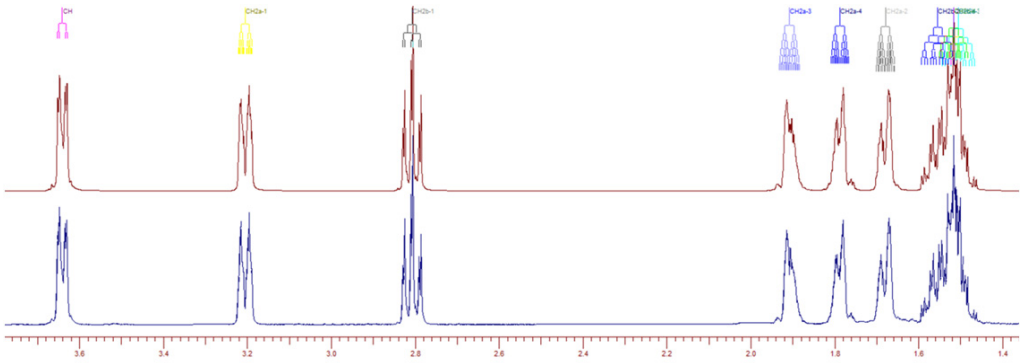


Figure 7.3. Spectral simulation of the ^{1}H NMR spectrum of anabasine (1.4-3.7 ppm range) with the PERCH NMR software: simulated spectrum (top) and observed spectrum (bottom).

7.3 Summary and Conclusions

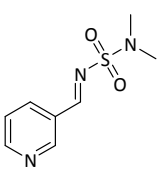
In summary, five and six step syntheses of the racemic tobacco alkaloids anatabine and anabasine, starting from 3-pyridinecarboxaldehyde with overall yields of 21% and 18%, respectively, were accomplished. Furthermore, the route is formally suitable for the synthesis of both enantiomers of these minor tobacco alkaloids provided that enantiomerically pure precursors are available. The work presented in this chapter culminates our recent efforts in the synthesis of homoallylic amines as precursors for structures with pharmaceutical and/or biological relevance. The route is thus proven to be suitable for synthesis of natural products and derivatives thereof.

7.4 Experimental Section

General remarks

The allylation and ring-closing reactions were performed under a dry argon atmosphere using anhydrous solvents. THF was distilled over Na/benzophenone and DCM was distilled over CaH_2. The anhydrous solvents were then stored under argon. DMF and MeOH were purchased as anhydrous. *N,N*-dimethylsulfamide was readily prepared from commercial dimethylsulfamoyl chloride and 30% aqueous ammonia.[7] All other reagents were purchased and used as received. NMR spectra were recorded with Bruker Avance 600 MHz NMR spectrometer: ^1H and ^{13}C NMR spectra were recorded in combination with the following 2D-techniques; DQF-COSY, HSQC, and HMBC by using pulse sequences provided by the manufacturer. Chemical shifts are expressed on the δ scale (in ppm) using TMS (tetramethylsilane) as internal standard. Coupling constants are given in Hz. Coupling patterns are given as s, singlet; d, doublet; t, triplet; etc.^1H NMR spectra were analyzed by PERCH software with spin simulation/iteration techniques.[8] HRMS were measured in ESI^+ mode with Bruker micrOTOF-Q or Fisons ZABSpecETOF spectrometers. Melting points were recorded with a Stuart Scientific apparatus. Flash chromatography was performed using Silica Gel 60 (Fluka, 0.04-0.063 mm, enriched with 0.1% Ca) or aluminum oxide (Fluka, 0.05-0.15 mm, pH 7.0±0.5). TLC was recorded on silica or alumina plates and the spots were visualized by UV-light. R_f–values are reported on silica or alumina TLC plates depending on if the flash chromatography was performed using silica or alumina, respectively.

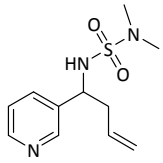
_N,N_-(Dimethylsulfamoyl)-3-pyridinylaldimine (2)



3-Pyridinecarboxaldehyde (**1**) (0.95 mL, 10 mmol) and *N*,*N*-dimethylsulfamide (1.25 g, 12.5 mmol) were dissolved in toluene (100 mL) and water was azeotropically distilled using a Dean-Stark apparatus. Additional equivalent of *N*,*N*-dimethylsulfamide (1.29 g, 10 mmol) was added in portions over the course of 22 h. The mixture was refluxed in a Dean-Stark apparatus for 45 h. After removal of the solvent under reduced pressure, the residue was dissolved in DCM and filtered. Solvents were evaporated under reduced pressure and the crude product (1.86 g, 8.7 mmol, 87%) was used as such in the next step. For analytical purposes, the product can be crystallized from isopropanol. Light yellow crystalline solid. mp 102-105 °C. ^1H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 9.08 (d, $J_{o',p}$ = 2.0 Hz, 1 H, $H_{o'}$), 8.97 (s, 1 H, C*H*N), 8.84 (dd, $J_{o,p}$ = 1.9 Hz, $J_{o,m}$ = 4.9 Hz, 1 H, H_o), 8.30 (ddd, $J_{p,o}$ = 1.9 Hz, $J_{p,o'}$ = 2.0 Hz, $J_{p,m}$ = 7.9 Hz,

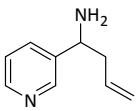
1 H, H_p), 7.48 (dd, $J_{m,o}$ = 4.9 Hz, $J_{m,p}$ = 7.9 Hz, 1 H, H_m), 2.91 (s, 6 H, N(CH_3)$_2$) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 168.0 (*C*HN), 154.8 (C_o), 152.6 ($C_{o'}$), 136.7 (C_p), 128.4 ($C_{m'}$), 124.1 (C_m), 38.3 (N(*C*H$_3$)$_2$) ppm. HRMS calcd for $C_8H_{11}N_3O_2S$ $[M]^+$ 213.0567, found 213.0579.

_N_-(1-Pyridin-3-yl-but-3-enyl)-_N_,_N_-dimethylsulfonamide (3)



Compound **2** (1.85 g, 8.7 mmol) was dissolved in anhydrous THF (90 mL). Zinc (1.15 g, 17.6 mmol, 2 equiv.) and allyl iodide (1.6 mL, 17.5 mmol, 2 equiv.) were added and the resulting mixture was stirred overnight at room temperature. The reaction was quenched by adding 1 M HCl until pH ≈ 3 and extracted with Et_2O (100 mL). The organic phase was washed with saturated $NaHCO_3$ solution (2 × 50 mL). The aqueous phase was then extracted with Et_2O (4 × 50 mL), the organic layers were combined and dried over anhydrous Na_2SO_4. After evaporation of the solvents, the crude product was purified by flash chromatography (eluent: EtOAc + 1% Et_3N; silica enriched with ca. 0.1% Ca) affording **3** as yellow solid (1.70 g, 6.7 mmol, 77%). mp 89-91 °C. R_f = 0.4 (EtOAc + 1% Et_3N). ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 8.59 (dd, $J_{o',m}$ = 0.8 Hz, $J_{o',p}$ = 2.3 Hz, 1 H, $H_{o'}$), 8.55 (dd, $J_{o,p}$ = 1.6 Hz, $J_{o,m}$ = 4.8 Hz, 1 H, H_o), 7.65 (ddd, $J_{p,o}$ = 1.6 Hz, $J_{p,o'}$ = 2.3 Hz, $J_{p,m}$ = 7.9 Hz, 1 H, H_p), 7.31 (ddd, $J_{m,o'}$ = 0.8 Hz, $J_{m,o}$ = 4.8 Hz, $J_{m,p}$ = 7.9 Hz, 1 H, H_m), 5.68 (dddd, $J_{CH=,CH2b}$ = 6.9 Hz, $J_{CH=,CH2a}$ = 7.7 Hz, $J_{CH=,CH2}$*cis* = 10.3 Hz, $J_{CH=,CH2}$*trans* = 16.9 Hz, 1 H, –C*H*=CH$_2$), 5.20 (dddd, J_{CH2}*cis*$_{,CH2a}$ = –0.8 Hz, J_{CH2}*cis*$_{,CH2b}$ = –0.8 Hz, J_{CH2}*cis*$_{,CH2}$*trans* = –1.6 Hz, J_{CH2}*cis*$_{,CH=}$ = 10.3 Hz, 1 H, –CH=CH_{2}*cis*), 5.19 (dddd, J_{CH2}*trans*$_{,CH2a}$ = –1.2 Hz, J_{CH2}*trans*$_{,CH2b}$ = –1.3 Hz, J_{CH2}*trans*$_{,CH2}$*cis* = –1.6 Hz, J_{CH2}*trans*$_{,CH=}$ = 16.9 Hz, 1 H, –CH=CH_{2}*trans*), 4.75 (d, $J_{NH,CH}$ = 5.5 Hz, 1 H, N*H*), 4.48 (ddd, $J_{CH,NH}$ = 5.5 Hz, $J_{CH,CH2b}$ = 6.3 Hz, $J_{CH,CH2a}$ = 7.9 Hz, 1 H, C*H*), 2.58 (ddddd, $J_{CH2a,CH2}$*cis* = –0.8 Hz, $J_{CH2a,CH2}$*trans* = –1.2 Hz, $J_{CH2a,CH=}$ = 7.7 Hz, $J_{CH2a,CH}$ = 7.9 Hz, $J_{CH2a,CH2b}$ = –13.8 Hz, 1 H, CH_{2a}), 2.56 (s, 6 H, N(CH_3)$_2$), 2.55 (ddddd, $J_{CH2b,CH2}$*cis* = –0.8 Hz, $J_{CH2b,\ CH2}$*trans* = –1.3 Hz, $J_{CH2b,CH}$ = 6.3 Hz, $J_{CH2b,CH=}$ = 6.9 Hz, $J_{CH2b,CH2a}$ = –13.8 Hz, 1 H, CH_{2b}) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 149.2 (C_o), 148.6 ($C_{o'}$), 137.1 ($C_{m'}$), 134.3 (C_p), 132.5 (*C*H=), 123.4 (C_m), 120.3 (CH=*C*H$_2$), 55.2 (*C*H), 41.8 (*C*H$_2$), 37.5 (N(*C*H$_3$)$_2$) ppm. HRMS calcd for $C_{11}H_{18}N_3O_2S$ $[M+H]^+$ 256.1114, found 256.1141.

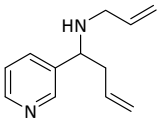
1-(Pyridin-3-yl)but-3-en-1-amine (4)



Compound **3** (1.64 g, 6.4 mmol) was refluxed in 1,3-diaminopropane (6.4 mL) for 1 h. After cooling to room temperature, the mixture was diluted with DCM (60 mL) and

washed with water (5 × 30 mL). The aqueous layers were then extracted with DCM (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to yield **4** as a yellow oil (0.85 g, 5.7 mmol, 89%). ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 8.58 ($J_{o',m}$ = 0.8 Hz, $J_{o',p}$ = 2.3 Hz, 1 H, $H_{o'}$), 8.50 (dd, $J_{o,p}$ = 1.7 Hz, $J_{o,m}$ = 4.8 Hz, 1 H, H_o), 7.70 (ddd, $J_{p,o}$ = 1.7 Hz, $J_{p,o'}$ = 2.3 Hz, $J_{p,m}$ = 7.9 Hz, 1 H, H_p), 7.27 (ddd, $J_{m,o'}$ = 0.8 Hz, $J_{m,o}$ = 4.8 Hz, $J_{m,p}$ = 7.9 Hz, 1 H, H_m), 5.74 (dddd, $J_{CH=,CH2a}$ = 6.3 Hz, $J_{CH=,CH2b}$ = 8.0 Hz, $J_{CH=,CH2cis}$ = 10.1 Hz, $J_{CH=,CH2trans}$ = 17.2 Hz, 1 H, –C*H*=CH_2), 5.13 (dddd, $J_{CH2trans,CH2b}$ = –1.2 Hz, $J_{CH2trans,CH2a}$ = –1.6 Hz, $J_{CH2trans,CH2cis}$ = –1.9 Hz, $J_{CH2trans,CH=}$ = 17.2 Hz, 1 H, –CH=CH_{2trans}), 5.12 (dddd, $J_{CH2cis,CH2b}$ = –0.9 Hz, $J_{CH2cis,CH2a}$ = –1.1 Hz, $J_{CH2cis,CH2trans}$ = –1.9 Hz, $J_{CH2cis,CH=}$ = 10.1 Hz, 1 H, –CH=CH_{2cis}), 4.06 (dd, $J_{CH,CH2a}$ = 5.3 Hz, $J_{CH,CH2b}$ = 8.1 Hz, 1 H, C*H*), 2.46 (ddddd, $J_{CH2a,CH2cis}$ = –1.1 Hz, $J_{CH2a,CH2trans}$ = –1.6 Hz, $J_{CH2a,CH}$ = 5.3 Hz, $J_{CH2a,CH=}$ = 6.3 Hz, $J_{CH2a,CH2b}$ = –13.8 Hz, 1 H, CH_{2a}), 2.38 (ddddd, $J_{CH2b,CH2cis}$ = –0.9 Hz, $J_{CH2b,CH2trans}$ = –1.2 Hz, $J_{CH2b,CH=}$ = 8.0 Hz, $J_{CH2b,CH}$ = 8.1 Hz, $J_{CH2b,CH2a}$ = –13.8 Hz, 1 H, CH_{2b}) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 148.6 (C_o), 148.6 ($C_{o'}$), 140.8 ($C_{m'}$), 134.6 (*C*H=), 133.9 (C_p), 123.4 (C_m), 118.4 (CH=*C*H_2), 53.1 (*C*H), 44.0 (*C*H_2) ppm. HRMS calcd for $C_9H_{13}N_2$ $[M+H]^+$ 149.1073, found 149.1072.

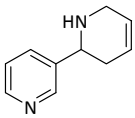
_N_-(Prop-2-enyl)-1-(pyridin-3-yl)but-3-en-1-amine (5)



Compound **4** (149 mg, 1.0 mmol) was dissolved in anhydrous DMF (10 mL). KOH (173 mg, 3.1 mmol, 3 equiv.) was added and the mixture was stirred for 15 min. Allyl iodide (137 μL, 1.5 mmol, 1.5 equiv.) was added and the mixture was stirred at room temperature for 30 min. The reaction mixture was cooled down on ice bath and the reaction was quenched by adding methanol (4 mL). The reaction mixture was diluted with Et_2O (20 mL) and washed with sat. $NaHCO_3$ solution (2 × 6 mL). The aqueous layers were extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to yield the product as orange oil (111 mg, 0.59 mmol, 59%). ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 8.53 (dd, $J_{o',m}$ = 0.8 Hz, $J_{o',p}$ = 2.3 Hz, 1 H, $H_{o'}$), 8.51 (dd, $J_{o,p}$ = 1.7 Hz, $J_{o,m}$ = 4.8 Hz, 1 H, H_o), 7.69 (ddd, $J_{p,o}$ = 1.7 Hz, $J_{p,o'}$ = 2.3 Hz, $J_{p,m}$ = 7.8 Hz, 1 H, H_p), 7.27 (ddd, $J_{m,o'}$ = 0.8 Hz, $J_{m,o}$ = 4.8 Hz, $J_{m,p}$ = 7.8 Hz, 1 H, H_m), 5.83 (dddd, $J_{CH=',CH2a'}$ = 5.2 Hz, $J_{CH=',CH2b'}$ = 6.8 Hz, $J_{CH=',CH2cis'}$ = 10.0 Hz, $J_{CH=',CH2trans'}$ = 17.4 Hz, 1 H, –C*H'*=CH_2'), 5.71 (dddd, $J_{CH=,CH2a}$ = 6.0 Hz, $J_{CH=,CH2b}$ = 8.3 Hz, $J_{CH=,CH2cis}$ = 10.3 Hz, $J_{CH=,CH2trans}$ = 17.1 Hz, 1 H, –C*H*=CH_2), 5.11 (dddd, $J_{CH2trans,CH2b}$ = –1.2 Hz, $J_{CH2trans,CH2cis}$ = –1.8, $J_{CH2trans,CH2a}$ = –1.8 Hz, Hz, $J_{CH2trans,CH=}$ = 17.1 Hz, 1 H, –CH=CH_{2trans}), 5.10 (dddd, $J_{CH2trans',CH2cis'}$ = –1.4, $J_{CH2trans',CH2b'}$ = –1.4 Hz, $J_{CH2trans',CH2a'}$ = –1.8 Hz, Hz, $J_{CH2trans',CH='}$ = 17.4 Hz, 1 H, –CH=C$H_{2trans'}$), 5.09 (dddd, $J_{CH2cis',CH2b'}$ = –1.1 Hz, $J_{CH2cis',CH2a'}$ = –1.3 Hz, $J_{CH2cis',CH2trans'}$ = –1.4 Hz, $J_{CH2cis',CH='}$ = 10.0 Hz, 1 H, –CH=C$H_{2cis'}$), 5.07 (dddd, $J_{CH2cis,CH2b}$ = –1.1 Hz, $J_{CH2cis,CH2a}$ = –1.3 Hz, $J_{CH2cis,CH2trans}$ = –1.8 Hz, $J_{CH2cis,CH=}$ = 10.3 Hz, 1 H, –CH=CH_{2cis}), 3.76 (dd, $J_{CH,CH2a}$ = 5.8 Hz, $J_{CH,CH2b}$ =

7.9 Hz, 1 H, C*H*), 3.11 (dddd, $J_{CH2a',CH2cis'}$ = −1.3 Hz, $J_{CH2a',CH2trans'}$ = −1.8 Hz, $J_{CH2a',CH=}$ = 5.2 Hz, $J_{CH2a',CH2b'}$ = −14.2 Hz, 1 H, C$H_{2a'}$), 3.02 (dddd, $J_{CH2b',CH2cis'}$ = −1.1 Hz, $J_{CH2b',CH2trans'}$ = −1.4 Hz, $J_{CH2b',CH=}$ = 6.8 Hz, $J_{CH2b',CH2a'}$ = −14.2 Hz, 1 H, C$H_{2b'}$), 2.43 (ddddd, $J_{CH2a,CH2cis}$ = −1.3 Hz, $J_{CH2a,CH2trans}$ = −1.8 Hz, $J_{CH2a,CH}$ = 5.8 Hz, $J_{CH2a,CH=}$ = 6.0 Hz, $J_{CH2a,CH2b}$ = −13.9 Hz, 1 H, CH_{2a}), 2.41 (ddddd, $J_{CH2b,CH2cis}$ = −1.1 Hz, $J_{CH2b,CH2trans}$ = −1.2 Hz, $J_{CH2b,CH}$ = 7.9 Hz, $J_{CH2b,CH=}$ = 8.3 Hz, $J_{CH2b,CH2a}$ = −13.9 Hz, 1 H, CH_{2b}) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 149.4 ($C_{o'}$), 148.7 (C_o), 139.0 ($C_{m'}$), 136.4 (*C*'H=), 134.8 (C_p), 134.5 (*C*H=), 123.5 (C_m), 118.4 (-CH=CH_2), 116.1 (-C'H=*C*'H_2), 59.2 (*C*H), 50.0 (*C*'H_2), 42.7 (CH_2) ppm. HRMS calcd for $C_{12}H_{17}N_2$ $[M+H]^+$ 189.1386, found 189.1391.

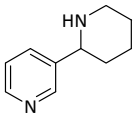
1,2,3,6-Tetrahydro-2,3'-bipyridine, anatabine (6)



Compound **5** (58.0 mg, 0.31 mmol) was dissolved in anhydrous DCM (3 mL). *p*-Toluenesulfonic acid monohydrate (118 mg, 0.62 mmol) was added and the mixture was stirred for 10 min. Grubbs´ second-generation catalyst (NHC)(PCy_3)Cl_2Ru=CHR (25.5 mg, 0.030 mmol, 10 mol-%) was added and the resulting mixture was stirred at room temperature for 18 h. The solvent was evaporated and the residue dissolved in EtOAc (30 mL) and 1 M HCl (10 mL) and the phases were separated. The organic layer was extracted additionally with 1 M HCl (3 × 10 mL). The combined aqueous layers were alkalized (pH = 14) by adding $NaOH_{(s)}$. The basic solution was extracted with EtOAc (4 × 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated to yield the crude product that was first stirred with activated carbon and then purified by flash chromatography (eluent: EtOAc:MeOH 95:5 + 1% Et_3N, neutral alumina) yielding anatabine (29.8 mg, 0.19 mmol, 60%) as yellow oil. R_f = 0.5 (EtOAc:MeOH 95:5 + 1% Et_3N). ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 8.62 (dd, $J_{o',m}$ = 0.8 Hz, $J_{o',p}$ = 2.3 Hz, 1 H, $H_{o'}$), 8.52 (dd, $J_{o,p}$ = 1.7 Hz, $J_{o,m}$ = 4.8 Hz, 1 H, H_o), 7.74 (ddd, $J_{p,o}$ = 1.7 Hz, $J_{p,o'}$ = 2.3 Hz, $J_{p,m}$ = 7.9 Hz, 1 H, H_p), 7.27 (ddd, $J_{m,o'}$ = 0.8 Hz, $J_{m,o}$ = 4.8 Hz, $J_{m,p}$ = 7.9 Hz, 1 H, H_m), 5.87 (ddddd, $J_{CH=,CH2b'}$ = −1.8 Hz, $J_{CH=,CH2b}$ = 1.9 Hz, $J_{CH=,CH2a'}$ = −2.4 Hz, $J_{CH=,CH2a}$ = 5.6 Hz, $J_{CH=,CH='}$ = 10.1 Hz, 1 H, C*H*=CH'), 5.82 (ddddd, $J_{CH=',CH2a}$ = −1.4 Hz, $J_{CH=',CH2a'}$ = 2.0 Hz, $J_{CH=',CH2b}$ = −2.7 Hz, $J_{CH=',CH2b'}$ = 4.4 Hz, $J_{CH=,CH='}$ = 10.1 Hz, 1 H, CH=C*H*'), 3.90 (dd, $J_{CH,CH2a}$ = 3.8 Hz, $J_{CH,CH2b}$ = 10.4 Hz, 1 H, C*H*), 3.63 (ddddd, $J_{CH2a',CH='}$ = 2.0 Hz, $J_{CH2a',CH=}$ = −2.4 Hz, $J_{CH2a',CH2a}$ = −3.2 Hz, $J_{CH2a',CH2b}$ = −4.3 Hz, $J_{CH2a',CH2b'}$ = −17.0 Hz, 1 H, NH-CH_{2a}'-CH=), 3.50 (ddddd, $J_{CH2b',CH2a}$ = −1.4 Hz, $J_{CH2b',CH=}$ = −1.8 Hz, $J_{CH2b',CH2b}$ = −2.5 Hz, $J_{CH2b',CH='}$ = 4.4 Hz, $J_{CH2b',CH2a'}$ = −17.0 Hz, 1 H, NH-CH_{2b}'-CH=), 2.27 (dddddd, $J_{CH2b,CH=}$ = 1.9 Hz, $J_{CH2b,CH2b'}$ = −2.5 Hz, $J_{CH2b,CH='}$ = −2.7 Hz, $J_{CH2b,CH2a'}$ = −4.3 Hz, $J_{CH2b,CH}$ = 10.4 Hz, $J_{CH2b,CH2a}$ = −17.2 Hz, 1 H, CH-CH_{2b}-CH=), 2.26 (dddddd, $J_{CH2a,CH='}$ = −1.4 Hz, $J_{CH2a,CH2b'}$ = −1.4 Hz, $J_{CH2a,CH2a'}$ = −3.2 Hz, $J_{CH2a,CH}$ = 3.8 Hz, $J_{CH2a,CH=}$ = 5.6 Hz, $J_{CH2a,CH2b}$ = −17.2 Hz, 1 H, CH-CH_{2a}-CH=) ppm. ^{13}C

NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 148.8 (C_o), 148.7 ($C_{o'}$), 139.8 ($C_{m'}$), 134.1 (C_p), 126.2 (*C*'H=), 125.1 (*C*H=), 123.6 (C_m), 55.3 (*C*H), 46.0 (*C*'H_2), 33.9 (*C*H_2) ppm. HRMS calcd for $C_{10}H_{13}N_2$ $[M+H]^+$ 161.1073, found 161.1079.

1,2,3,4,5,6-Hexahydro-2,3'-bipyridine, anabasine (7)



A solution of compound **6** (29.3 mg, 0.18 mmol) in anhydrous methanol (1.8 mL) containing Pd/C (10% Pd) (9.7 mg, 5 mol-%) was hydrogenated (p_{H2} = 1 atm) at room temperature for 3 h. The mixture was filtered through a pad of celite and the filtrate was concentrated to yield anabasine (24.3 mg, 0.15 mmol, 83%) as light yellow oil. ^{1}H NMR (600.13 MHz, $CDCl_3$, 25 °C): δ = 8.59 (dd, $J_{o',m}$ = 0.8 Hz, $J_{o',p}$ = 2.3 Hz, 1 H, $H_{o'}$), 8.49 (dd, $J_{o,p}$ = 1.7 Hz, $J_{o,m}$ = 4.8 Hz, 1 H, H_o), 7.72 (ddd, $J_{p,o}$ = 1.7 Hz, $J_{p,o'}$ = 2.3 Hz, $J_{p,m}$ = 7.9 Hz, 1 H, H_p), 7.25 (ddd, $J_{m,o'}$ = 0.8 Hz, $J_{m,o}$ = 4.8 Hz, $J_{m,p}$ = 7.9 Hz, 1 H, H_m), 3.64 (dd, $J_{CH,CH2a-4}$ = 2.7 Hz, $J_{CH,CH2b-4}$ = 11.1 Hz, 1 H, CH), 3.21 (dddd, $J_{CH2a-1,CH2a-3}$ = 1.5 Hz, $J_{CH2a-1,CH2a-2}$ = 2.6 Hz, $J_{CH2a-1,CH2b-2}$ = 4.1 Hz, $J_{CH2a-1,CH2b-1}$ = −11.6 Hz, 1 H, CH_{2a}-1), 2.81 (ddd, $J_{CH2b-1,CH2a-2}$ = 2.7 Hz, $J_{CH2b-1,CH2a-1}$ = −11.6 Hz, $J_{CH2b-1,CH2b-2}$ = 12.2 Hz, 1 H, CH_{2b}-1), 1.91 (dddddd, $J_{CH2a-3,CH2a-1}$ = −1.5 Hz, $J_{CH2a-3,CH2a-2}$ = 2.6 Hz, $J_{CH2a-3,CH2a-4}$ = 3.0 Hz, $J_{CH2a-3,CH2b-4}$ = 3.7 Hz, $J_{CH2a-3,CH2b-2}$ = 4.1 Hz, $J_{CH2a-3,CH2b-3}$ = −13.5 Hz, 1 H, CH_{2a}-3), 1.79 (ddddd, $J_{CH2a-4,CH2a-2}$ = −1.6 Hz, $J_{CH2a-4,CH}$ = 2.7 Hz, $J_{CH2a-4,CH2a-3}$ = 3.0 Hz, $J_{CH2a-4,CH2b-3}$ = 4.0 Hz, $J_{CH2a-4,CH2b-4}$ = −13.2 Hz, 1 H, CH_{2a}-4), 1.68 (dddddd, $J_{CH2a-2,CH2a-4}$ = −1.6 Hz, $J_{CH2a-2,CH2a-1}$ = 2.6 Hz, $J_{CH2a-2,CH2a-3}$ = 2.6 Hz, $J_{CH2a-2,CH2b-1}$ = 2.7 Hz, $J_{CH2a-2,CH2b-3}$ = 3.9 Hz, $J_{CH2a-2,CH2b-2}$ = −13.2 Hz, 1 H, CH_{2a}-2), 1.55 (ddddd, $J_{CH2b-2,CH2a-1}$ = 4.1 Hz, $J_{CH2b-2,CH2a-3}$ = 4.1 Hz, $J_{CH2b-2,CH2b-1}$ = 12.2 Hz, $J_{CH2b-2,CH2b-3}$ = 12.8 Hz, $J_{CH2b-2,CH2a-2}$ = −13.2 Hz, 1 H, CH_{2b}-2), 1.52 (dddd, $J_{CH2b-4,\ CH2a-3}$ = 3.7 Hz $J_{CH2b-4,CH}$ = 11.1 Hz, $J_{CH2b-4,CH2b-3}$ = 12.9 Hz, $J_{CH2b-4,CH2a-4}$ = −13.2 Hz, 1 H, CH_{2b}-4), 1.51 (ddddd, $J_{CH2b-3,CH2a-2}$ = 3.9 Hz, $J_{CH2b-3,CH2a-4}$ = 4.0 Hz, $J_{CH2b-3,CH2b-2}$ = 12.8 Hz, $J_{CH2b-3,CH2b-4}$ = 12.9 Hz, $J_{CH2b-3,CH2a-3}$ = −13.5 Hz, 1 H, CH_{2b}-3) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 148.7 ($C_{o'}$), 148.6 (C_o), 140.6 ($C_{m'}$), 134.2 (C_p), 123.5 (C_m), 59.8 (*C*H), 47.6 (*C*H_2-1), 34.8 (*C*H_2-4), 25.7 (*C*H_2-2), 25.2 (*C*H_2-3) ppm. HRMS calcd for $C_{10}H_{15}N_2$ $[M+H]^+$ 163.1230, found 163.1238.

7.5 References and Notes

[1] (a) Källström, S.; Saloranta, T.; Minnaard, A. J.; Leino, R. *Tetrahedron Lett.* **2007**, *48*, 6958–6961. (b) Hietanen, A.; Saloranta, T.; Rosenberg, S.; Laitinen, E.; Leino, R.; Kanerva, L. T. *Eur. J. Org. Chem.* **2010**, 909–919.

[2] See for example: (a) Balasubramanian, T.; Hassner, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2201–2205. (b) Felpin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305–6312. (c) Amat, M.; Cantó, M.; Llor, N.; Bosch, J. *Chem. Comm.* **2002**, 526–527. (d) Ayers, J. T.; Xu, R.; Dwoskin, L. P.; Crooks, P. A. *The AAPS Journal* **2005**, *7*, 752–758. (e) Jurčík, V.; Arai, K.; Salter, M. M.; Yamashita, Y.; Kobayashi, S. *Adv. Synth. Catal.* **2008**, *350*, 647–651. (f) Spangenberg, T.; Breit, B.; Mann, A. *Org. Lett.* **2009**, *11*, 261–264. (g) Giera, D. S.; Sickert, M.; Schneider, S. *Synthesis* **2009**, *22*, 3797–3802. (h) Beng, T. K.; Gawley, R. E. *Org. Lett.* **2011**, *13*, 394–397.

[3] Armstrong, D. W.; Wang, X.; Lee, J.-T.; Liu, Y.-S. *Chirality*, **1999**, *11*, 82-84.

[4] See for example: (a) Denton, T.T.; Zhang, X.; Cashman, J. R. *Biochem. Pharmacol.* **2004**, *67*, 751–756. (b) Clemens, K. J.; Caillé, S.; Stinus, L.; Cador, M. *Int. J. Neuropsychoph.* **2009**, *12*, 1355–1366.

[5] Huisman, M.; ten Have, R.; van Leusen, A. M. *Synth. Commun.* **1997**, *27*, 945–952.

[6] Collaboration wiht Ari Hietanen and Liisa T. Kanerva (Laboratory of Synthethic Drug Chemistry, University of Turku), *unpublished results.*

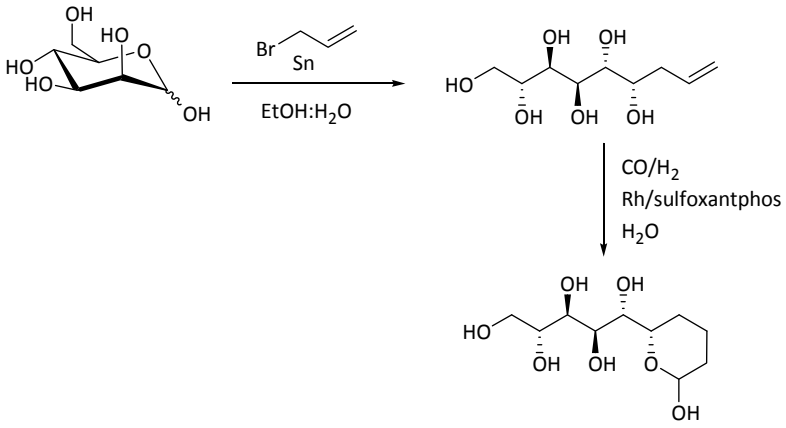
[7] Petersen, S. *Chem. Ber.* **1950**, *83*, 551–558.

[8] Laatikainen, R.; Niemitz, M.; Weber, U.; Sundelin, J.; Hassinen, T.; Vepsäläinen, *J. Magn. Res. Ser. A*, **1996**, *120*, 1–10.

8 SUMMARY AND CONCLUSIONS

In this thesis, new routes towards synthesis of fine chemicals of pharmaceutical relevance were explored by combining virtually simple transformations into novel reaction sequences. All the reaction sequences were initiated by metal-mediated Barbier-type allylation of selected aldehydes or aldimines. The obtained products containing a carbon–carbon double bond, accompanied by hydroxyl or amino group, were further derivatized by utilizing some well-known catalytic tools from the organic chemistry toolbox.

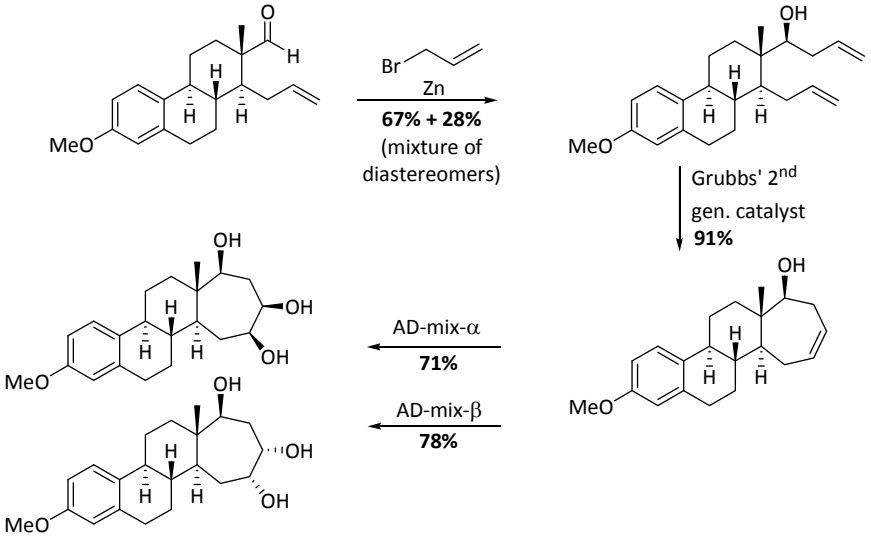
In Chapter 3, unprotected D-mannose and L-rhamnose were successfully allylated in aqueous media using tin as the mediating metal. The obtained homoallylic polyols were then subjected for rhodium-catalyzed hydroformylation yielding highly functionalized lactols as a result of tandem hydroformylation-cyclization reaction (Scheme 8.1). The hydroformylation was likewise performed in aqueous media thus significantly reducing the need for resource-consuming protection/deprotection procedures.



Scheme 8.1 Metal-mediated allylation – hydroformylation sequence for unprotected monosaccharides yielding functionalized lactols.

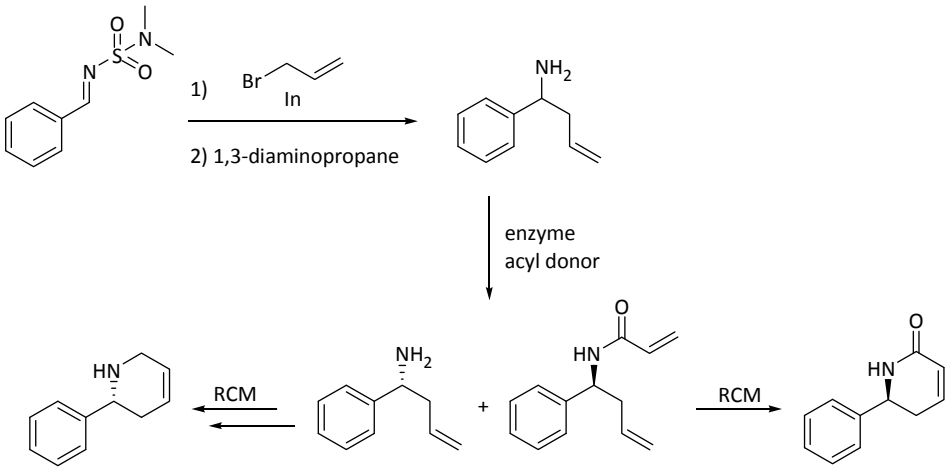
Furthermore, inspired by the spontaneous aggregation behavior of the mannose derived polyol, the conformations of mannose, glucose and galactose derived homoallylic polyols were studied by NMR spectroscopic techniques (Chapter 4). The mannose derived structure, in contrast to corresponding glucose and galactose derivatives, seemed to adapt a highly ordered linear conformation supporting the originally suggested amphiphilic nature of this molecule.

In Chapter 5, a sequence consisting of metal-mediated allylation, ring-closing olefin metathesis and asymmetric dihydroxylation was applied for an estradiol based steroid derivative (Scheme 8.2). The obtained amphiphilic steroid structures were evaluated in biological assays. While general correlations between the number or configuration of OH-groups and the pharmacological effect were not found, the synthesis and investigation of further analogs is strongly encouraged based on the significant pharmacological differences of the presented analogs.



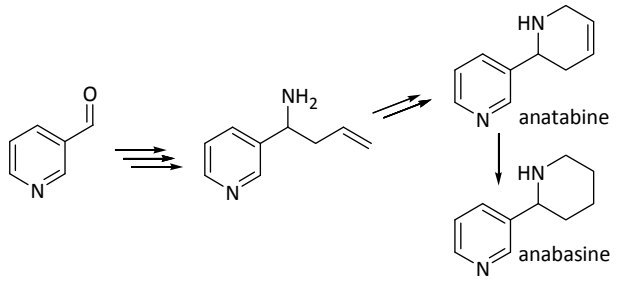
Scheme 8.2. Metal-mediated allylation – ring-closing olefin metathesis – asymmetric dihydroxylation sequence for an estradiol derivative yielding novel amphiphilic steroidal compounds.

Finally, a series of homoallylic amines were synthesized by Barbier-type metal-mediated allylation of *N*,*N*-dimethylsulfamoyl protected aldimines followed by facile deprotection by transamination (Chapter 6). Enzymatic kinetic resolution utilizing an acyl donor with a terminal double bond was successfully applied for the racemic amines giving access to highly valuable enantiopure amines and amides that were further derivatized to enantiopure nitrogen-containing heterocycles using ring-closing olefin metathesis as a key step (Scheme 8.3).



Scheme 8.3. Synthesis of enantiopure N-heterocycles and the corresponding precursors using Barbier-type metal-mediated allylation of *N*,*N*-dimethylsulfamoyl protected aldimines, enzymatic kinetic resolution and ring-closing olefin metathesis as key steps.

In Chapter 7, the general synthesis route described in Chapter 6 was successfully applied for the synthesis of naturally occurring nicotine alkaloids (±)-anatabine and (±)-anabasine as highlighted in Scheme 8.4.



Scheme 8.4 A straightforward synthesis of (±)-anatabine and (±)-anabasine.

In summary, this thesis describes the exploitation of Barbier-type metal-mediated allylation for a versatile substrate scope including unprotected monosaccharides, a steroid derivative and activated aldimines. The obtained homoallylic alcohols and amines were successfully converted into highly functionalized products by utilizing selected catalytic tools from the organic chemistry toolbox. All the products synthesized in this thesis can be regarded as fine chemicals with high potential in pharmaceutical applications. More importantly, a number of catalytic tools were successfully challenged in the reaction sequences presented in this thesis, hence strengthening the attractiveness of the catalysis compartment in the organic chemistry toolbox. The synthetic chemistry community is

thus highly encouraged to seek for further challenges for all the available catalytic tools in novel synthesis routes, and hence continue the journey towards the most ambitious goal in this field, i.e., the ideal synthesis.

9 POSTLUDE

Synthetic organic chemistry, as a field of science, has traditionally aimed in the synthesis of products and materials finding applications that have enabled and remarkably enhanced the current standard of living at least in the developed countries. However, the current generations and the generations to come will not only benefit from this development but they also need to face the problems encountered with synthetic chemistry production and products. It appears that all the synthetic transformations that are thermodynamically favored will also be possible to execute by a synthetic organic chemist as long as the outer resources (time and money) are not be the limiting factors. This should not, however, be the ultimate goal for synthetic organic chemistry. Instead, in the future research, the focus should be shifted from the destination (product) to the journey towards the destination (methods). In other words, the question should not only be *what* is done but more importantly *how* it is performed. In particular, the main emphasis should be laid on the sustainability of the synthesis routes. In the long run, these new environmentally benign synthesis routes will certainly benefit even other goals of successful industry such as cost efficiency and profitability. Furthermore, at least equally important is to emphasize the importance of the research devoted to the fate of the synthesized products. The unnatural (modified) chemicals will certainly have an impact on local ecosystems that, in turn, will always contribute to the global environmental snowball effect. In conclusion, the 21st century synthetic chemistry generation should strongly focus on development of sustainable synthetic routes and products, hence giving a reason for future chemists to still agree that "*the synthetic organic chemistry has resulted in a number of achievements that have strongly contributed to the well-being of modern societies".*

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