Towards the Asymmetric Synthesis of Chiral Precursors of Novartis Drug and Drug Candidates

via

Organometallic Henry Reactions and Organocatalytic Michael Additions

Thèse présentée à la Faculté des Sciences

Institut de Chimie

Université de Neuchâtel

Pour l'obtention du grade de docteur ès Sciences

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Soutenue le 12 décembre 2011

Université de Neuchâtel

2011

Université de Neuchâtel

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IMPRIMATUR POUR LA THESE

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This pH.D. was not a lonely and isolated experience, but is the result of a teamwork. Thus I want to here to thank all of the persons who collaborate to this project.

First of all, I would like to express my deep and sincere gratitude to my supervisor Prof. Gottfried Sedelmeier, who accepted me as his pH.D. student. He offered me so much advice with his great enthusiasm for science, patiently supervising me and driving me in the right direction. Many thank for their kindness.

I am also very grateful to Prof. Reinhard Neier for accepting to supervise this doctoral work and for the time he spent to read and correct this thesis. It was always nice to meet him in Neuchatel.

I would like to thank the members of the jury for the time they spent to red and correct this work.

I had the great opportunity to undertake my pH.D. within Novartis Pharma, Basel. Thus, I would like to thank Dr. Heiko Potgeter and Dr. Stephan Abel for accepting me within their department. Conducting a pHD within the industry is really a very nice experience. I am also very grateful to Novartis Pharma for the financial support.

This thesis would not have been possible without the help and support of the CHAD-China and Basel (Brigitte Berod, Alain Litzler, Markus Blatter, Dominique Grimler and Urs Scholer>), who purchased me some starting materials and catalysts. Mr. Grimler, I want to thank you for your help on the technical level and personal level, having not only shared me your invaluable lab experience. Without you, this pH.D. would have been much more difficult.

I am also very grateful to all the person of the analytical team Novartis Basel for the characterization of the compounds, I synthesized. I want to thank especially Dr. Trixie Wagner and his colleague Philippe Piechont for the X-Ray analysis. Dr. Trixie Wagner, many thanks for your help and support by the interpretation of my X-Ray structures.

Many thanks also to the “Side product isolation” teams of Dr. Eric Francotte and Dr. Ernst Küsters for the chiral separation of two key intermediates of Aliskiren.

Many thanks also to the “hydrogenation team” who conducted for me hydrogenation experimentation in the course of the Aliskiren project. I also want to thank Andreas Moser and Daniel Naehring for having taught me and allowed me to use their hydrogenation system.

I would like to thank Dr. Gerhard Penn, Dr. Thierrry Schalmach, Dr. Thomas Ruch for their advice and the interesting discussions we had about Aliskiren and KAE609. I also express my sincere gratitude to Dr Donnatienne Denni-Dischert , who gave me the possibility to join Novartis for six years within the team of Dr Thomas Ruch and to come back for four years. Without her help, this thesis would have

not be possible. I also want to thank Dr Thomas Ruch for accepting me as master student and for my first nice experience in Novartis.

I want to say also to the colleagues of WKL684 and WSJ153, that I was very fortunate to work with tem. It really was a nice experience. Many thanks to Michele Gasser, Angelique Schneider and Markus Blatter, who accepted me in their laboratory/team and for their technical support. Many thanks for teaching me about the separation of side-products.

Whitin Novartis CHAD-Basel, I especially want to thank the “dream team” of the CDU-CH3: Michele Gasser, Stefanie Knobloch, Angelique Schneider, Dominique Grimler, Markus Blatter and at last but not at least Gilles Gerber. They made from my stay in Basel an unforgettable time. Many thanks for their comprehension, patience, and the very funny moment we had in the lab and outside. Many thanks also for their help during the preparation of this manuscript. My since gratitude goes also to Anita Ehrsam, Bernard Fest, Markus Spaeti and Mathieu Wissenmeyer for their friendship that started six years ago and I hoped, will continue in the future. For their kindness, many thanks to Sylvia Baumann, Naval Ravi and Rene Marquart.

At last but not at least, a special thank to my family; without them I could not do this pH.D. I sincerely thank my mother for her unequivocal support, her patience, comprehension and encouragements. Many thanks to my father who gave me the virus of organic chemistry. I hoped, he could not read this thesis. Many thank also to my grandfather and grandmother for being such a model. A special thank also to Markus who supported me every days, particularly when I was on peaks of stress.

A ma mère, pour mon père,

Maman, cette these n'aurait pu se faire sans toi.

Papa, cette thèse a été faite pour toi.

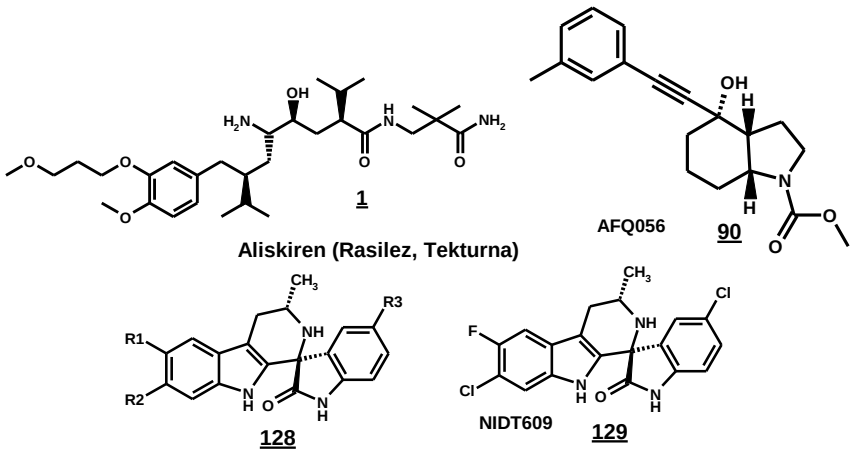
« Le chimiste, par le jeu de l'analyse et du raisonnement… »

A. Wurtz

Résumé

L'industrie pharmaceutique doit répondre à une demande croissante de mise sur le marché de substances enantiomériquement pures, rendant nécessaire le développement de voies de synthèse asymétrique alternatives, efficaces pour pouvoir produire en masse des médicaments ou des candidats-médicaments.

C'est dans ce contexte que se situe ce travail de thèse, qui concerne trois types de substances médicamenteuses actives. Afin d'introduire la stéréochimie requise par les molécules cibles, nous avons basé notre étude sur le développement de procédures faisant intervenir comme réactions clefs : des additions Michael par voie organocatalytique et des réactions Henry catalysée par des complexes de cuivre.



Au terme de ce travail, nous sommes en mesure de proposer de nouvelles stratégies pour la synthèse de l'Aliskiren, inhibiteur de la rénine. Parmi toutes les voies de synthèse que nous avons testées pour préparer des précurseurs de l'Aliskiren, l'une a été appliquée avec succès, après optimisation, pour une production au KiloLab. Cette nouvelle approche basée sur la préparation d'un dérivé-clef, de type nitré, enantiomériquement pur, a fait l'objet d'un brevet en 2011. Nous avons également défini trois autres voies de synthèse potentiellement utilisables, après optimisation, pour préparer l'Aliskiren. En outre, nous avons pu mettre en évidence la possibilité d'une séquence de type domino en « one-pot », impliquant l'enchaînement suivant de réactions: Knoevenagel/Michael/Henry/acétylation/ isomérisation.

Notre étude a également porté sur la préparation d'un nouveau candidat-médicament à activité anti-Parkinsonienne (AFQO56). Nous avons évalué la faisabilité d'une addition, de type aza-Michael par voie organocatalytique. Nous avons pu, dans le meilleur des cas, isoler les précurseurs de l'AFQ056 qu'avec une enantiosélectivité modérée.

En outre, un certain nombre de travaux que nous avons menés ont eu pour but de développer une voie asymétrique d accès au candidat-médicament Novartis KAE 609 à potentialité anti-malaria. Bien que nous n'ayons pas réussi à isoler les précurseurs chiraux souhaités du KAE609, nous proposons, une voie d'accès générale et rapide à ses précurseurs du type indolylnitroalcènes. Un procédé de synthèse en une seule étape d'une série de précurseurs d'analogues du KAE 609, potentiellement bioactifs pourrait ainsi être appliqué.

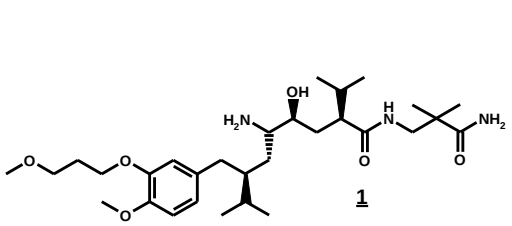
Mots cles

Addition de Michael par voie catalytique - Réactions de Henry catalysée par des complexes de cuivre – Enamine – Ion iminium - Synthèse de molécules bio-actives -

Summary

The increasing demand for the marketing of enantiomerically pure substances has forced the pharmaceutical companies to develop efficient enantioselective procedures for the large scale synthesis of their drug candidates or commercial drugs.

In this work, we focused our attention on the preparation of three Novartis pharmaceutically active substances. We planed to introduce the desired stereochemistry into the targeted molecules *via* asymmetric copper-ligand based and chiral amine promoted organocatalytic procedures and focused our attention on the two well known C-C bond-forming reactions that are the Henry reactions and the Michael additions.



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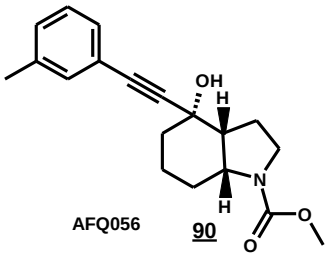
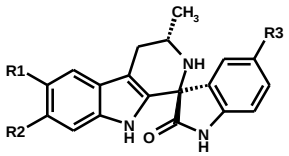
Aliskiren (Rasilez, Tekturna)



AFQ056 **90**



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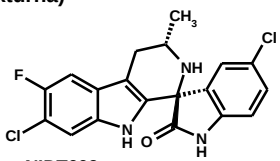


NIDT609 **129**

We were able to propose novel alternative routes to the renin inhibitor Aliskiren (Rasilez). We focused our attention on the asymmetric preparation of β-and δ-hydroxyl nitro compounds, *via* different successful catalytic asymmetric strategies, involving as key steps, enamine and iminium promoted Michael additions and copper catalyzed *syn*-selective asymmetric Henry reactions. Among the synthetic routes we reported for the preparation of Aliskiren precursors, the first one was successfully applied after optimization to a Kilo-Lab campaign. A novel approach based on the preparation of a novel key nitro derivative, has been patented in 2011. After optimizations, the three last investigated routes should/could be applied to the potential preparation of Aliskiren. During our investigations on the chemistry of the nitro group, we also prepared stable tetrahydropyranol derivatives, from in-situ generated nitroalkene derivatives and different aldehydes, by a one-pot-domino sequence involving the asymmetric Knoevenagel/Michael/Henry/acetalization/ isomerisation reactions.

We also studied the preparation of a novel anti-Parkinson drug candidate (AFQ056) and examined the organocatalyzed aza-Michael addition of a selection of N-nucleophiles to cyclohexenone. In the best case, we are able to isolate two desired aza-Michael products with moderate enantiomeric ratios and poor isolated yields. We also described a successful approach to the 1,5,6,7-tetrahydroindol-4-one building block of AFQ056, involving an intramolecular proline catalyzed alkylation step. Our chemistry can be used in a continuous manufacturing process.

Few investigations have also been performed to evaluate the viability of an asymmetric preparation of the Novartis promising anti-malaria drug candidate KAE609 from Novartis. Although we failed to isolate the desired chiral indolylnitroalkane precursors of KAE609, we prepare the indolylnitroalkene

analogues with high yields**.** We proposed thus a general one-step procedure to synthesize a range of precursors for potential bioactive analogues of KAE609.

Keywords

Asymmetric drug synthesis-Organocatalyzed Michael addition - Enamine catalysis - Iminium catalysis - Copper catalyzed *syn*-asymmetric Henry reaction - One-pot-domino multi component sequence

Abbreviations

ACE	Angiotensin Converting Enzyme
Alox	Aluminium oxide
Ang I	Angiotensin I
Ang II	Angiotensin II
API	Active Pharmaceutical Ingredient
AT_1	Angiotensin II type I receptor
Arom.	Aromatic
BINOL	1,1'-Bi-2-naphthol
Boc_2O	Di-*tert*-butyl dicarbonate
BOX	Bisoxazoline
Bz	Benzyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DHF	Dihydrofuran
dia.	Diastereoisomer
DIBAH	Diisobutylaluminium hydride
DMA	*N,N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DPEN	Diphenyl ethylene diamine
d.r.	Diastereoisomeric ratio
EtOH	Ethanol
e.r.	Enantiomeric ratio
G.C.	Gas Chromatography
Hex	Hexan
HPLC	High performance liquid chromatography

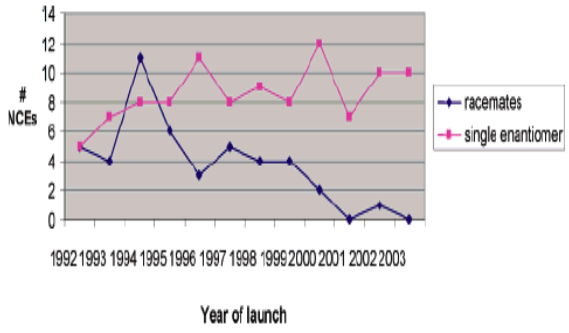
HRMS	High resolution mass spectroscopy
IC_{50}	Half maximal (50%) inhibitory concentration (IC)
iPr	*iso*Propyl
iPrOH	*iso*Propanol
IR	Infra red
M	mol/L
MeOH	Methanol
min.	Minutes
MIP	(Methoxydimethyl)methyl
monosubs.	Monosubstituted
mmol	millimoles
MOP	2-Methoxy-2-propyl
MS	Mass spectroscopy
NETE	α-ester nitroethylene
NMP	1-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
P	Pic
P. *falciparum, vivax, ovale, malariae*	*Plasmodium falciparum, vivax, ovale, malariae*
RAA	Renin-Angiotensin-Aldosterone
Rf	Retention factor
RT	Room temperature
SALAN	Salicylideneanilinato
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium iodide
TBS, TBDMS	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
THF	Tetrahydrofuran

THP	Tetrahydropyran
TFA	Trifluoroacetic acid
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
TPC	Phase transfer catalysis
t_R	Retention time
Z, CBz	Carboxybenzyl
δ	Chemical shift

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

Recent trends in the pharmaceutical industry demonstrate that the number of APIs (Active Pharmaceutical Ingredients) launched on the market or presents in the global pipeline, as single enantiomers has increased (Figure 1, by Farina[1] in 2006). Until 1992, (but really until 2001) racemic mixtures are indeed no longer registered[1] by the drug authorities, who require a level of undesired isomer(s) no higher than fractions of percent.



Form of active ingredient among the top 10 selling prescription drugs, US, 2005

Rank*	Product	Active Ingredient	Form of Ingredient
1	Lipitor	atorvastatin	single enantiomer
2	Zocor	simvastatin	single enantiomer
3	Nexium	esomeprazole	single enantiomer
4	Prevacid	lansoprazole	racemate
5	Advair Diskus	fluticasone salmeterol	single enantiomer racemate
6	Plavix	clopidogrel	single enantiomer
7	Zoloft	sertraline	single enantiomer
8	Epogen	epoetin alfa	biologic
9	Procrit	epoetin alfa	biologic
10	Aranesp	darbepoetin alfa	biologic

*Ranking based on "Top 10 Prescription Products by US Sales" from IMS Health, IMS National Sales Perspectives, Jan. 2006.

Figure 1[1,2]: Single enantiomers *versus* racemates

Moreover, in the recent years the interest in the specific pharmacological and toxicological activities of enantiomers of drugs or drug candidates (establishment of the importance of three dimensional spatial relationships between a drug compound and its action site in a macromolecular target[3]) grew up and emphasized this new tendency. It resulted in the so called "chiral switch", and so, as reported in Figure 2[4], many racemic medications have been remarketed as single enantiomers (chiral switch). The difference of biological properties between a distomer and its corresponding eutomer has been then evaluated and proved.

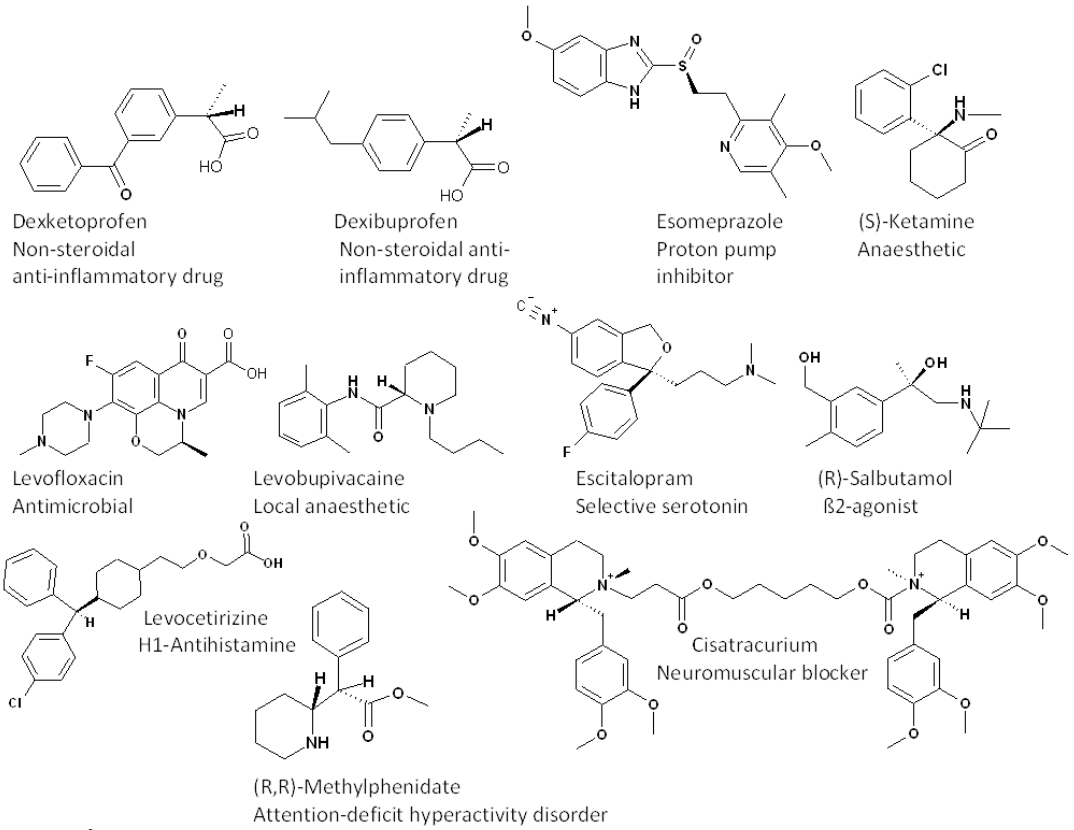


Figure 2[4]: From racemates to enantiomeric pure medications: some examples

This important new trend resulted in the huge interest and development of novel strategies (Figure 3) to prepare the enantiopure APIs, avoiding an increase of the production costs.

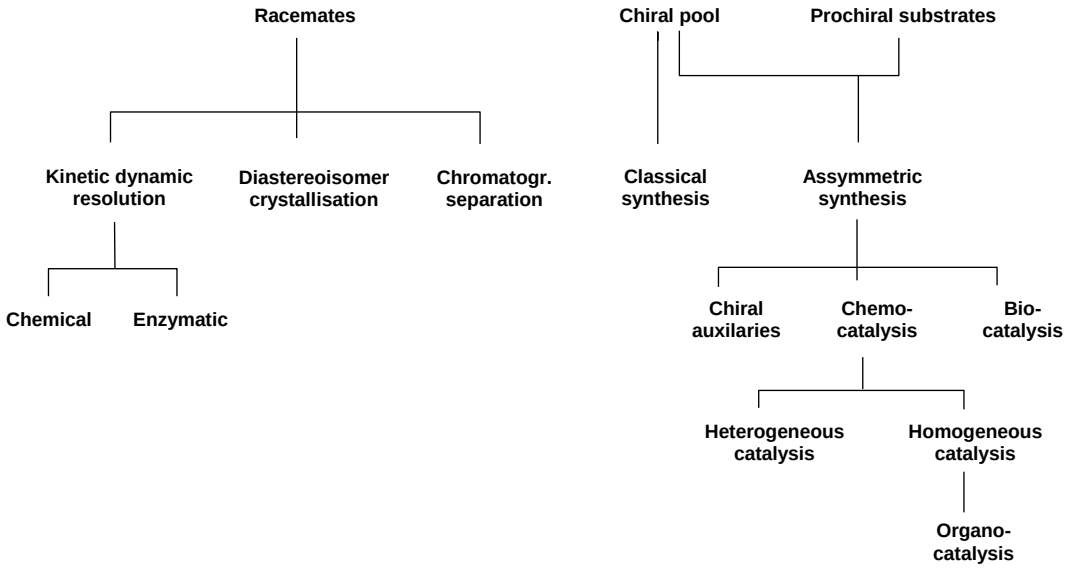


Figure 3: Available methodologies for the preparation of enantiopure chiral drugs

As shown in Table 1, one of the preferred approaches is based on the use of the so-called chiral pool ("chirality from nature"), resulting in the conversion of cheapest and commercially available enantiopure appropriate starting materials to enantiopure drugs or candidates; its success resulting from the huge commercial availability of chiral key building block intermediates. Other alternative successful methodologies to prepare at lower costs enantiopure medications are grounded on the

classical chemical or enzymatic resolution approach, or on crystallization (in case of diastereoisomers) methods. The progress made in the field of preparative analytical chiral technologies yielded also the increasing use of chromatography separation methods.
Nevertheless, all these techniques required a large amount of expensive starting materials, and long synthetic routes. For that reason, the development of enantioselective synthetic methods would be a major revolution in the field of drug production, but few have found an application until 2003 on large scale production of APIs (Table 1)[1].

Entry	Type	1992	1994	1996	1998	2000	2002	2003
1	use of chiral pool	3	6	6	4	7	4	4
2	resolution approach	1		3		2	4	2
3	enantioselective synthesis	1	1	2	5	2	2	4

Table 1: Used methodologies to introduce chirality

Intensive efforts have been made, and are still required for the development of efficient and robust enantioselective synthesis, based on the considerable advances made in the field of asymmetric synthesis, providing[5] thus general methods of producing drugs from prochiral or chiral substrates in large scale[6]. The field of asymmetric synthesis includes various successful approaches[7a,b] (Figure 3) based on the utilization of chiral auxiliaries, metal complexes (homogeneous and heterogeneous phase), bio-catalysts, and in the last years, also of organocatalysts (as proof the number of papers published in the last years (Figure 4)). In all these cases high selectivity can be achieved by using the proper catalyst, ligand substrate and reaction conditions.

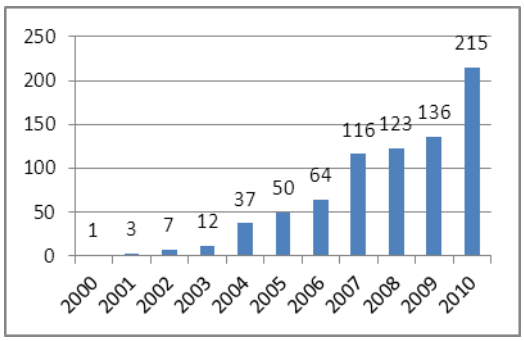


Figure 4: Number of publications edited from 2000 to 2010, on the topic organocatalysis (SciFinder Research)

Among the large number of C-C bond forming reactions, which have been explored and resulted in successful applications in the field of metal catalyzed and organocatalytic asymmetric synthesis, the nitroaldol or Henry reaction[21] and the Michael addition[7] represent powerful methods for the preparation of valuable and easily transformable synthetic intermediates.

The progress made in the field of asymmetric synthesis and the request of the pharmaceutical industry to produce enantiopure APIs in the quickest, cheapest and "green" manner, resulted in the development of a new way of thinking: "the atom economy"[8] was introduced.

I. Atom economy strategies

The objectives of the pharmaceutical companies have always been to find the best way in term of yields, selectivities and safety to quickly produce a drug. In 1991, Trost[8] introduced a new vision of the "chemical thinking" and suggested novel guidelines to assess the efficiency of a given process by "looking at the number of atoms of the reagent(s) actually ending up in the desired product(s)".

The concept of atom economy[9], and the idea of using it as first condition for the improvement of chemical syntheses relies to the field of green chemistry, that was first introduced by Anastas in the early 1990s[10] and forced the chemical community to reevaluate the criteria of chemistry and to look at a chemical reaction in a more "global" manner, considering aspects such as the origin of the reactants, the amount of energy necessary to make it work and the outcome of the generated waste[11].

The atom economy benefits from and is based on the progresses made in the field of catalysis. Although the major drawback of catalysis is the necessary recovery of the catalyst, it remains the first big step made for atom economy and the progress made in this field continues to prove its power. More recently, the chemical community turned its attention to the development of alternative efficient solvent- free procedures, and pointed out the utilization of water, supercritical fluids, or ionic liquids as potential alternative media.

Theses progresses made in the development of efficient alternative methods and techniques led also to the emergence of new ways of synthesis planning allowing the preparation of complexe molecules in an ecologically and economically favorable way, such as tandem, cascade or domino reaction[12]. Such reactions are defined as one-pot processes involving "two or more bond-forming reactions under identical conditions, in which the subsequent transformation takes place at the functionalities obtained in the former transformation"[12f], or "coupled catalysis that occurs sequentially and via two (or more) mechanistically distinct processes"[13]. The advantages of making several transformations in one operation are considerable, not only in terms of waste (one solvent, absence of work-up and purification steps) but also in terms of time, labor and resource management.

The progress made in the design of tandem/domino/cascade reaction remained a challenge until Robinson[14] reported his one-pot synthesis of tropinone (Figure 5).

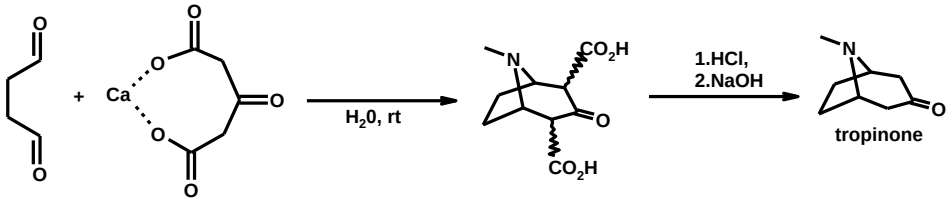


Figure 5: Robinson syntheses of tropinone

II. Asymmetric synthesis

Asymmetric synthesis, and especially the metal-chiral ligand based catalysis and the organocatalysis, is one of the most important and popular strategy to prepare enantiopure compounds. The enormous interest and progresses attached to chiral catalysts in asymmetric synthesis led to the award of the Nobel Prize for chemistry in 2001 to Knowles and Noyori (for their work on chirally catalyzed hydrogenation reactions) and to Sharpless (for his work on chirally catalyzed oxidation reactions)[15]. The pioneering work of these three Nobel laureates paved the way for the further development of asymmetric catalysis[16].

While the use of metal catalysts or metal-ligand catalysts dominated up to the end of the last century, a change in perception in recent years led to a switch in favor of organocatalysts. The utilization of small chiral organic molecules as metal-free catalysts, especially in the synthesis of pharmaceuticals afforded the 'green' advantage of the non contamination of the final product with traces of heavy metals[17a-d,16].

II.1. Induction of asymmetry

II.1.1. Ligand- metal complexes based catalysis

In asymmetric synthesis, the effort made in the field of ligand- metal based catalytic asymmetry led to the preparation of a wide range of complexes from various chiral ligands and metal species (among them copper and zinc were the most widely used) being able to chelate monodentate or bidentate species (Figure 6)[18].

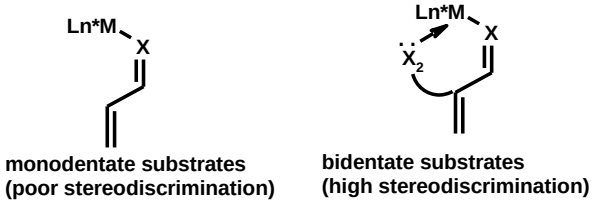


Figure 6: Plausible coordination ways of monodentate or bidentate species with chiral ligand-metal based complexes

II.1.2. Organocatalysis

In organocatalyzed asymmetric reactions, two modes of activation of the substrates have been proposed[7b]: *i*) the generating asymmetry can result from the formation of covalent adducts between the catalyst and the substrate(s) within the catalytic cycle, the so called ''covalent catalysis'' *ii*) second from non-covalent interactions such as hydrogen bonding or the formation of ion pairs can provide organocatalyzed asymmetric reaction, the so-called ''non-covalent catalysis'' (Figure 7).

In ''covalent catalysis'', the activation of the substrate can occur for example, by single step Lewis-acid–Lewis-base interaction or by multi-step reactions such as the formation of enamines from aldehydes and secondary amines. In ''non-covalent catalysis", the activation process is based on the formation of hydrogen-bonded adducts[19] between substrate and catalyst or on

protonation/deprotonation processes. An other activation process belonging to this category is the phase-transfer catalysis (PTC) by organic phase-transfer catalysts, even if the PTC promotes reactivity not only by altering the chemical properties of the reactants but also involves a transport phenomenon[7b].

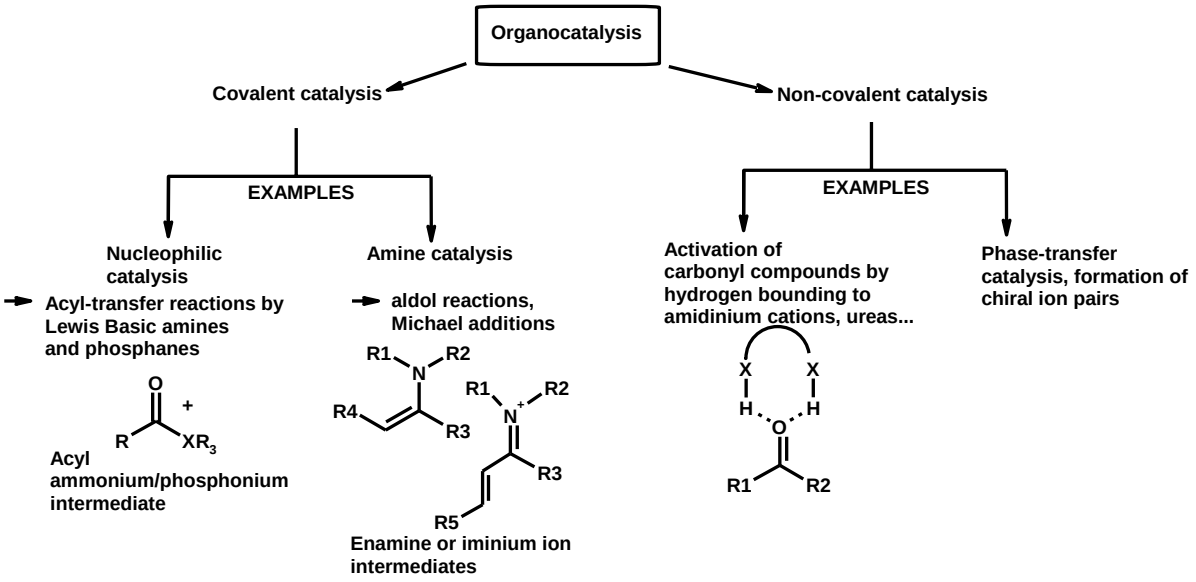


Figure 7: Example of asymmetric synthesis

Most of the organocatalysts can be categorized either as Lewis bases/acids or Brønsted bases/acids. Lewis base catalysts initiate the catalytic cycle *via* nucleophilic addition to the substrate, resulting in the formation of a complex, which undergoes the reaction and then releases the product and the catalyst. In Lewis acid catalyzed cycle, the nucleophilic substrate is activated in the same manner. In the case of Brønsted base and acid catalysts, the catalytic cycles are initiated *via* a (partial) deprotonation or protonation step[20].

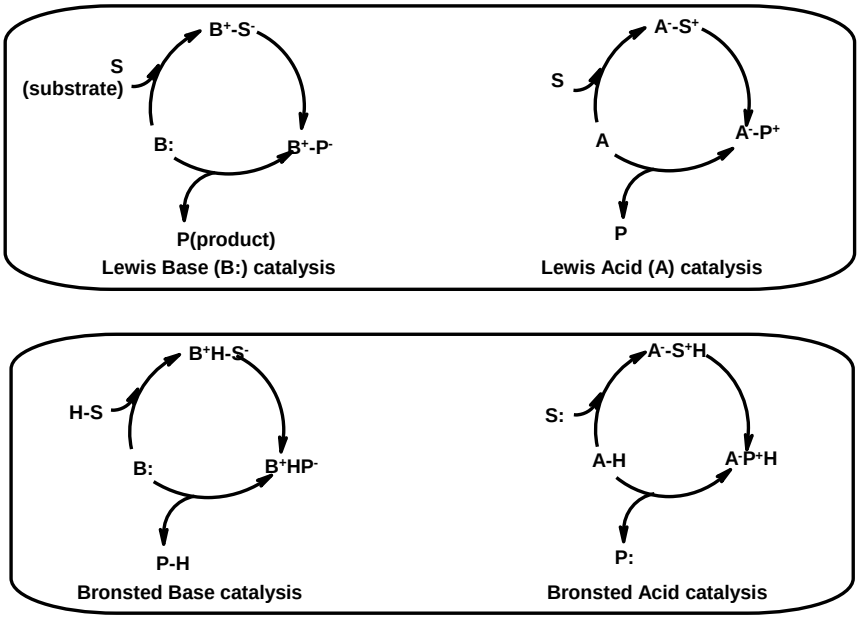


Figure 8[20]: The general catalytic cycles proposed for the Lewis base/Lewis acid organocatalysts and for the Brønsted base/Brønsted acid catalysts

II.2. Henry reaction

One example of a well documented asymmetric catalytic reaction is the Henry reaction[21]. Discovered in 1895, the Henry reaction[22] consists essentially in the reaction of an *in situ* generated reactive nitronate species (resulting from the deprotonation of an alkylnitro compound bearing α- hydrogens) with a carbonyl group, yielding in the formation of a nitroalcohol product bearing two new stereocenters (Figure 9).

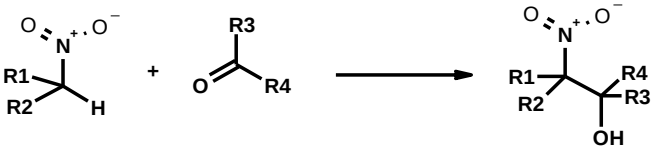


Figure 9: Principle of the Henry reaction (Nitro aldol reaction)

Such derivatives are very useful in organic synthesis, being easily transformed into a variety of nitrogen- or oxygen-containing derivatives[23]: nitroalkenes (dehydration), aminoalcohols or amino ketone compounds (reduction[24]), aldehydes or carboxylic acids (Nef reaction[25]), and into other derivatives (substitution by carbon and heteroatom nucleophile[26])

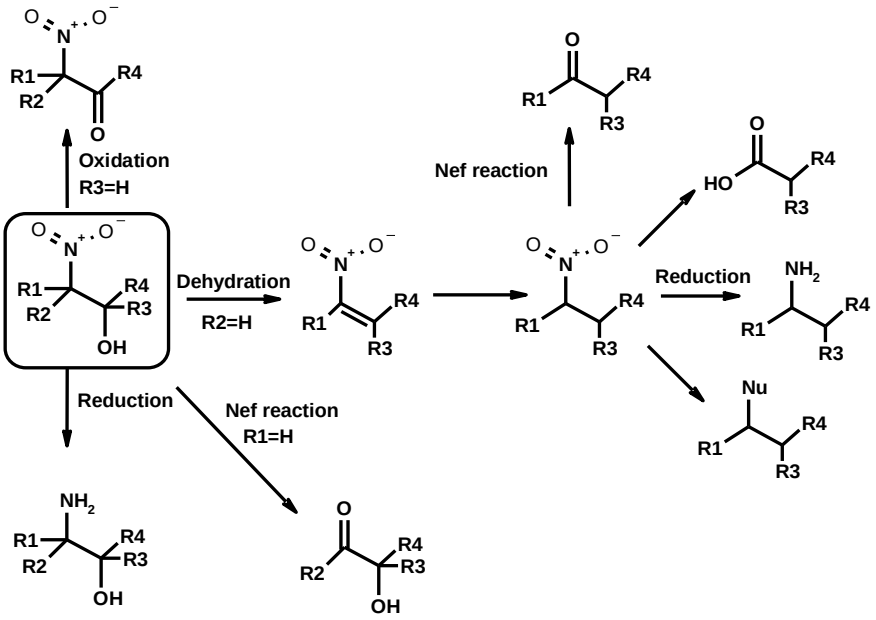


Figure 10[21b]: Possible transformations of the nitro-alcohol obtained by a Henry reaction

The Henry reaction may be conducted under many different conditions, using diverse catalytic systems providing moderate-to-good enantioselectivities. The control of the configuration at the new formed stereocenters is often crucial. The reversible nature of many nitroaldol reactions, and the racemization of the carbon group in α position to the nitro functionality makes the control of the configuration difficult.

Since the first asymmetric version of the Henry reaction was reported by Shibasaki[27] in 1992, the interest in this area has grew up considerably and many procedures and methodologies have been published in the literature based on the development of various metal and non metal based catalysts. The development of new catalytic processes for asymmetric Henry reactions has been always based on the two following approaches: a) activation of the nitroalkane reactant *via* the *pre*-formation of a silyl nitronate species b) direct reaction without any previous activation of the reactants.

II.2.1. Activation through the formation of silyl nitronate species

The development of strategies based on the *pre*-activation of the nitroalkane derivatives relied on the pioneering work of Seebach[28], who reported the preparation of silyl nitronates from primary and secondary nitroalkanes and their reactions with some carbonyl compounds, catalyzed by fluoride-ion. On this basis, different methodologies providing *anti* selective Henry reaction have been developed using chiral quaternary ammonium salt fluorides (Maruoka[29]) or combinations of an achiral fluoride source and a chiral metal complex (Jorgensen[30]).

II.2.2. Direct asymmetric reaction

All the methodologies developed on this area are based on a cooperative activation of the nitroalkane and carbonyl components during a catalytic cycle: *i*) the nitroalkane by base-promoter

transfer *ii*) the carbonyl species by coordination to an acidic center[21c]. These approaches including metal based or organocatalysis, resulted in the preparation of Henry products with good yields and enantioselectivities.

It is also worth to mention, that few researches on biocatalytic Henry reactions have been conducted. A recent paper published by Griengl[31] describes the use of lyase from *Hevea brasiliensis* as biocatalyst buffered media to prepare nitro aldol products with moderate to good yields and enantioselectivities.

II.2.2.1. General catalysts

Henry reactions can be catalyzed by many types of catalysts and conditions; the first promoters of choice were strong bases as alkoxides or hydroxides in alcoholic or aqueous solvents[21a]. Organic bases such as 1,1,3,3 tetramethylguanidine or cyclic analogues in ether or THF and triethylamine or Hünig Base in alcoholic solvent have also been employed to perform Henry reactions[21a].

II.2.2.2. Metal based chiral catalysis

II.2.2.2.1. Rare earth-BINOL complex

In the field of metal catalyzed *syn*-asymmetric Henry reactions, many types of metal catalysts have been employed. The first example of this category ((S)-Binaphtol in conjunction with Lathanum oxide) was published by Shibasaki[27]. His pioneering work is based on bifunctional multimetallic catalysis[32] (Figure 11) using rare earth metals; the good yields and enantioslectivities result from the cooperative action of Lanthanum and phenoxi-Li as Lewis acid and Brønsted base centers.

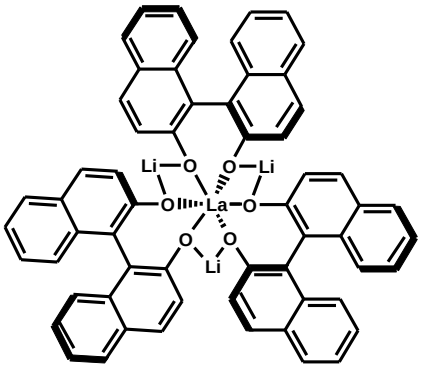


Figure 11: Heterodimetallic ambifunctional catalysts for Henry reactions

Fine-tuning of the substituents of the ligand on 6 and 6' positions and addition of water and BuLi (resulting in the formation of more active catalyst) lead to the improvement of the conversion rates and the *syn/anti* selectivity[33](Figure 12).

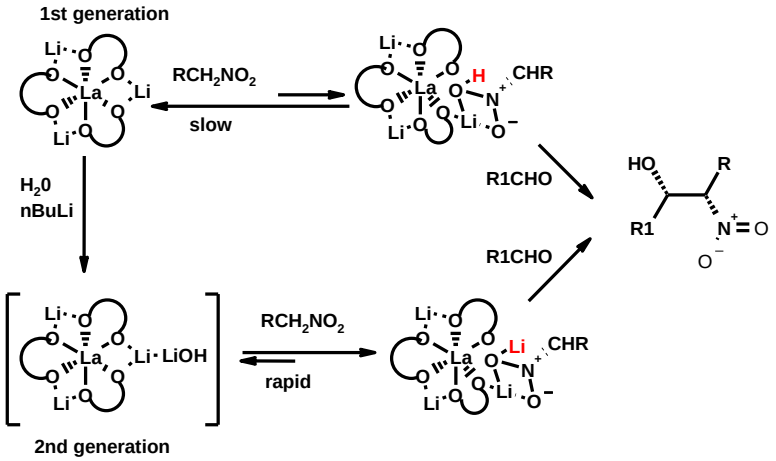


Figure 12[21c]**:** Explanation of the difference in the activities of the first and second generation of catalysts

Following the works of Shibasaki other efficient catalysts have been designed. Saá [34], for example, reported the utilization of catalysts containing a central La atom coordinated to three BINOL ligands, modified by attachment of an aminoalkyl side chain. He also proved that the addition of DBU and proton sponge to the reaction mixture enhanced rates and selectivities.

II.2.2.2.2. Dinuclear zinc catalysts

Other types of metal based catalysts for asymmetric Henry reactions using a central zinc atom have been designed. The more efficient example was published by Trost[35] revealing a new class of dinuclear zinc complex with a semi-azacrown ligand (Figure 13).

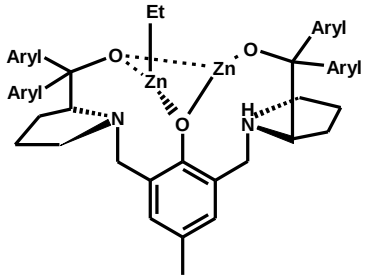


Figure 13: Dinuclear zinc complex

Additional trinuclear zinc complexes from trimeric thioaza macrocyclic ligand and diethylzinc have also been described by Martell[36] to perform asymmetric Henry reactions.

II.2.2.2.3. Copper-based catalysts

II.2.2.2.3.1. Bis(oxazoline) ligand

The first example of complexes (Figure 14) from copper (II) salts and bis(oxazoline) ligands for the asymmetric Henry reaction of nitromethane and α-ketoester, has been reported by Jorgensen[37]. This procedure includes the presence of base additives (triethylamine) at room temperature and the

formation of a transition state intermediate, where only the aldehyde component coordinates to the copper atom.

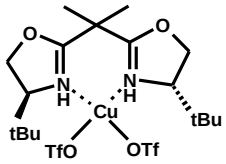


Figure 14: Jorgensen copper (II)–BOX complex

In this method, the ratio of complex and base additive (triethylamine seems to be the best one) plays an important role in the selectivitities observed (up to 94%), triethylamine being an active participant as promoter of the reactive nitronate species and deactivator of the Lewis acid catalyst (Figure 15).

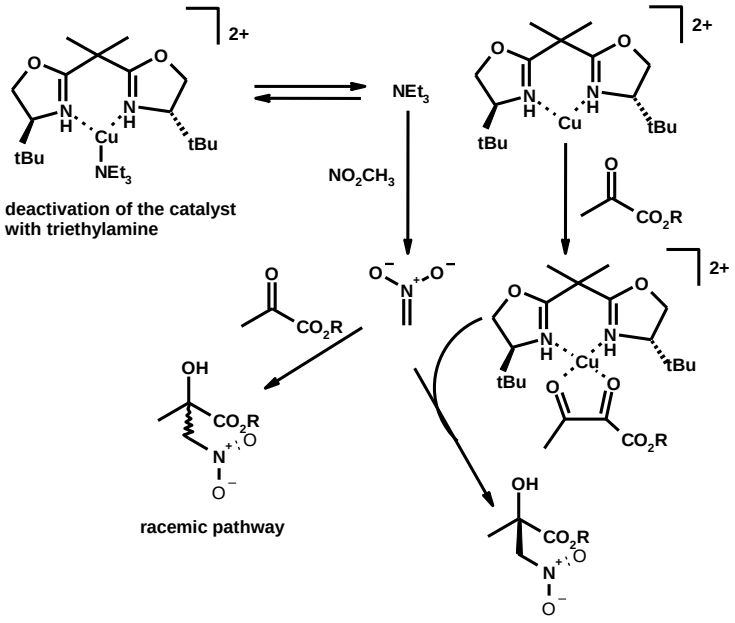


Figure 15: Proposed role of triethylamine and complex for the copper(II)-BOX complex catalyzed Henry reactions

Related, but less effective catalysts have also been described by Du[38], who performed the same Henry reaction using complexes of $Cu(OTf)_2$ salt and bisoxazoline and thiazoline ligands.

A more efficient analogue has been designed first by Evans[39] and later by Singh[40], based on a copper(II)-BOX complex, which would form a transition state species with the reactants where both aldehyde and nitronate components coordinate to the copper atom, resulting in the observed preferential configuration of the Henry adducts (Figure 16). The design of such catalysts are also based on the postulate that weakly Lewis acidic metal complexes bearing moderate charged ligands facilitate the formation of the nitronate species, as first step of the catalytic process[21d].

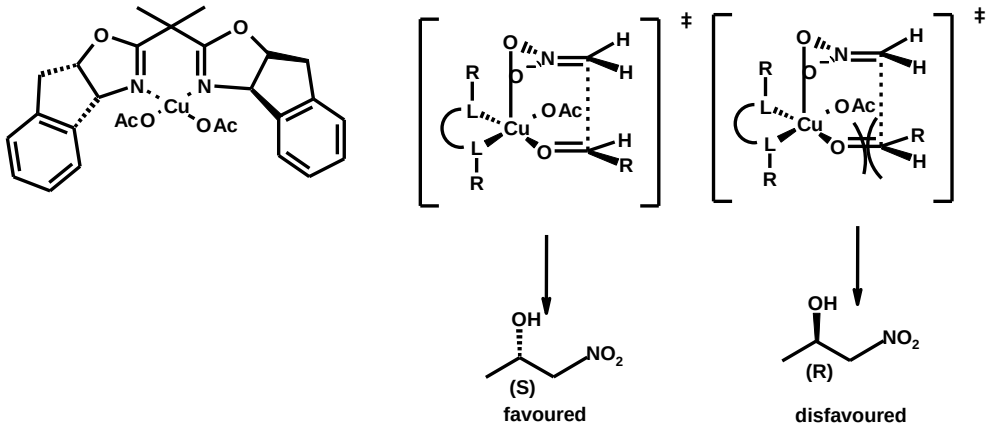


Figure 16: Evans' catalyst and proposed transition state species

Related tridentate-bis-(oxazoline) ligands have also been reported to catalyze asymmetric Henry reactions. Du[38] designed also C2- symmetric tridentate- bis-thiazazoline and bis-oxazoline ligands (A, B, Figure 17) that perfom asymmetric Henry reactions *via* the formation of a "chiral pocket" around the metal center, bis(thiazazoline) ligands leading to better enantioselectivities (up to 70%) than bis(oxazoline) ligands (up to 66%).

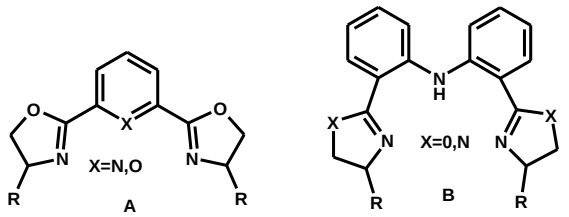


Figure 17: tridentate-ligands

The most interesting aspect of the utilization of complex type B is the reversal of the enantioselectivity by variation of the Lewis acid used. Thus, using complex formed from B type ligands and $Cu(OTf)_2$ salts, provided (S)-product with up to 86% ee, while the utilization of $ZnEt_2$ generated (R)-products with up to 85% ee. An explanation for these results is based on the fact that the central NH moiety cannot be deprotonated by triethylamine, and also acts as hydrogen bond donor, orienting the nitronate species, resulting in the attack of the nucleophile only from the *Si*-face. At the opposite, $ZnEt_2$ can deprotonate the amino moiety allowing the formation of a dinuclear complex, whose environment forces the approach of the nucleophile from the *Re*-face.

II.2.2.2.3.2. Imine ligand

Imine ligands have also been reported by Zhou[41] and Pedro[42] as being able to form complexes with copper II salts and so to react *via* the same process described by Evans asymmetric Henry reactions (Figure 18).

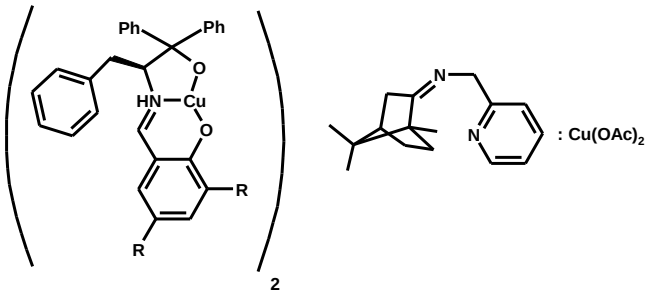


Figure 18: Zhou's and Pedro's copper (II)-imine ligand complexes

II.2.2.2.3.3. Chiral diamine ligands

Chiral diamine complexes of copper (II) salts have also been described as useful catalysts for asymmetric reactions. Copper (II) complexes of (-)-sparteine have been, for example, reported [43] to perform Henry reactions with different catalytic activities depending on the nature of the copper salt used. Indeed, $Cu(OAc)_2$ complexes promote Henry reactions without addition of an external base, while complexes from $CuCl_2$ salt require the presence of triethylamine (even if in small quantities) to perform smooth reactions. This difference of reactivity of the complexes was explained by the difference in bond and torsion angles around the copper (II) center.

Copper complexes of C2 symmetrical diamine ligands (Figure 19) have also been designed and are described[44,45] as efficient catalysts for nitroaldol reactions of nitromethane with various aldehydes with up to 99% yields and 90% ee.

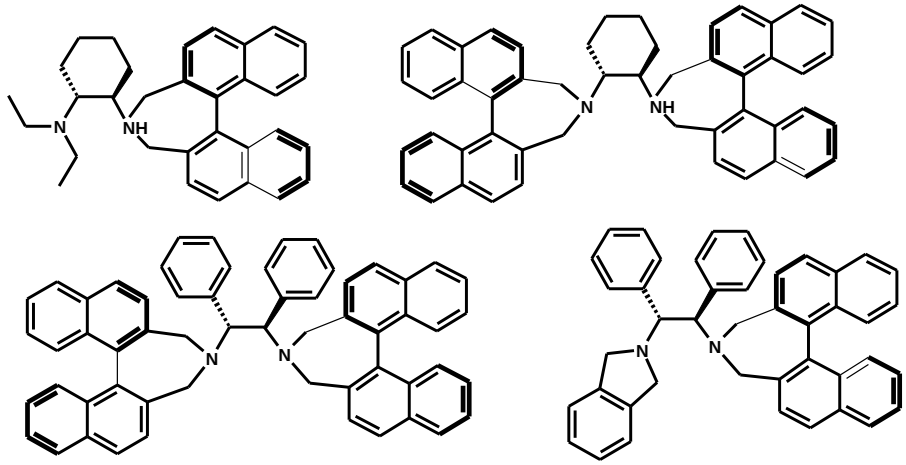


Figure 19: Chiral diamine ligand for copper catalyzed Henry reactions

As copper (I) complexes are challenging to handle, copper (II) complexes from tertiary amine ligands presented above (Figure 19) have been designed, based on the postulates of D. Evans[39] that their relative strong basicity and coordination ability would influence the catalytic activity.

II.2.2.2.3.4. Chiral bifunctional diamine ligands

In 2009, Mao[46] published conditions and designed bifunctional Schiff base ligands for copper catalyzed asymmetric Henry reactions. He based his approach on the work of Gröger and Shibasaki[47] who developed bifunctional catalysts for various asymmetric transition metal processes, proving that

such catalysts are Lewis acid-Lewis base systems, which are able to assemble both reactants in an ordinate transition state, bringing the substrates and nucleophiles into a close environment (Figure 20).

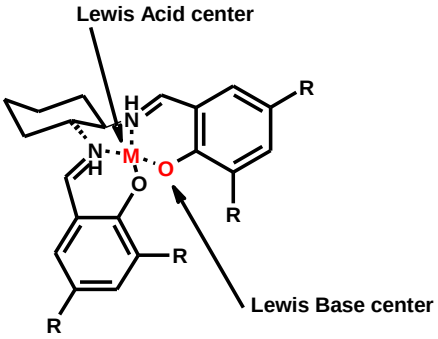


Figure 20[46]**:** Lewis acid-Lewis base system

Indeed, the related catalysts designed by Mao were supposed to activate the aldehyde (electrophile substrate) *via* the Lewis acid center. The Lewis base center is supposed activate the nitroalkane partner (nucleophile substrate) resulting in a double activation process.

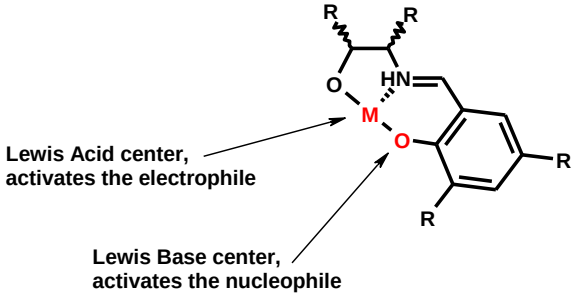


Figure 21[46]**:** Bifunctional copper based catalyst for asymmetric Henry reactions

The results observed by Mao proved the possibility of the utilization of such bifunctional copper based complexes for asymmetric Henry reactions of nitromethane with various aldehydes, providing Henry product with (S) configuration. It is here notable to say that the utilization of cobalt salts instead of copper salts resulted in a reverse enantioselectivity, with poor ee. The (S) selectivity observed could be explained by the formation of the following transition state as postulated by Evans[39], where the three aromatic rings shield one site of the complex, so that the attack of the nitronate occurs on the Si face of the carbonyl group (Figure 22).

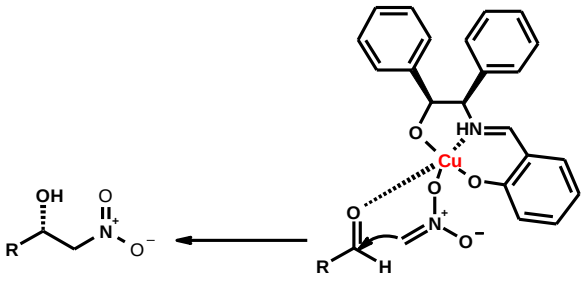


Figure 22: Proposed transition state models for the enantioselective Henry reactions

Reduced C_2 and C_1 symmetric Schiff base analogues were also described by Woggon in 2009, and 2011 as efficient copper based complex ligands for the asymmetric Henry reaction of various aldehydes with nitromethane with high (S)-enantioselectivity, and with 4-nitrobutyrate (and various prochiral nitroalkane)[48,49] with high enantioselectivity and *syn/anti* ratios (Figure 23). After screening

a wide range of ligands (for more informations on the variation done on R1 and R2, see[48,49]) and metal salts, his group identified the following derivative of Figure 23 to be the best one in term of enantio-and diastereoselectivity, when used in combination with $Cu(OAc)_2$ salt.

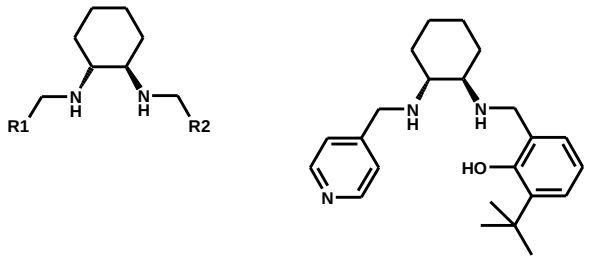


Figure 23: Examples of chiral ligands developed by Woggon and co-workers

Woggon proposed a mechanism of action for his catalytic asymmetric Henry reaction, in which the acetate unit of the *in-situ* generated complex **I** is replaced by the two reactants (intermediate **II**) so that the nitronate attacks preferentially one of the face of the aldehyde. After release of the product addition of aldehyde and CH_3NO_2 regenerates the intermediate **I**, closing the cycle (Figure 24).

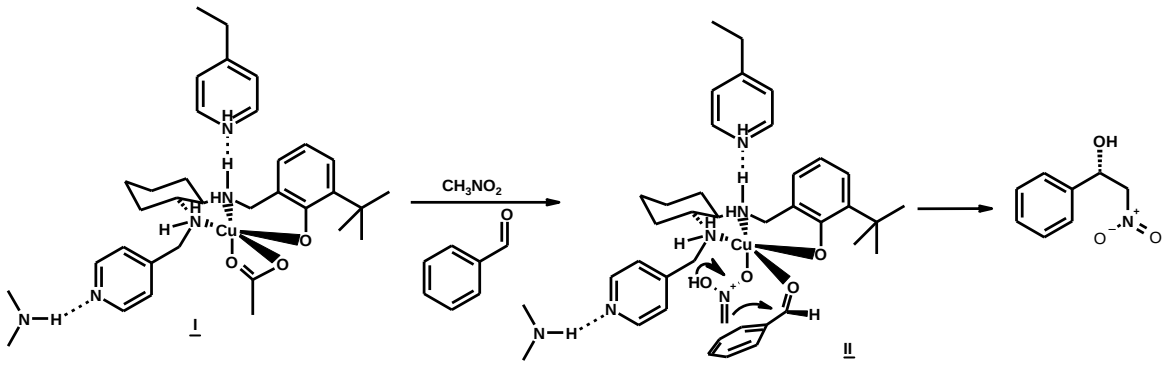


Figure 24: Proposed mechanism of Henry reaction catalyzed by Woggon catalysts

In the same way, he explains the excellent *syn*-selectivity by the fact, that both, aldehyde and nitro partners coordinating with one oxygen atom, are not anti-periplanar oriented (as demonstrated by Cossio[50]), and by the bulky pocket around the metal center.

II.2.2.2.4. Other metal based catalysts

Cobalt (II) ketoimine and cobalt (II)-SALEN complexes have also revealed good catalytic activity for Henry reaction in the presence of an external base (Hünig Base)[51].

II.2.2.3. Organocatalysis for the enantioselective Henry reaction

In view of the importance of the stereocontrol of the formation of nitroaldol products, a limited number of organocatalytic methods have been reported in the literature[21b].
The following design principles[21c] for an organocatalyst being able to perform Henry reactions with high chemical and stereochemical efficiency are: 1) the presence of a basic moiety (or external base)

to deprotonate the nitroalkane to the active nitronate species, 2) some unit capable of binding the nitro (or nitronate) group either through hydrogen bonding or purely electrostatic interactions, 3) some unit capable of forming a hydrogen bond with the acceptor carbonyl. So far, cinchona alkaloids, phase transfer catalysts, thioureas and guanidines[52] have been employed to this purpose.

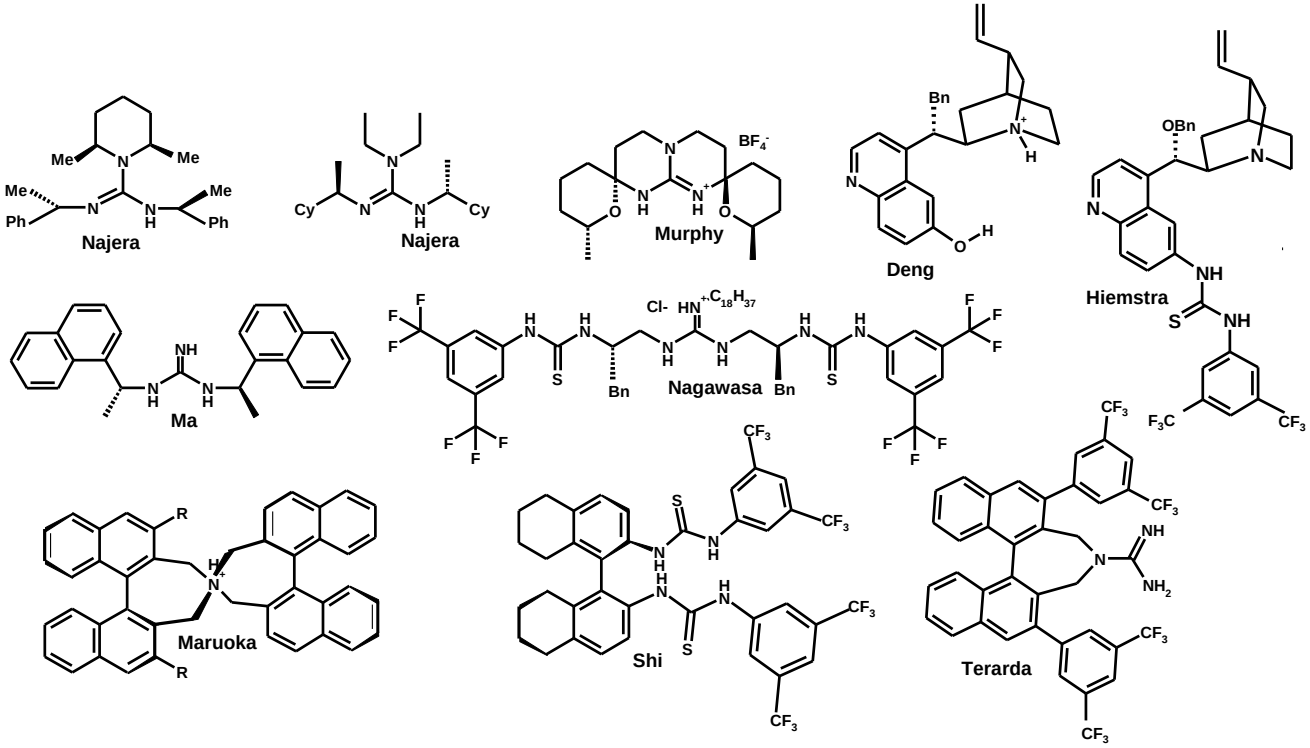


Figure 25[53]: Some reported organocatalysts for Henry reactions

The first organocatalysts for asymmetric Henry reactions have been described by Najera[53], who reported the preparation of different C_1 and C_2 symmetric guanidines and their modest (ee< 56%) in the Henry reactions of nitromethane with isovaleraldehyde and benzaldehyde at room temperature. Later, related guanidines have been described by Murphy[54] and Ma[55], while didn't afford better enantioselectivities and *syn*-diastereoselectivties.

In 2005, Nagawasa[56] designed the bifunctional organocatalyst, bearing guanidine and thiourea moieties. This catalyst showed the best results in terms of enantioselectivity for the reaction of nitromethane with α-branched aldehydes (up to 88%) and in terms of enantioselectivity (up to 95%) and *syn* diastereoselectivity (up to 99%) for the reaction of various nitroalkanes and aldehydes. The same tendency was also observed for the reaction of nitroalkanes and α-ketoesters.

The authors[56c,d] explained the good *syn*-selectivity by the fact, that the *anti*, *anti* conformational transition state (nitro group and R1 are in an *anti* relationship, carbonyl group and R2 are *anti*) of the three possible transition states, is the more favorable in term of reduced steric repulsion (Figure 26).

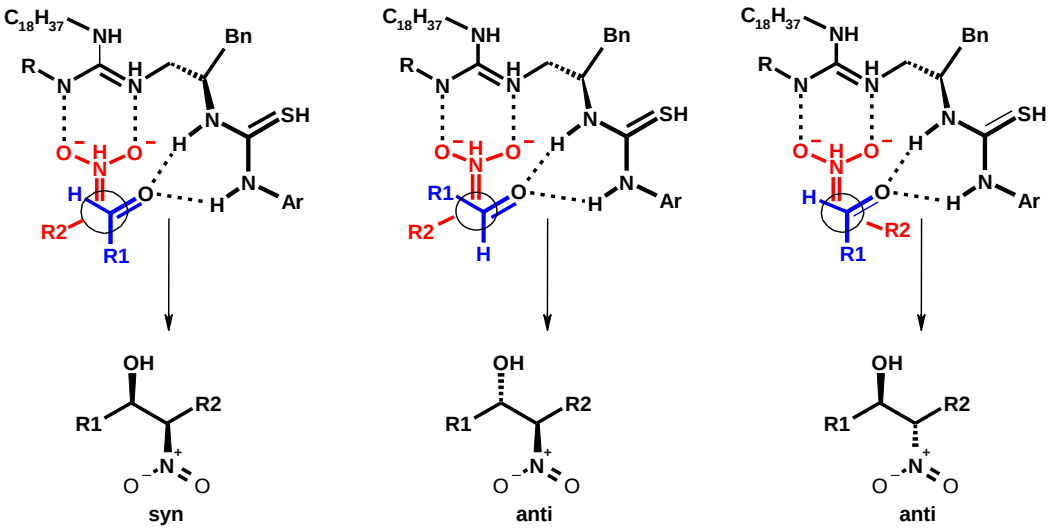


Figure 26[56d]**:** Possible transition state models of the organocatalyst **E** for Henry reactions

Because of the high enantioselectivity of these catalysts, they could be a good choice for the preparation of the *syn*-intermediate of Aliskiren.

Chiral guanidine bases performing *anti*- diastereoselective Henry reaction have also been designed recently by Terada[57], who reported their activities in the Henry reactions of various nitroalkanes with aldehydes.

Chiral N-spiro-ammonium organocatalysts, for example the C_2 symmetric catalyst (Figure 25), have also been reported by Maruoka[58] as efficient phase transfer catalyst for Henry reactions of silyl nitronates with aldehydes. Thiourea pattern has also been used for the design of organocatalysts. Shi[59] reported for example the efficient axially chiral bis(arylthiourea)-based organocatalyst .

The Cinchona alkaloids are not only organocatalysts but also metal-ligand based catalysts of choice, which has been explained by different factors16b. The most important one is their ability to coordinate to metal centers with the nucleophilic nitrogen of the quinuclidine ring and to bind the substrate on the quinolinic ring. The relative positions of both quinuclidine and quinolinic ring can also explain their efficacy as catalysts for the Henry reactions (Figure 27).

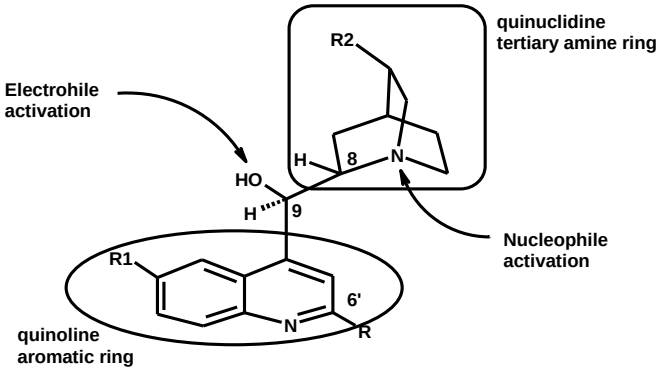


Figure 27[16b]**:** Cinchona alkaloids scaffold and mode of activation

As reported by Herrera[21b] and Singh[16b], some cinchona derived catalysts have also been tested in the Henry reactions. Hiemstra[60] and Deng[61] designed also related derivatives (Figure 25).

II.2.2.4. Application to the preparation of active pharmaceutical ingredients or intermediates

In order to illustrate the importance of the development of asymmetric methods for the Henry reaction, it is worth to mention some of its applications in the pharmaceutical industry, as summarized by Luzzio in 2001[21a].

For example, Shibasaki[62] applied La-(R)Binaphthol complexes for the preparation of (S)-propanolol (Figure 28).

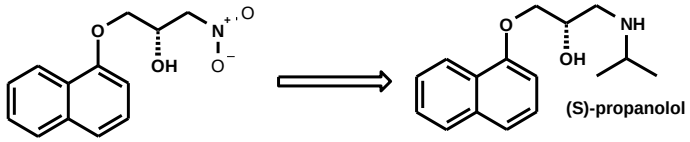


Figure 28: Preparation of (S)-propanolol

The same procedure was employed for the preparation of N-phthalimido-1-nitrobutane, a precursor of the HIV inhibitors KNI227 and KNI273 (Figure 29)[63].

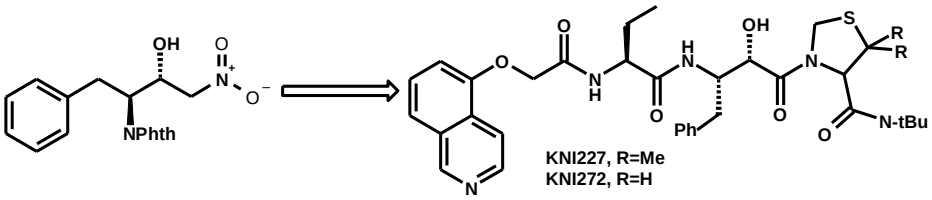


Figure 29: Preparation of the HIV inhibitors KNI227 and KNI-273

Shibasaki[64] reported the preparation of a precursor of (S)-Pindolol, a β-adrenergic antagonist, in the presence of a Lanthanum/Lithium (R)-(+)-Binol complexe (Figure 30).

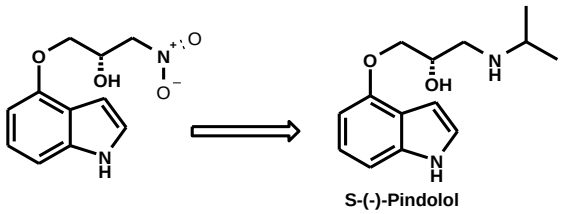


Figure 30: Preparation of (S)-Pindolol

E. J. Corey described[65] also the utilization of cinchona alkaloid derivatives as catalysts for the preparation of a precursor of the HIV protease inhibitor, Amprenavir (Figure 31).

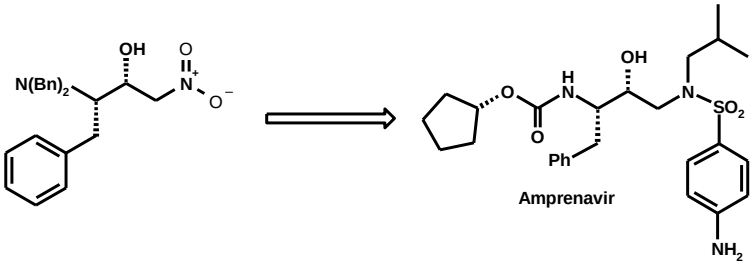
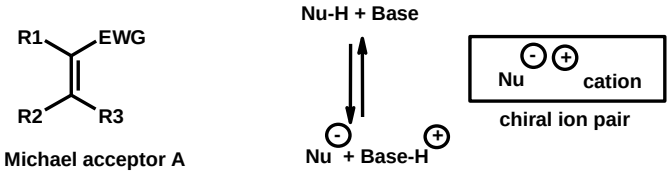


Figure 31: Preparation of Amprenavir

II.2.3. Michael addition: nucleophilic addition to electron defficient C=C double bonds

As shown in Figure 32[7b], in a Michael addition[66], a nucleophile Nu- (usually generated by deprotonation of the precursor NuH) is added to the β position of an α,β-unsaturated acceptor A. Addition of Nu- to a prochiral acceptor A generates a new chiral center at the β-position of the acceptor A. The reaction of the generated intermediate enolate anion with an electrophile E+ can afford a second chirality center at the α-position of the acceptor. The process suggests that the enantioface differentiation in the addition to the β-carbon can be performed in 2 ways: 1) by deprotonation of the Nu-H nucleophile by a chiral base , that would result in the formation of a chiral ion pair **I**, which could add to the acceptor asymmetrically 2) by deprotonation of the Nu-H nucleophile in one phase by a non-chiral base, and the transfer of the anion Nu- into the organic phase by a chiral phase-transfer catalyst, resulting again in the formation of a chiral ion pair.



EWG: electron-withdrawing group, such as ketone, ester, aldehyde, nitrile, nitro group etc..

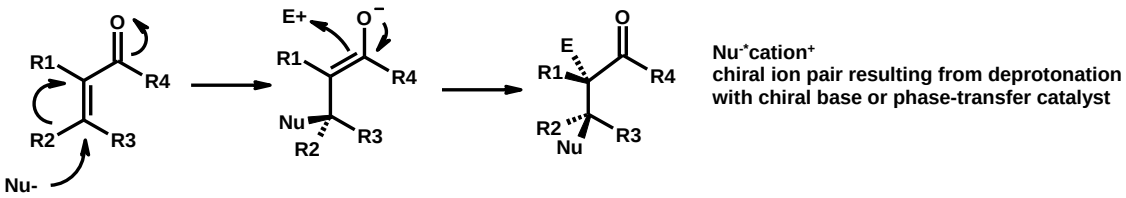


Figure 32: Principle of the Michael addition

Asymmetric versions of Michael reactions can also be performed using metal-ligand based catalysis.
In recent years, two efficient and practical approaches have been developed to provide a chiral environment for the attacking nucleophile, yielding to asymmetric Michael reactions. It consists first on the activation of the acceptor *via* the reversible formation of an chiral iminium ion, the face-selective reaction with the nucleopile affording an enamine intermediate, that can be either hydrolyzed, or can react with an electrophile, yielding after hydrolysis a new β-chiral carbonyl compound.
The second approach is the enamine pathway. If the nucleophile is an enolate anion, it can be converted into a reversible chiral enamine by condensation of the original carbonyl compound and a chiral secondary amine.
Having both the same origin, but being interdependent, enamine and iminium catalysis are nominated as the "ying and the yang"[67] by List[67].
The combination of these approaches yielded in the development of many tandem sequences as described for example by List[68] or Mac Millan[69], and resulted in the development powerful multiple component domino cascades[12h,70].

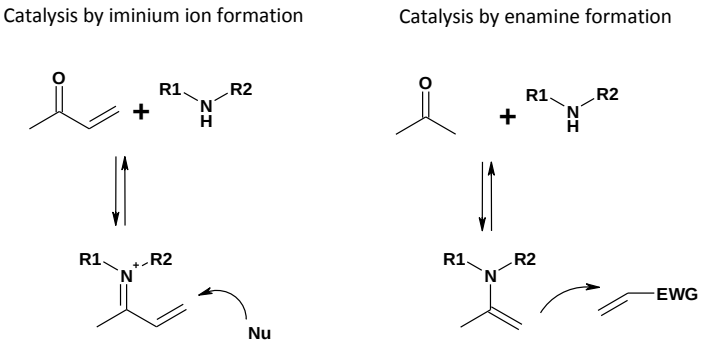


Figure 33: Catalysis by iminium ion and enamine formation

II.2.3.1. Intermolecular Michael additions of C- nucleophiles

II.2.3.1.1. Metal ligand based catalysts

Few examples of ligand-metal based complexes have been developed to catalyze Michael additions[71]. Mentionable are for example manganese-bisoxazoline complexes developed by Jackson[72], the dinuclear zinc[73] or lanthanum[74] complexes of linked BINOL, aluminium-SALEN complexes[75] , aluminum-lithium[76] or ytrium BINOLATE complexes[77]. Scandium (III) salts in combination with chiral biquinolinedioxide or bis(hydroxymethyl)bipyridine[78] , chiral ruthenium-amido complexes[79], palladium enolates [80], and copper (II) -bisoxazoline complexes[81] have also been reported to perform asymmetric Michael additions.

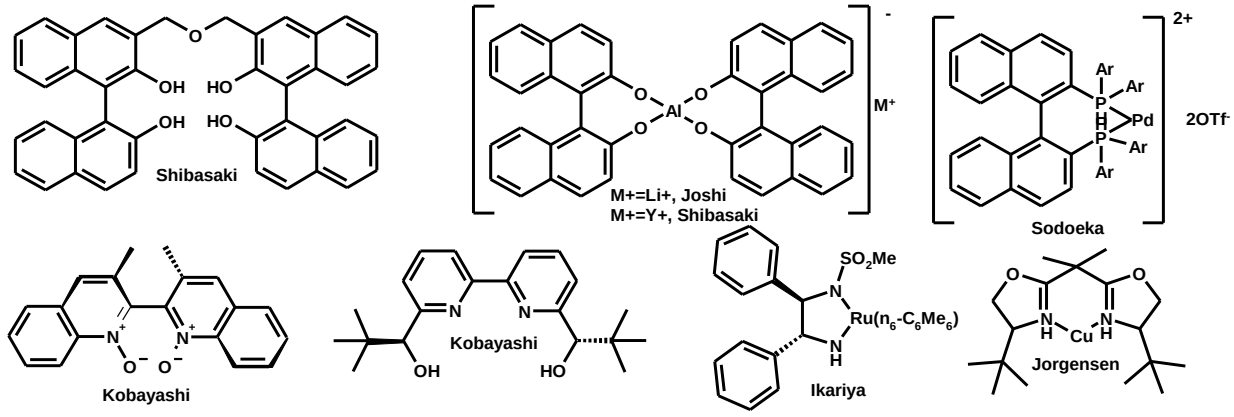


Figure 34: Metal based Ligands for asymmetric Michael reaction

II.2.3.1.2. Chiral base and phase-transfer catalysts

Chiral bases and phase transfer catalysts have been proved to perform efficient asymmetric synthesis as reported by Berkessel and Gröger[7b]. The first example was reported in 1975 by Wynberg and Herman[82a]. More recently, Deng[83] and Soos[84] reported the exploitation of related cinchona alkaloids (Figure 35) and Jorgensen[85] reported also the catalytic activity of a new class of 6'-hydroxy cinchona alkaloids, with a non-biaryl atropisomeric functionalization in 5' position of the quinolinic ring, and for example the aminated derivative. Ammonium catalysts derived from natural compounds (such as

tartaric acid[86]) or synthetic molecules (such as 1,1'-2,2'-binaphtol[87]) have also be reported to perform asymmetric Michael additions.

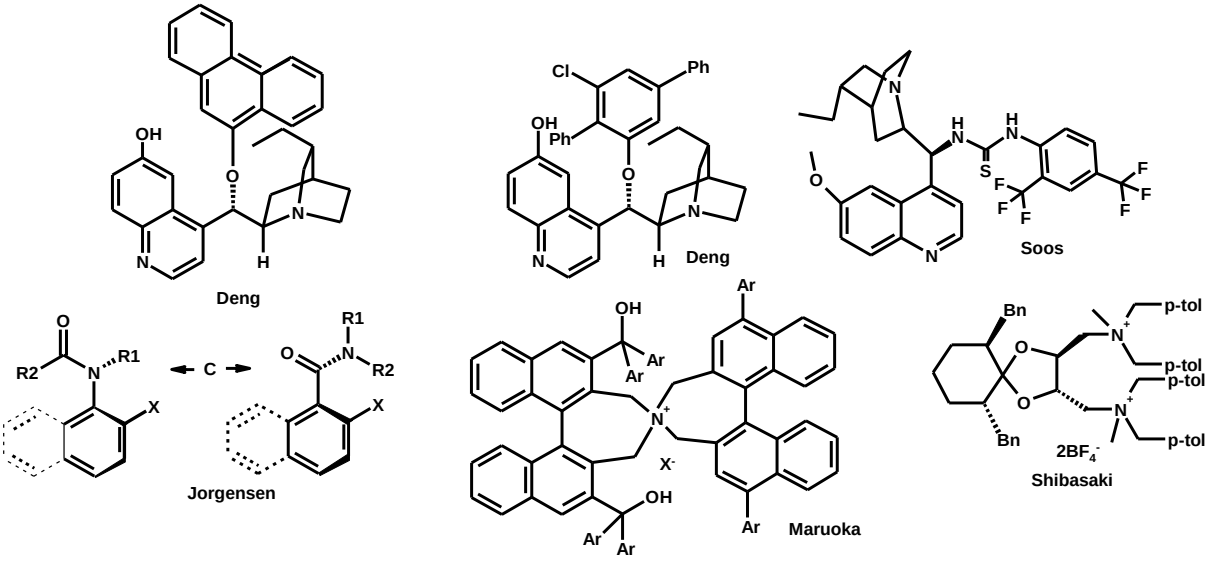


Figure 35: Example of modified cinchona alkaloids for Michael additions

II.2.3.1.3. Organocatalysts for asymmetric Michael addition of C- nucleophiles

Organocatalytic Michael additions of C-nucleophiles to electron deficient C=C double bounds, involving enamine and iminium processes have been well described in the literature[7a-b,d, ,88]. The most common organocatalyst is proline (Figure 36).

It can indeed react with carbonyl compounds to form reversible iminium ions or with Michael acceptor or enamine intermediates, yielding the corresponding Michael products with high yields and enantioselectivities, due to its capacity to form higly organized transition states with extensive hydrogen-bound networks[7a,d]. The utilization of proline in the catalytic system afforded successful results in Michael reactions involving highly reactive donors and acceptors; while the proline catalyzed addition of aldehydes to simple enones have been less studied.

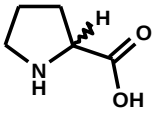


Figure 36: Proline

For example, one successful utilization of proline, has been described by Hanessian and Pham[89]. Proline in combination with *trans*-2,5-dimethylpiperazine affords additions of a variety of nitroalkanes to acyclic enones with excellent enantioselectivity up to 93%, *via* (according to the authors) a "complex multi component chiral catalytic system".

Such as proline, proline derived organocatalyts have also been reported to perform efficient organocatalytic Michael addition.

In 2005, Gellman and Chi[90] achieved Michael addition of simple aldehyde to relatively non activated enones with up to 95-99% ees, using diphenylprolinol ether (Figure 37) as catalyst (1-5%).

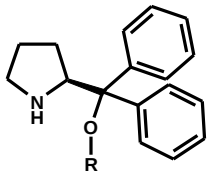


Figure 37: Diphenylprolinol ether

The combination of pyrrolidine and catechol as co-catalyst has also been described by the same group[90], the catechol additive being supposed to activate electrophilically the enone *via* hydrogen-bond donation to the carbonyl group (Figure 38).

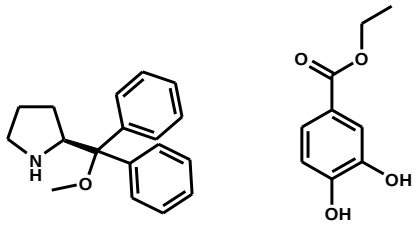


Figure 38: Diphenylprolinol ether and cathecol used by Gellman and Chi[90]

Other derivatives have been reported in the literature, such as chiral imidazolidinones (Figure 39), first prepared by MacMillan[91] from L-phenylalanine, methylamine, acetone or pivalaldehyde respectively. Using the MacMillan catalysts in combination with cathecol, Gellman[92] developed an efficient aldehyde-enone Michael addition. The most interesting results obtained by Gellman, involve the isolation of an imidazolidinone-enamine intermediate, as proof for the enamine process, while prior to him the activation of α,β-unsaturated aldehydes was supposed to proceed *via* an iminium activation[93]. In conclusion, imidazolidinones are able to activate carbonyl compounds by nucleophilic activation, in addition to their well known electrophilic activator nature[94].

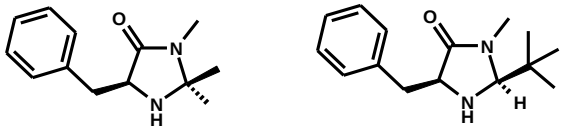


Figure 39: Mac Millan's chiral imidazolidinones

In addition, as cited above, the most used mode of activation for various Michael additions of stabilized carbon nucleophiles involved either enamine or iminium processes. They had thus application for the reaction of activated nucleophilic malonates or nitroalkanes[95] to simple enones or of unactivated ketones or aldehydes with activated Michael acceptor (nitroalkenes)[96].

It is also notable to mention that malonates have also been successfully used by Jorgensen[97] for enantioselective additions to α,β-unsaturated ketones and, α,β-unsaturated aldehydes (*via* iminium ion activation).

(S)-2-[bis(3,5-bistrifluoromethylphenyl) trimethylsilanyloxymethyl]pyrrolidine (Figure 40), for example, can perform Michael additions of several malonates to α,β-unsaturated aldehydes in good yields and in good to excellent enantioselectivities[97b].

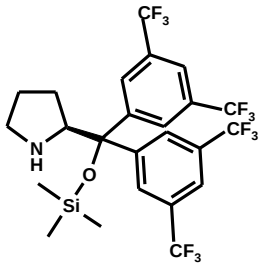


Figure 40: (S)-2-[bis(3,5-bistrifluoromethylphenyl) trimethylsilanyloxymethyl]pyrrolidine

The group of Ley[98a] reported also the use of pyrrolidine analogues (Figure 41) for the Michael additions of malonates to various cyclic and acyclic enones with excellent enantioselectivities in the presence of piperidine.

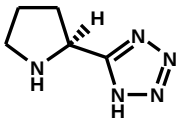


Figure 41: 5-pyrrolidin-2-yltetrazole

The addition of nitroalkanes to various cyclic and acyclic enones has also been developed by the same group[98b,c] using stoichiometric amounts of *trans*-2,5-dimethylpiperazine and 5-pyrrolidine-2-yltetrazole as organocatalyst, with up to 98% ees. The mechanism of the reaction has not really been confirmed. It is postulated that the catalyst forms an iminium complex with the enone derivative.
In 2005, Jorgensen[99] reported also the use of a mixed chiral imidazolidine-2-yl tetrazole for the reaction, *via* iminium activation, of nitroalkanes with cyclic or acyclic enones with up to 92% ee (Figure 42). The same group described also the preparation of phenylalanine derived catalysts (Figure 42) and their application as imimium activator for the addition of dialkylmalonates and nitroalkanes to a variety of enones with good enantioselectivities (up to 79%)[95a,b].

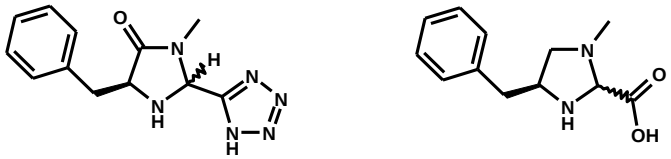


Figure 42: Chiral imidazolidin-2-yl tetrazole and phenylalanine derived catalyst

α,α-diarylprolinol salts (Figure 37) in the presence of *p*-nitro-benzoic acid proved also[100] to be efficient iminium activators in term of regio-, chemo-, diastereo- and enantioselectivities observed; the higher ees having been obtained for the reaction of linear or branched alkyl/aryl/heteroaryl substituted aldehydes with cyclic, aromatic α,α-dicyanoolefins, while the same reaction performed in the presence of free prolinol derivatives didn't afford good results, probably due to the formation of an unreactive hemiaminal compound[101].

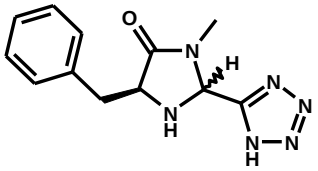


Figure 43: Chiral imidazolidine-2-yl tetrazole

II.2.3.2. Intermolecular nitro-Michael additions of C- nucleophiles

Nitro alkenes are highly reactive partners for the addition of nucleophilic species. Because of the strong electron withdrawing properties of the nitro group and the excellent conjugation with the double bond, the negative charges, generated during the nucleophilic additions, are highly stabilized, resulting in a species less reactive than the nucleophile itself[102].

II.2.3.2.1. Metal based complexes

As examples for the nitro-Michael reactions, the C_2-symmetric bis(oxazoline) Magnesium complexes of Barnes[103] , the bis(N,N-dibenzyl-trans-cyclohexanediamine)–Ni(II) complex of Evans[104] can be mentioned (Figure 44).

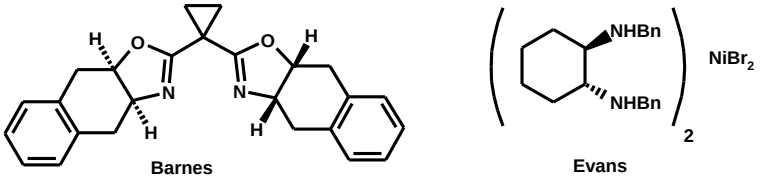


Figure 44: Ligand-metal based catalysts for the nitro-Michael reactions

II.2.3.2.2. Organocatalysts for intermolecular nitro-Michael additions of C-nucleophiles

Many research projects[105] have been conducted in recent years on the asymmetric organocatalytic conjugate addition of carbonyl compounds to nitroolefins, resulting in the development of a wide range of organocatalysts. Proline derived organocatalyts have been, for example, also used for nitro Michael additions with high yields and good to excellent enantioselectivities, such as homoproline by Oriyama[106], (S)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine by Hayashi[107] , the S-homo-Pyrrolidine-2-yltetrazole[108] by Ley, chiral pyrrolidin-pyridine by Yu[109], octahydro-indole-2-carboxylic acid by Herrera[110] and related (S)-2,3-dihydro-1H-indole-2-carboxylic acid and analogue by Loh[111], pyrrolidinyl-sulfamides by Chen and Xiao[112].

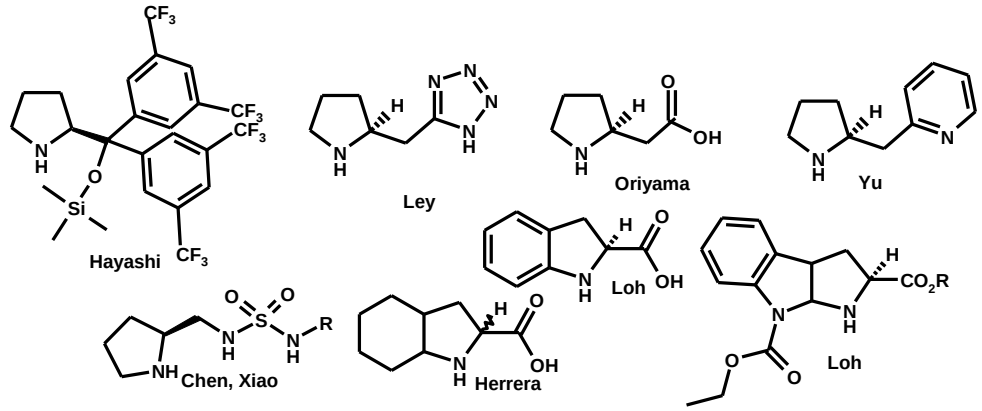


Figure 45: Proline related organocatalysts

Gong[113] , Wang[114] or Cordova[115] reported also efficient related organocatalysts in the nitro-Michael addition of various ketones.

Chiral thiourea derivatives (Figure 46) were also tested with success in asymmetric nitro-Michael addition. Tsogoeva[116] , Jacobsen[117], Tang [118] and Zu[119] reported some examples performing highly enantioselective additions.

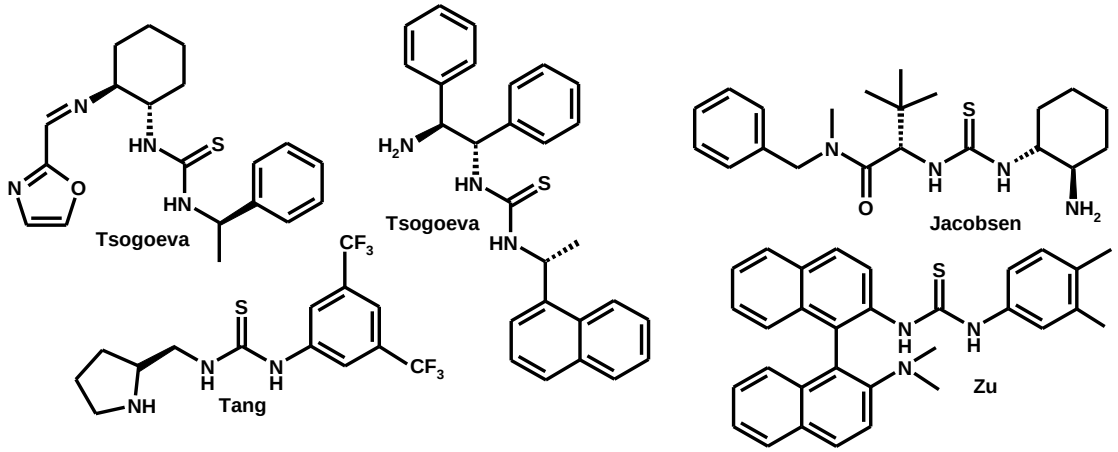


Figure 46: Chiral thiourea derivatives

More "exotic" examples have also been designed, such as chiral amines derived from (2R,3R)-(+)-tartaric acid by Barros and Phillips[120] , N-alkyl-3,3'-bimorpholine derivatives by Alexakis[121a,b] and/or Kanger [121c], or chiral trisimidazoline by Fujioka[122].

III. Conclusion

A lot of progresses have been made in order to develop efficient syntheses of bioactive compounds such as natural products and analogs, drugs, resulting from the successful development in academia of innovative methods in the field of asymmetric synthesis, including metal based catalysis and organocatalysis and from their direct application in industry processes.

This work will report some applications of these novel methodologies for the preparation of marketed drugs or drug candidates, *via* new alternative asymmetric pathways and discuss about the design of new catalysts and substrates, as well as the fine tuning of the reaction conditions to perform selected pharmaceutically important reactions under conditions applicable to an industrial synthesis. The example chosen for our studies is the synthesis of enantiomerically pure precursors of Aliskiren via organocatalytic Michael reactions and organometallic Henry reactions.

The cases of aza-Michael addition and Friedel-Crafts alkylation will be reported in the corresponding chapter 3 and 4. These studies are related to the enantioselective synthesis of two Novartis drug candidates AFQ056 and KAE609.

CHAPTER 2: ASYMMETRIC SYNTHESIS OF RENIN PROTEASE INHIBITOR ALISKIREN (TEKTURNA/RASILEZ)

I. Pharmacological activity

Aliskiren **1**, marketed as Tekturna in the US and as Rasilez in the EU, is the first non peptide-like renin protease inhibitor, being approved by the US authorities in March 2007 (in August 2007 in Europe) for the treatment of hypertension[123], 109 years after the discovery of renin by Tigerstedt and Bergman in 1898.

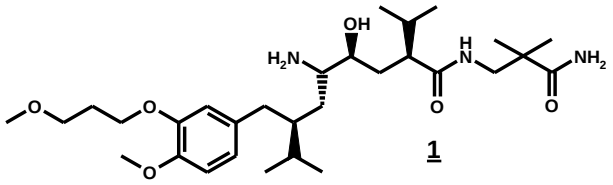


Figure 47: Aliskiren **1**

Hypertension is the major risk factor for the cardiovascular diseases and mortality and affects more than 13% of the population worldwide. It is caused by a disfunction (overactivation) of the renin-angiotensin-aldosterone cascade, a short term regulatory system to preserve blood pressure and blood volume[124] (Figure 48). When a decrease in blood pressure or in blood volume occurs, renin is released into the circulation from the juxtaglomerular cells in the kidney and angiotensinogen, the only known substrate for renin, is released from the liver into the circulation. Renin cleaves the angiotensinogen from its N-terminus into the inactive decapeptide angiotensin I (AngI), which is converted in the blood to the active peptide angiotensin II (AngII) by the angiotensin converting enzymes (ACE) located in the endothelium. AngII binds then to receptors located on the blood vessels in the kidney, the adrenal gland, and the pituitary gland and neurons, which results in the activation of various signaling pathways to reduce excretion of sodium, retain body fluid and increase blood pressure yielding in the suppression of renin secretion. Most of these effects are mediated *via* the AngII type 1 (AT1) receptors and emphasized by the production of the aldosterone and norepinephrine resulting from the secretion of Ang II in the body, resulting also in the vascular remodeling, sodium re-absorption and an increase of the blood pressure.

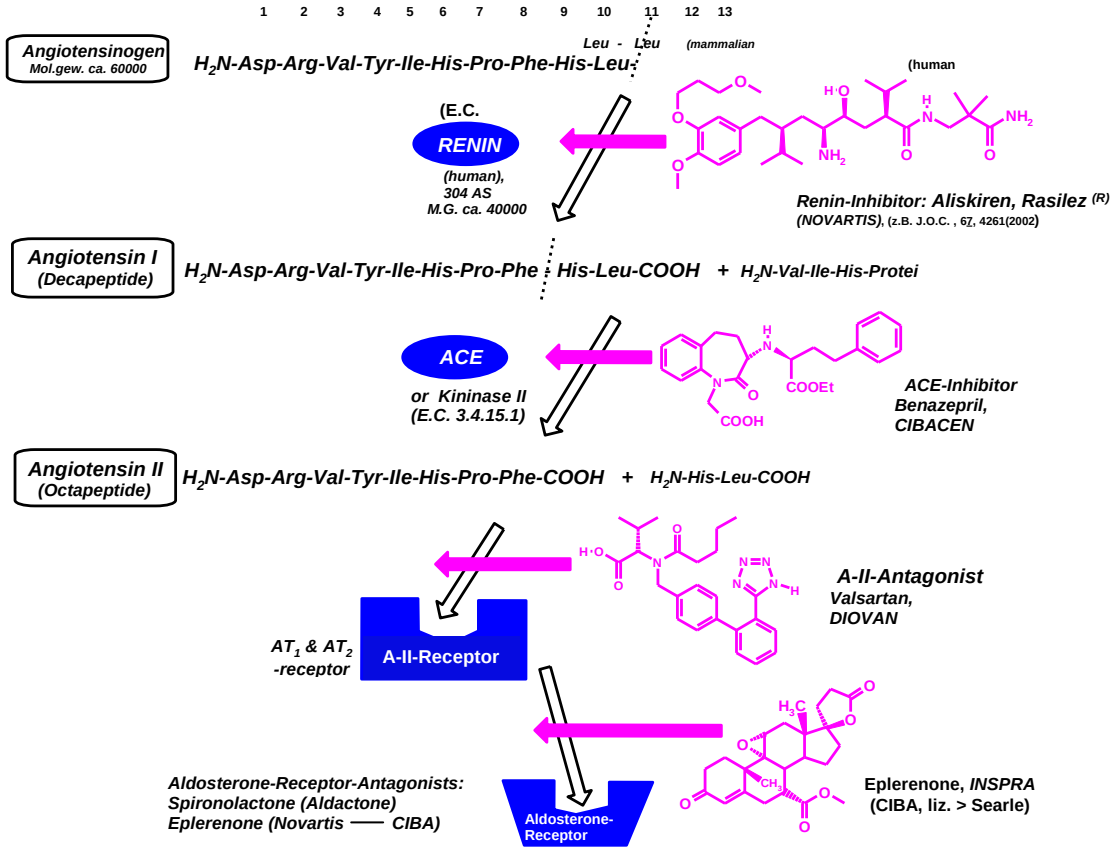


Figure 48[123]: The renin-angiotensin-aldosterone (RAA) cascade

As Skeggs[125] reported, a therapeutic benefit in the control of hypertension could be achieved by interfering with this RAA cascade at several points: by blocking the AT_1 receptors for AngII (such as by treatment later with for example Valsartan from Novartis), by inhibiting angiotensin converting enzyme (ACE) (such as for example by treatment later with the ACE inhibitor Benazepril from Novartis), or by preventing the formation of AngI through direct inhibition of renin. The author realizes so early that "Since renin is the initial and rate limiting substance in the renin-hypertensin system, it would seem that this last approach would be the most likely to succeed." Nevertheless, the first marketed medications relied only on the treatment of the patients with ACE or Ang II receptors blockers which successfully led to a decrease of blood pressure. Nevertheless, the activation of a concomitant feedback loop during the RAA cascade blockade results in the increase in the amount of Ang II, enhancing thus the secretion of renin, making the blockers inefficient towards the progression of cardiovascular diseases[126]. Thus, direct renin inhibition has been long considered as the most attractive and logical drug target in the RAA cascade since it catalyzes the first step of the system with the highest substrate specificity.

In the early 1980, Ciba-Geigy launched a research project to find out potent renin inhibitors leading to the discovery of Aliskiren in 1993.

Aliskiren interacts with several binding pockets in distinct regions around the active site of renin, particularly with the subpocket S3sp of renin[126a]. Binding to this sub-pocket is essential for strong renin inhibition by Aliskiren (Figure 49).

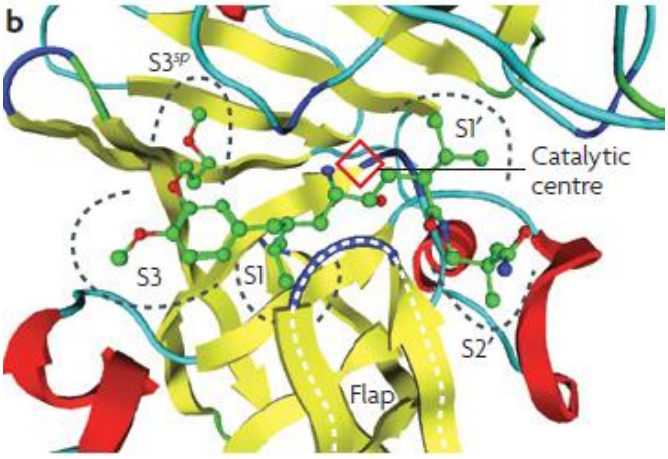


Figure 49[126a]**:** Graphic depiction of the binding of Aliskiren to the active site of renin

II. Preparation of Aliskiren base 1

The development of Aliskiren **1** has been extremely challenging due to the presence of the four adjacent *syn*-stereocenters of the all-carbon linear skeleton. The enantioselective synthesis of its unique chemical structure became the centre of many investigations (Figure 50).

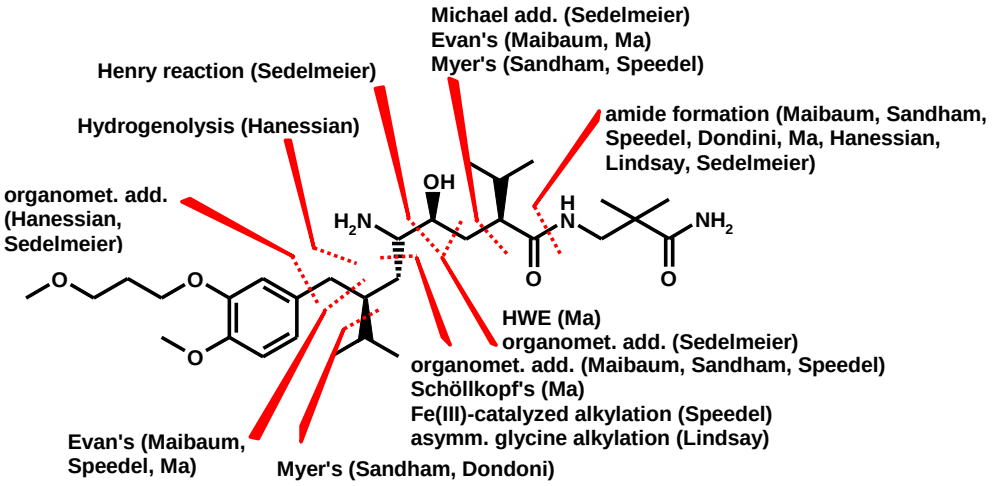


Figure 50[127]**:** Previous strategies of the synthesis of Aliskiren

The first reported synthesis[128] afforded Aliskiren **1** with poor stereoefficiency in more than 25 steps and required multiple chromatography preparations, making it not convenient for a large scale production.

The first multikilogram scale route[129] to Aliskiren **1** focused on synthesis of the key intermediate **2** of Figure 51, bearing already the *syn*-configurated 1,2-amino alcohols and 2,7-diisopropyl groups, the stereoselectivity being introduced by the use of Evans' methodology to prepare compound **3**.

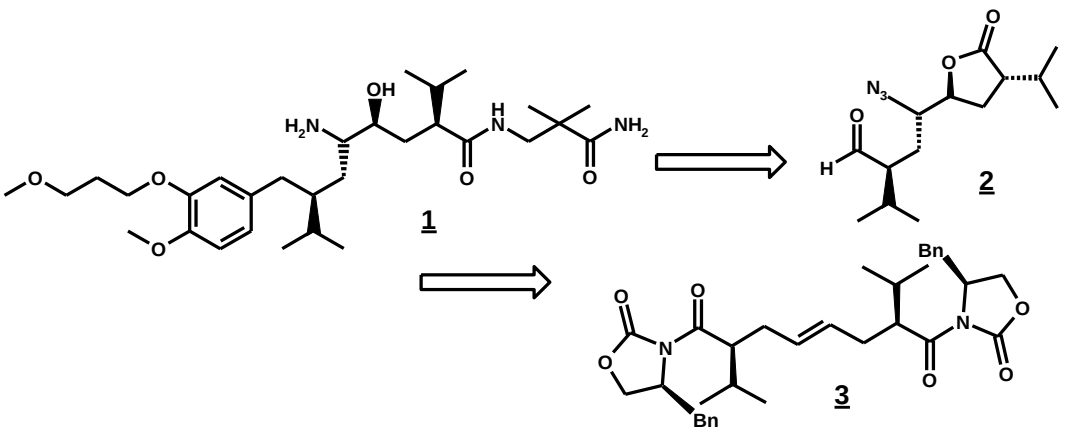


Figure 51: First multikilogram scale strategy for the synthesis of Aliskiren

An alternative and elegant version of the first industrial process was reported[130] a few years later, allowing the production of Aliskiren in a cost effective process. This new strategy involved innovative key steps, such as the nickel catalyzed trans-selective cross coupling alkenylation of the Grignard reagent of **4**, the bromolactonisation of **5** performing with high regio- and stereoinduction, and the transformation of **6** to **7** proceeding under complete regio- and stereocontrol with double inversion of the absolute configuration (Figure 52).

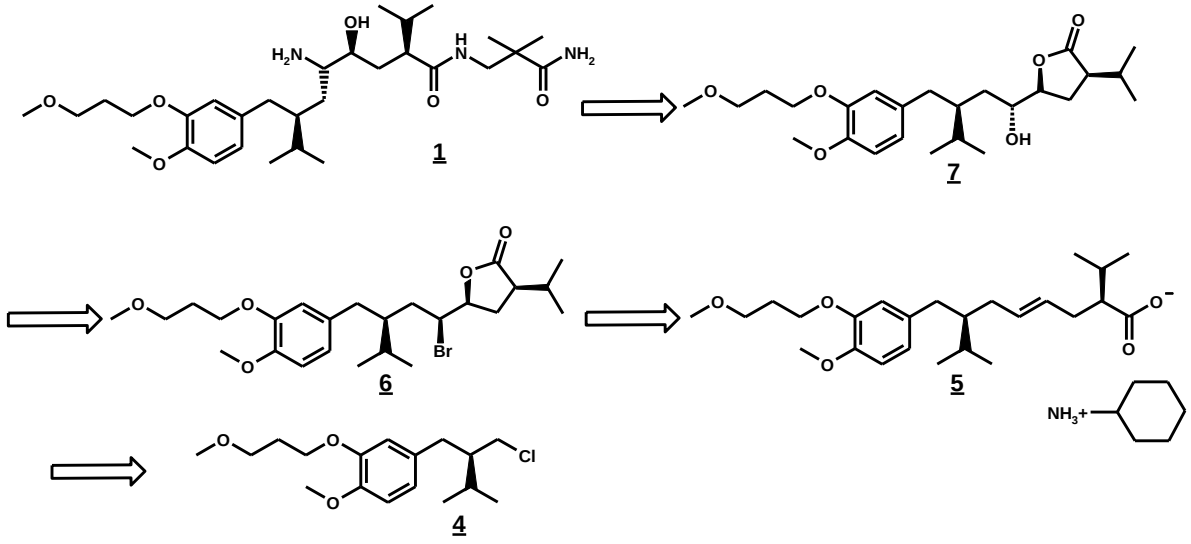


Figure 52: First large scale strategy for the synthesis of Aliskiren **1**

Many innovative routes have been investigated later to access the unique chemical structure of Aliskiren on a production scale[131].

We will present two synthetic routes to access two key intermediates of Aliskiren (Figure 54 and Figure 55), the C8 lactam-lactone **15** and C8 lactone **9**, by introducing the required stereo configuration of Aliskiren *via* metal catalyzed and organocatalytic asymmetric reactions, using the work reported in 2007 and 2008 by Sedelmeier[131i,j].

III. Novel successful alternative synthesis

III.1. Introduction

This work will report two different asymmetric strategies based on metal catalytic Henry reaction and organocatalytic Michael addition (Figure 53). Other alternative strategies for the preparation of some potential intermediates will be also described later.

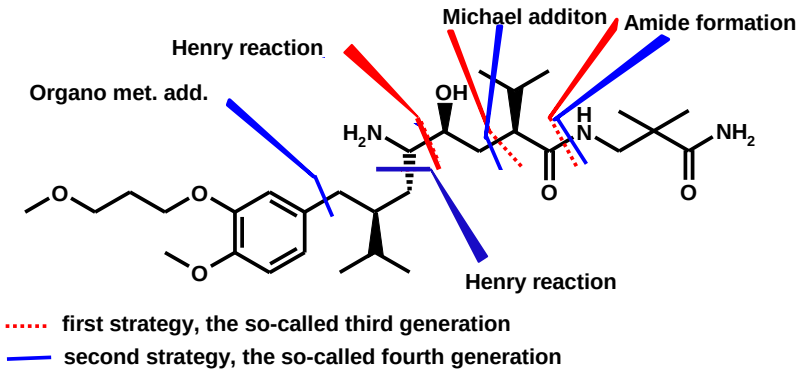


Figure 53: Key bond formation of both strategies for the synthesis of Aliskiren

Both strategies are based on the preparation of the following common C4 intermediate, the so called "Nitroalcohol A" **8** and the C8 lactone intermediate **9** (Figure 54), *via* two different pathways.

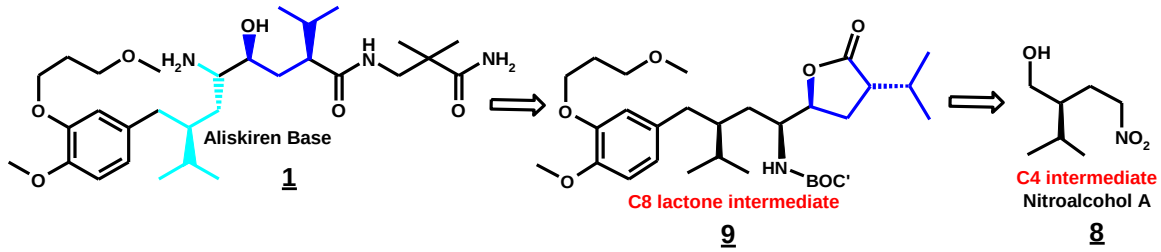


Figure 54: Retrosynthetic study of Aliskiren

The first synthesis involved the convergent approach published by Sedelmeier in 2008[131j], where the key "nitro compound A" **8** is obtained (as shown in Figure 55) *via* trimethylsilyl diphenylprolinol ether catalyzed Michael addition of nitroethylene to isovaleraldehyde. It is converted after protection of the alcohol moiety into its aldehyde analogue **12** via an oxidative Nef reaction. Both reagents react then together *via* a metal catalyzed asymmetric *syn*-selective Henry reaction to yield the corresponding γ-*syn*-nitroalcohol derivative **14**, bearing already all the *syn*-configurated functionalities of Aliskiren. The lactam-lactone intermediate **15** can be obtained as described in the Sedelmeiers[131i,j] process by TEMPO and bleach oxidation after deprotection of the hydroxyl group, reduction of the nitro group to amino unit and protection/activation of the amino group with a Boc unit. The resulting lactam moiety can then be selectively opened by the corresponding aryl lithium derivative or Grignard reagent thanks the introduction of the Boc group as an activating group at the lactam nitrogen. Saponification of the lactone moiety and reduction of the carbonyl group (or reverse process) and subsequent hydrogenolysis allow the formation of the appropriate carboxylic acid derivative, that can be converted to Aliskiren base **1** under classical peptide reaction conditions.

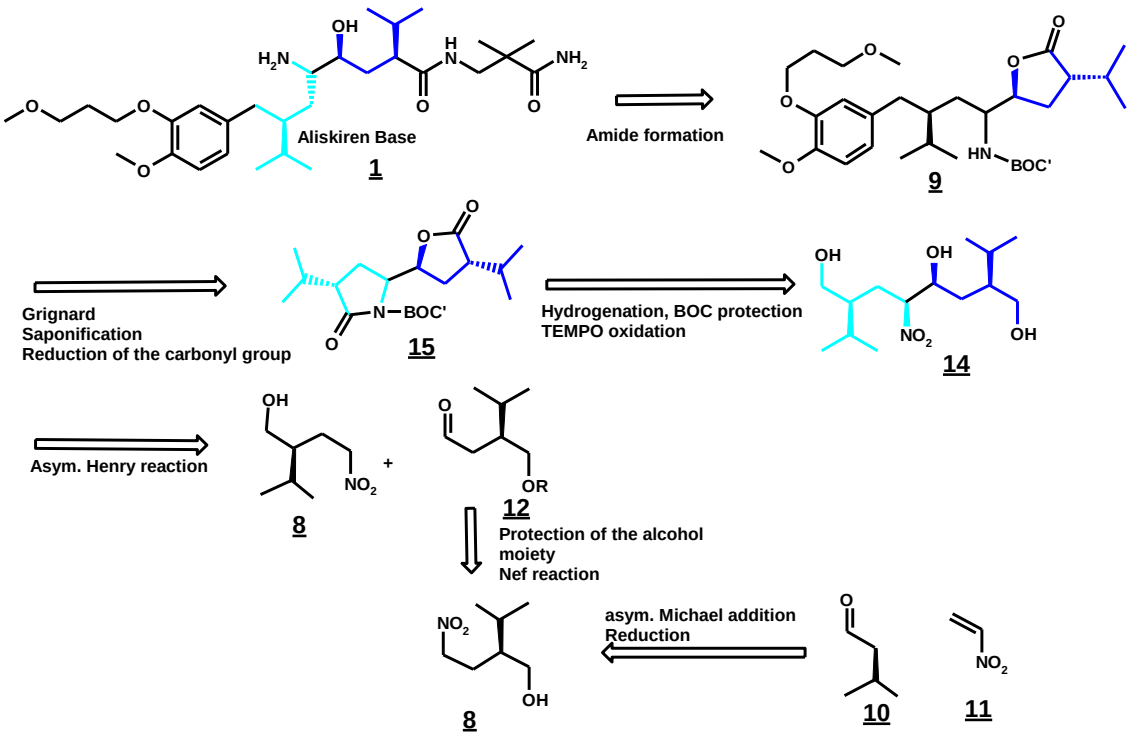


Figure 55: Retrosynthetic study of the preparation of **1** via the novel intermediates **12** and **14**

The second process is represented in Figure 56, involved also as key reaction step a ligand-metal based catalyzed asymmetric *syn*-selective Henry reaction to afford the Henry Product **18** from the novel nitro compound **17** and the already described aldehyde **12**. The challenge in the preparation of **59** from the corresponding alcohol **62**, is to retain the stereochemistry of the isopropyl group of **62** during the oxidation step. The major benefit of this synthesis is to afford Aliskiren base **1** in a short route, which can be developed into a process whose costs are acceptable.

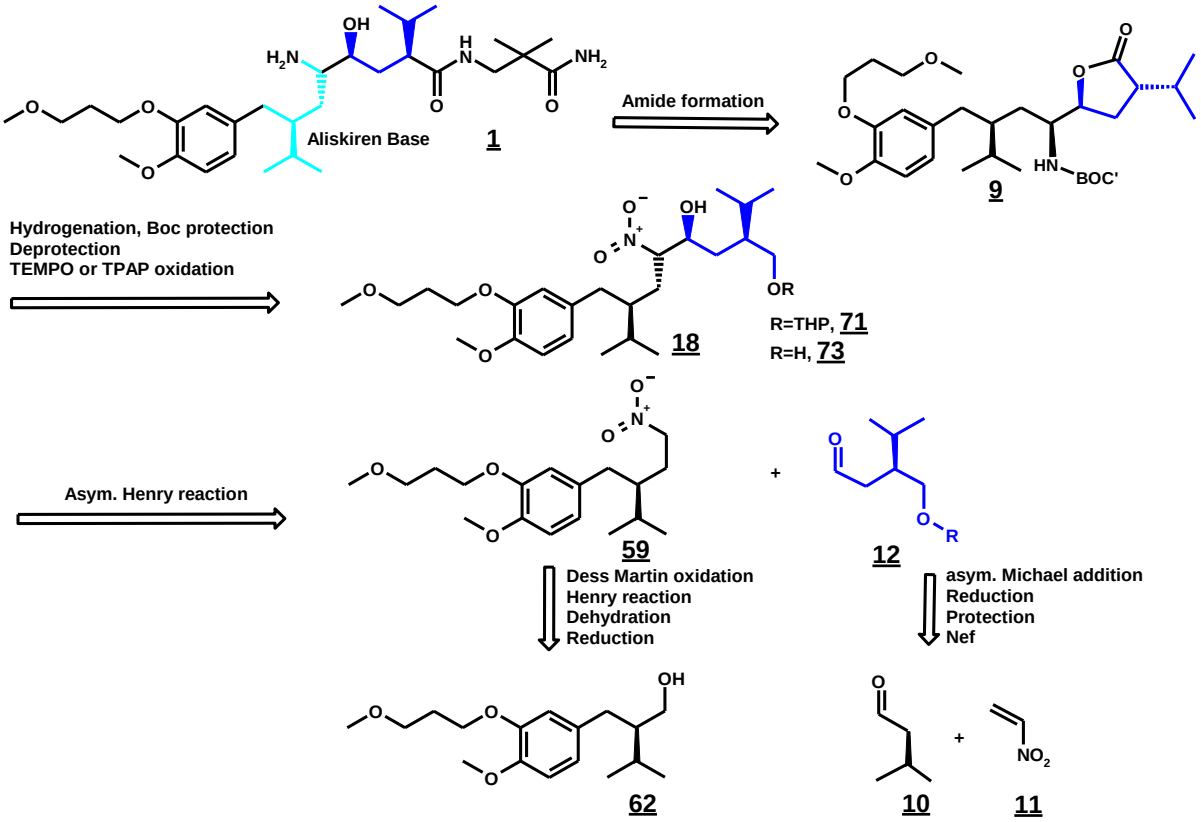


Figure 56: Retrosynthetic study of an alternative process for the preparation of Aliskiren

III.2. Preparation of the Aliskiren precursor 8 *via* enamine or iminium ion catalyzed enantioselective Michael addition

III.2.1. Introduction: the actual process

The first synthesis of the γ-nitro alcohol derivative **8** was reported in 2007 by Sedelmeier [131j]. It is prepared *inter alia* by an efficient organocatalytic Michael addition of nitroethylene to isovaleraldehyde, *via in situ* formation of an enamine intermediate with a proline derived catalyst. The subsequent *in situ* reduction of the generated aldehyde derivative with sodium borohydride allows the isolation of the key intermediate "nitroalcohol A" in good yield and with an excellent enantiomeric excess of 96% (Figure 57).

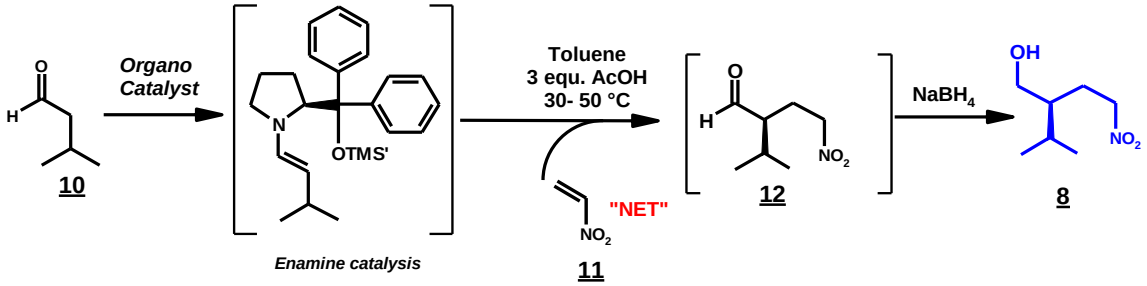


Figure 57: Actual process for the preparation of **8** *via* enamine catalysis

In spite of the high efficiency of this process, one drawback is the necessity of preparation and handling of large amounts of nitroethylene. We report here two novel methodologies to prepare **8** from isovaleraldehyde **10** avoiding the utilization of nitroethylene.

III.2.2. Novel alternative procedures

A wide range of procedures[1] are available in the literature for the enantioselective preparation of γ nitro alcohol derivatives *via* Michael addition, involving efficient ligand-metal complexes based catalyzed and organocatalyzed methodologies. We limited however our approach to the utilization of organocatalytic methods, involving enamine and iminium ion activation of the substrates with O-trimethylsilyl diphenyl prolinol ether **I** as catalyst, as represented on Figure 58.

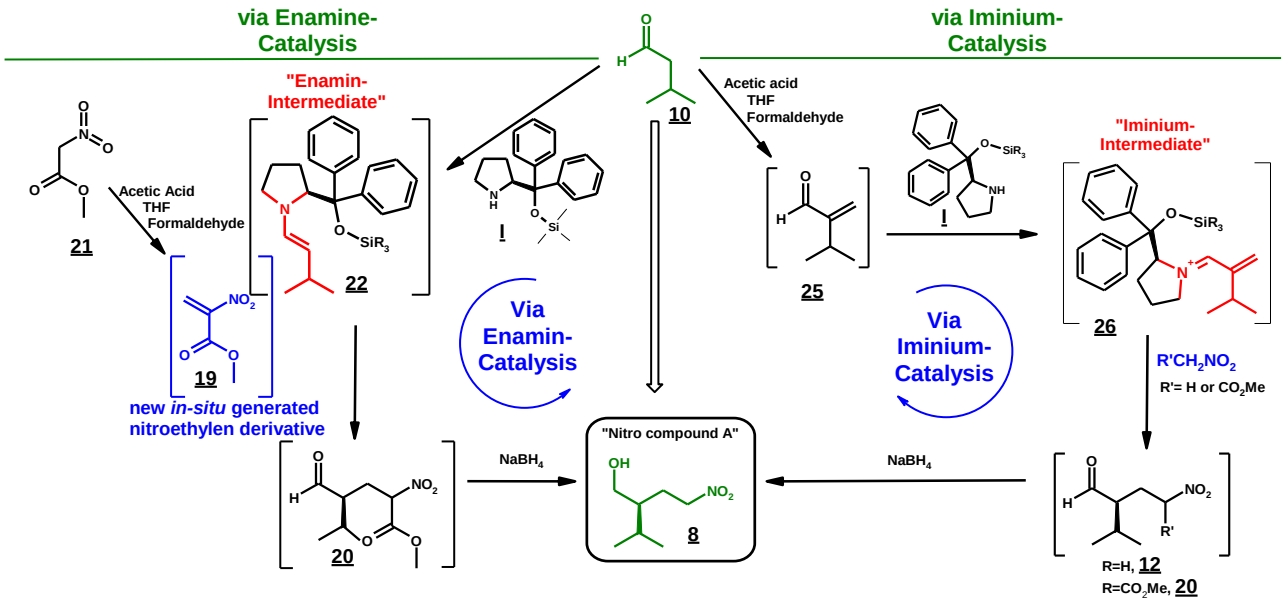


Figure 58: New processes to „Nitro alcohol A“ **8** via enamine and iminium ion intermediates **22** and **26**

Compound **8** will be thus prepared: 1) *via* the asymmetric Michael addition of an *in situ* generated α-substituted 2-Nitro-acrylic derivative **19** to isovaleraldehyde, *via* the formation of an enamine intermediate **22**, and 2) *via* the organocatalytic Michael addition of nitromethane or related derivatives to (*in-situ* generated) isopropylacroleine **25**, via the formation of the iminium ion intermediate **26**.

[1] see chapter 1

III.2.3. Enamine catalyzed Michael addition of isovaleraldehyde to nitroalkene derivatives

III.2.3.1. Introduction

In this first approach, a muticomponent OTMS-diphenyl prolinol ether **I** catalyzed Michael addition of isovaleraldehyde to the *in situ* generated nitroethylene derivative was envisaged (Figure 59), applying the conditions described by Sedelmeier and co-workers[131j], who performed the Michael addition of isovaleradehyde to nitroethylene in toluene in the presence of small amounts of the catalyst (2% mol.) and 2 equivalents of acetic acid (Figure 59). The advantage of the new process is the *in situ* preparation and immediate consumption of an highly reactive α-ester substituted nitroethylene reagent **19** through the condensation of the commercially available and safe nitro ester derivative **21** to aqueous formaldehyde. This process prevents the handling and use of risky intermediates.

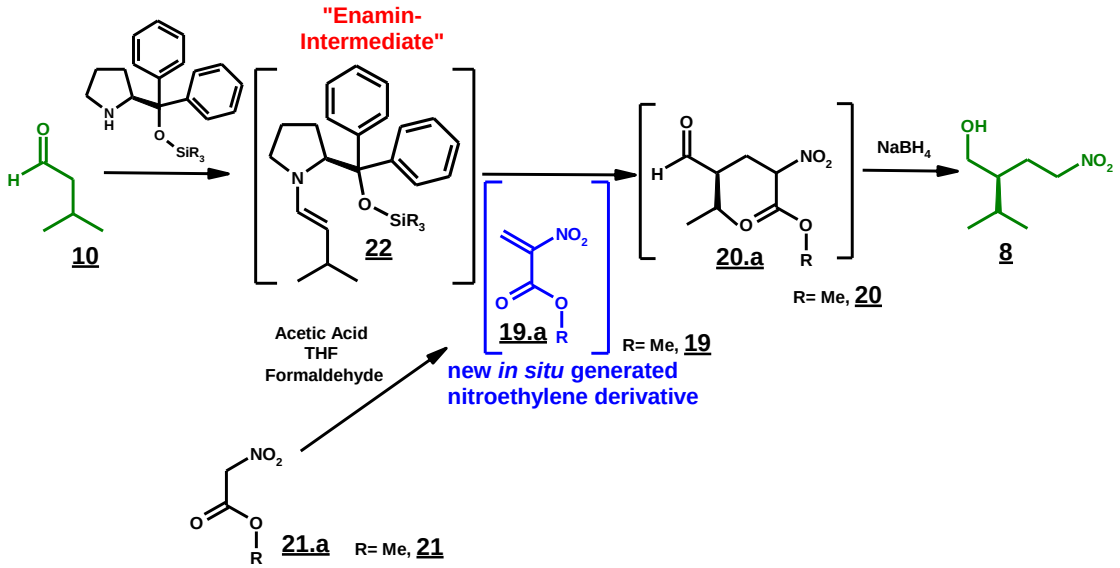


Figure 59: Enamine strategy

III.2.3.2. Results and discussion

III.2.3.2.1. Preparation of nitroethylene analogue

In a first study, we proved the possibility of formation of the nitroethylene analogue **19** under the Michael addition conditions published by Sedelmeier, by Knoevenagel condensation of commercially available and safe nitroacetate (1 equivalent) to aqueous formaldehyde[132] (1 equivalent) in the presence of acetic acid (3 to 5 equivalents) in THF at 40°C. The use of acetic acid appears to serve two functions: facilitating dehydration of the intermediate nitroaldol[133] and activation of the enamine process.

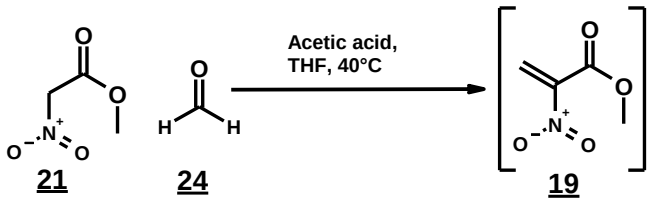


Figure 60: The „*in situ*"- synthesis of 2-nitro-acrylic acid methyl ester **19**

During the process, in the reaction mixture, only the existence of nitro acetate 21 was detected, the nitroethylene intermediate 19 being immediately consumed in the Michael addition. According to the DSC measurement (Figure 61) of commercially available nitro acetate 21, which revealed a decomposition start point at 150-160°C, the process is a safe alternative procedure.

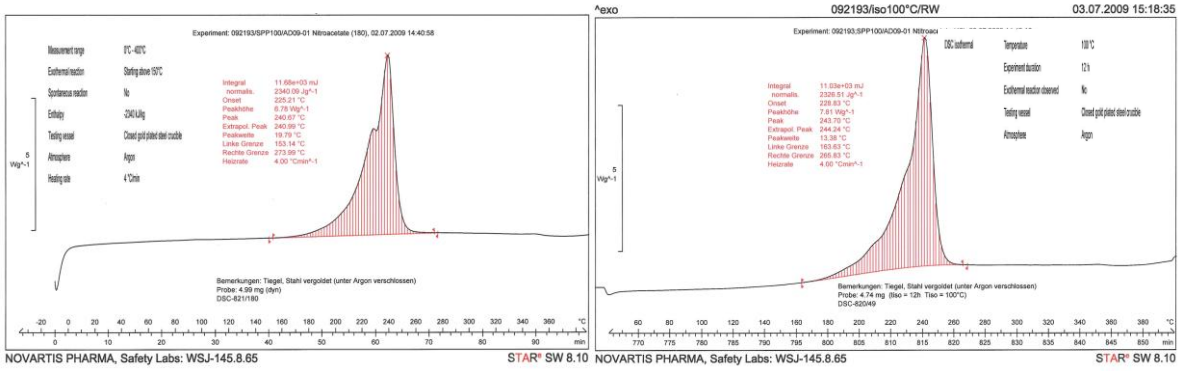


Figure 61: Dynamic and thermic DSC measurements of commercially available compound **21**

The *in situ* generated β-nitro acrylic ester should then react with isovaleraldehyde to form the desired aldehyde compound **20** (Figure 59).

III.2.3.2.2. Enamine formation

In order to prove the viability of the enamine process, we studied the *in situ* formation of **22**, generated from the condensation of isovaleraldehyde and OTMS diphenyl prolinol **I**. In a general procedure, an equimolar amount of aldehyde and catalyst (1.0 mmol scale) are dissolved in 0.75 mL d6-DMSO. ^{1}H NMR spectra in d_6-DMSO after 5 min revealed the presence of the characteristic signals[134] of the enamine: a *doublet* at δ 6.17-6.21 ppm with a coupling constant of *ca* 13.8 Hz attributed to the vinylic proton α to the nitrogen and at δ 3.79-3.84 ppm (^{3}J = 13.8 Hz) corresponding to β-vinylic proton. Based on NMR analysis, the enamine **22** is formed after 5 minutes at room temperature with a conversion of 75 % with a ratio *E*- and *Z*-enamine > 99:1, the only detectable product being the E-enamine (Figure 63).

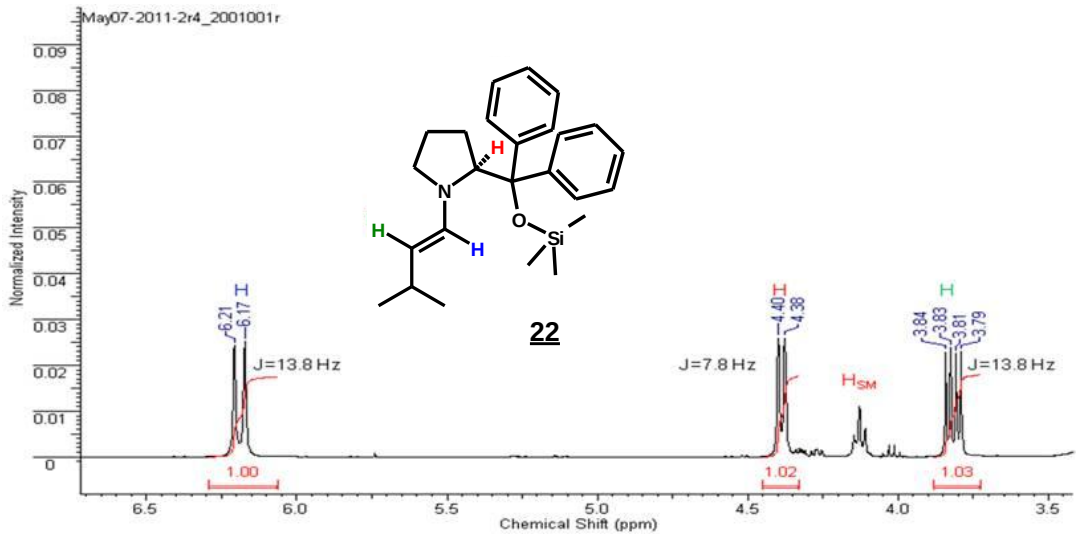


Figure 62: E-enamine formation. NMR study performed on a 1.0 mmol scale with 1 equivalent of catalyst and 1 equiv. of isovaleraldehyde in 0.75 mL DMSO-d^6- Analysis after 5 min, $C_{conversion}$= 75%

In order to prove the formation of the enamine **22** under reaction conditions of the Michael addition, an equimolar amount of aldehyde and catalyst (1.0 mmol scale) was mixed in THF at 35°C. NMR analysis (^{1}H, d_6-DMSO) revealed the formation of the enamine **22** after 20 minutes at room temperature with a conversion of 56 % and in a ratio of *E* and *Z*-enamine > 99:1, the only detectable product being the stable E-enamine (Figure 63).

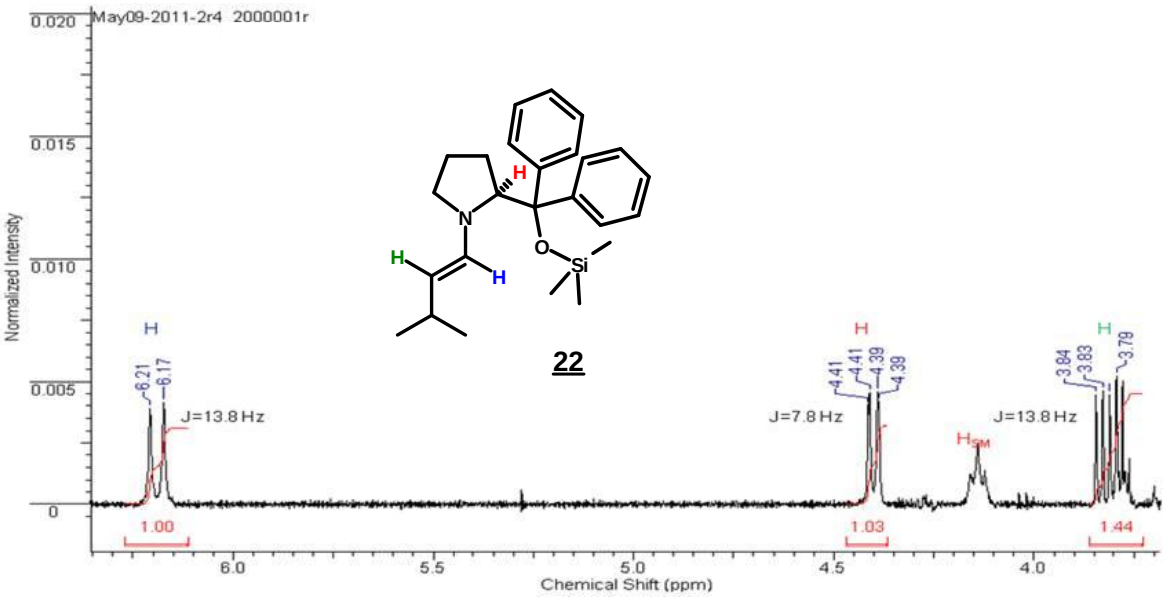


Figure 63: E-enamine formation. reaction was performed on a 1.0 mmol scale with 1 equivalent of catalyst and 1 equiv. of isovaleraldehyde in 1 mL THF at 35°C - DMSO-d^6 NMR Analysis after 20 min, $C_{conversion}$=56%

After two days in d_6-DMSO, we observed the coherent[134] formation of the oxazolidine **23**, resulting from the desilylation of **22**. **23** was also prepared by mixing an equimolar amount of aldehyde and diphenylprolinol in d_6-DMSO (Figure 64).

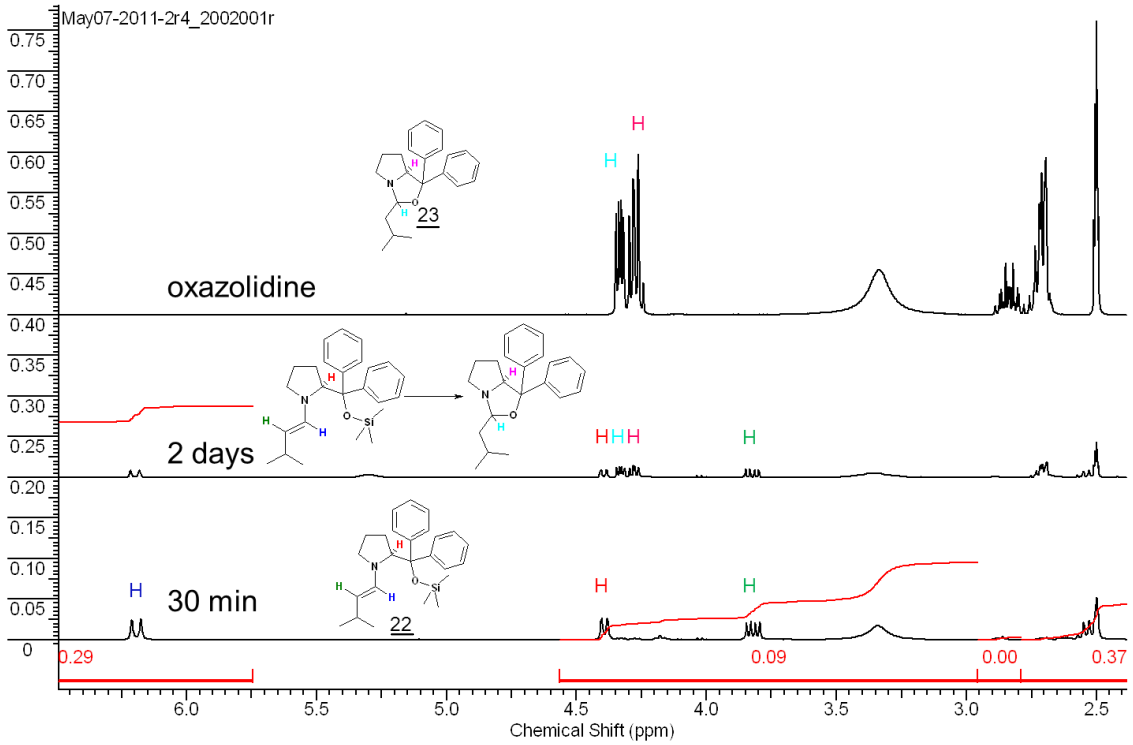


Figure 64: E-enamine formation. NMR study was performed on 1.0 mmol scale with 1 equivalent of catalyst and 1 equiv. of isovaleraldehyde in 0.75 mL dmso-d^6. The oxazolidine **23** was prepared at 1.0 mmol scale by mixing 1 equivalent of diphenylprolinol and 1 equiv. of isovaleraldehyde in 0.75 mL DMSO-d^6

III.2.3.2.3 Synthesis of the (S)-Aliskiren precursor 8 *via* organocatalyzed enantioselective Michael addition

We performed the OTMS diphenylprolinol ether **I** organocatalyzed Michael addition of isovaleraldehyde with the *in situ* generated nitroethylene derivative **19**, by adding simultaneously at 35°C an equimolar ratio of an aqueous solution formaldehyde (*ca* 37%) and nitroacetate **21** to a mixture of isovaleraldehyde (1.0 equivalent) , organocatalyst **I** (15%) and acetic acid (3.6 equivalents) in THF (Figure 65). The *in situ* formed nitroethylene analogue **19** reacted very fast (within 30 min) with the enamine, generated *in situ* by condensation of the proline related catalysts and isovaleraldehyde **10** to form the corresponding aldehyde intermediate **20**, with a diastereomeric ratio ((S,R) *versus* (S,S)) of 63:37 (^{1}HNMR analysis). Subsequent reduction of the aldehyde intermediate **20** with sodium borohydride (1.1 equivalents) after neutralization to pH=7 by addition of an aqueous solution of sodium hydroxide (2M) provided the desired nitro compound **8** with 66% yield and an enantiomeric excess of 96% (measured by chiral HPLC with a CHIRALPAK AD-H column at 205.5 nm). The reduction step can also be performed by addition of $NaBH_3OAc$ (15 equivalents) after neutralization to pH=7 with aqueous sodium hydroxide (2M) yielding **8** with an enantiomeric excess of 90%. The Michael addition and reduction steps were conducted in one-pot sequential mode to avoid racemization on the α-position of the aldehyde moiety of **20**.

To explain the formation of **8**, we postulated that, under the slightly basic reaction conditions of the borohydride reduction, the aldehyde intermediate **20** is saponified and the nitro carboxylic acid easily decarboxylated to afford the desired chiral nitroalcohol **8**.

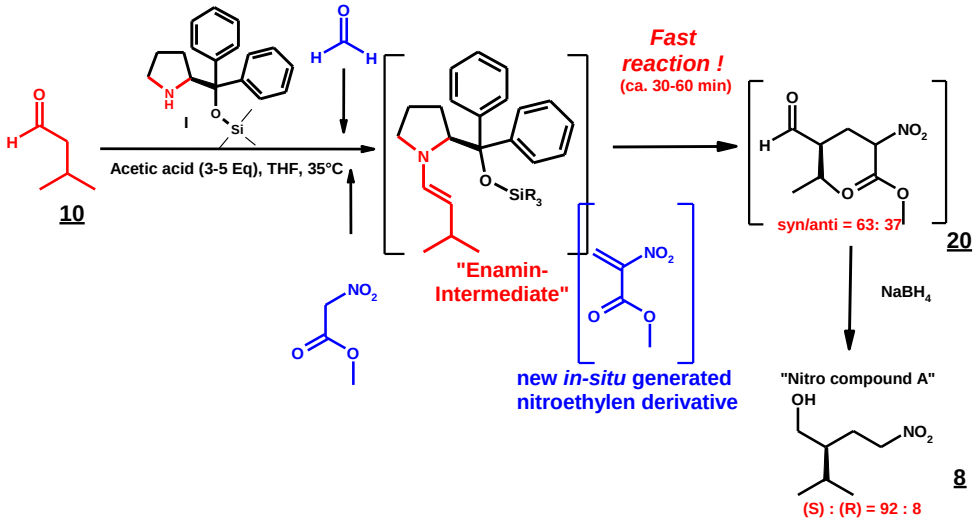
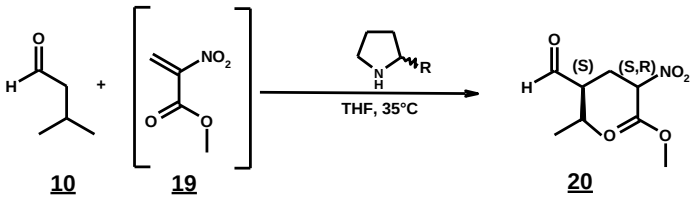
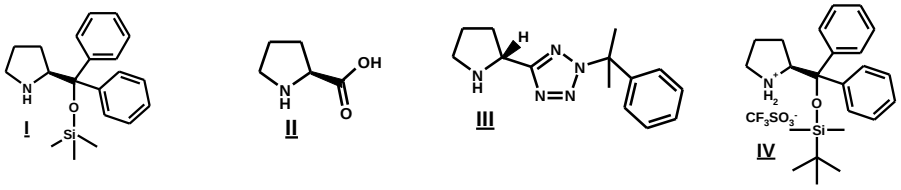


Figure 65: Synthesis of nitrocompound **8** *via* the formation of intermediate **20**

III.2.3.2.4. Screening of catalysts for the Michael addition of isovaleraldehyde to the α-substituted nitroethylene derivative 19

A selection of proline related catalysts was tested at 35°C (Table 2) to evaluate its influence on the stereoselectivity of the reaction.





Entry	1	2	3	4
Reaction conditions	a	a	a	b
(SS:SR) ratio measured by ^{1}H NMR on aldehyde intermediate	63:37	62:38	52:48	No conversion

Table 2: Screening of diverse catalysts-reaction conditions: reactions performed a) with isovaleraldehyde (1 eq.), nitroacetate (1 eq.), formaline (1 eq.), selected catalyst (15%), acetic acid (3.6 eq.) in THF at 35°C b) with isovaleraldehyde (1 eq.), nitroacetate (1 eq.), formaline (1 eq.), selected catalyst (15%), in THF, at 35°C

The L-proline **II** catalyzes the reaction affording moderate diastereoselectivity in the same range as the (S)-diphenyl prolinol silyl ether **I**, while its triflate salt **IV** doesn't perform any reactions (Table 2,

Entry 4). The tested catalyzed Michael addition performing under acidic conditions, the acid form of **IV** was tested without addition of any acidic additive (Table 2, Entry 4).This result seems to be in accordance with the data collected by Seebach *et al*, who tested a wide range of additives with pKa values (in water) from 0.7 to 10.2 in (S)-diphenylprolinol silyl ether **I** catalyzed Michael additions, and proved the direct correlation between the pKa value of the additive and the reaction efficiency, the most effective pKa value being around 7 [105].

The (R)-5-pyrrolidine-2-yltetrazole catalyst **III** affords **20** without any diastereoselectivity under the described reaction conditions.

III.2.3.2.5. Some drawbacks and advantages of the reaction

The utilization of (S)-diphenyl prolinol silyl ether **I** in THF at 35°C in combination with acetic acid are suitable conditions for the highly enantioselective Michael addition of isovaleraldehyde to nitroalkene **19**, *via* the activation of the aldehyde partner **10** by the formation of the enamine intermediate **22**. Nevertheless, under the same conditions, **22** can also perform aldolization reactions in the presence of formaldehyde **24** to afford the α,β-unsaturated aldehyde **25** (Figure 66). When an excess of formalin **24** was used to perform the Knoevenagel step, or when both, nitroacetate **21** and formalin **24** were not added concomitantly (resulting in an excess of **24** in the reaction mixture), we observed indeed the competitive formation of the 2-isopropylacroleine **25**, resulting in the consumption of isovaleraldehyde. Under our experimental conditions, self aldolization of aldehyde **10** was not detected, in accordance with the literature[135].

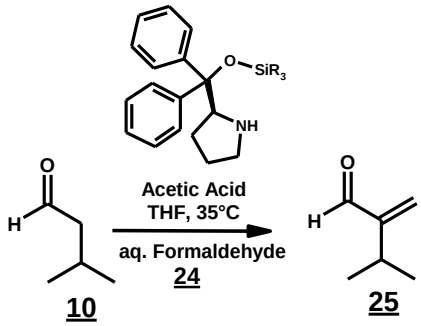


Figure 66: *In situ* formation of 2-isopropyl acroleine **25**

While the formation of **25** can be regarded as a major drawback of the process, yielding in the consumption of the starting material **10**, it can also be considered as a starting point for the development of a new methodology based on a multicomponent domino aldolisation-Michael[136a-c] addition sequence for the enantioselective preparation of the Aliskiren precursor **8**. Methodologies were indeed reported in the literature for the preparation of chiral γ-nitro aldehyde derivatives via enantioselective Michael addition of nitromethane or substituted nitroalkanes to α,β-unsaturated aldehydes[2].

[2] About enantioselective Michael addition of nitro methane or substituted nitroalkanes to α,β-unsaturated aldehydes: see Chapter 1 and references cited

III.2.3.2.6. Conclusion

We proved that the building block **8** could be rapidly prepared with good yield and enantioselectivity under safe and controlled reaction conditions *via* the use of 2-nitro-acrylic acid esters (as **19**). The advantage of this procedure is the possibility of its application on large scale and potentially as a continuous flow process.

III.2.4. Michael addition of nitromethane to 2-isopropyl acroleine 25 catalyzed by diphenylprolinol silyl ether I

III.2.4.1. Introduction

Several groups[136] have reported the utilization of diphenylprolinol silyl ether as catalyst for the reaction of nitromethane to α,β-unsaturated aldehydes, affording the desired Michael adducts with excellent yields and enantioselectivities. In all cases, the presence of an acid (benzoic acid, Hayashi[136b], Wang[136c]) or a base (LiOAc, Wang[136a]) as co-catalyst was required to perform the reaction. Benzoic acid is incorporated to assist the formation of the iminium ion intermediate, while the use of LiOAc promotes the formation of a more reactive nitronate nucleophile. Palomo *et al*[137] demonstrated the possiblity to perform the reaction in water.

We hoped that addition of nitromethane or nitro-acetic acid methyl ester **21** to a mixture of 2-isopropyl acroleine **25**, diphenylprolinol silyl ether **I** in the presence of a selected additive (see Table 3) and subsequent *in situ* reduction of generated Michael product, would afford the (S)-Aliskiren precursor **8** with good enantioselectivity (Figure 67).

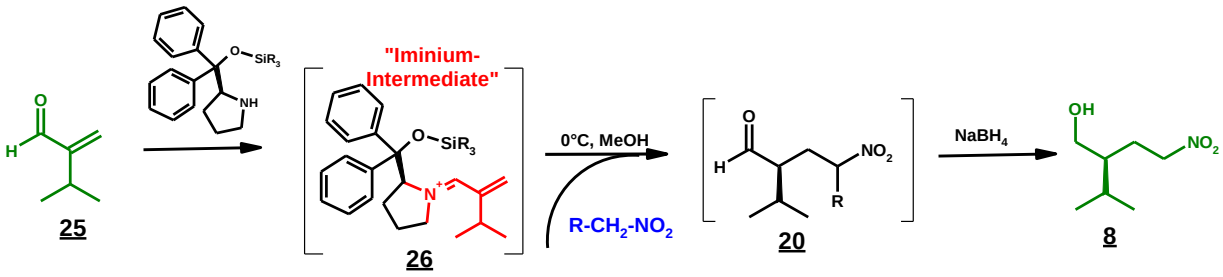


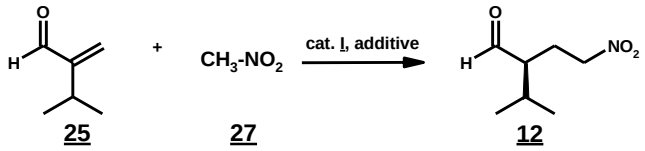
Figure 67: Preparation of **8** by Michael addition of nitromethane or related derivatives to the enone **25**, *via* the formation of an iminium ion **26**

III.2.4.2. Results and discussion

III.2.4.2.1. Addition of nitromethane to the α-substituted enone 25

A selection of acid and base additives was screened in an appropriate solvent (in most of the cases, an alcoholic solvent). The reactions were performed on a 0.5 mmol scale by adding 2 equiv. of nitromethane **27** at 0°C or 25°C to a solution containing one equivalent of **25**, 10% catalysts **I** and the

selected additive. The enantiomeric ratios (Table 3) of **12** were determined by chiral HPLC using CHIRALPAK AD-H column and were, after the *in situ* subsequent reduction of **12** to **8**, confirmed with the literature data[131j].



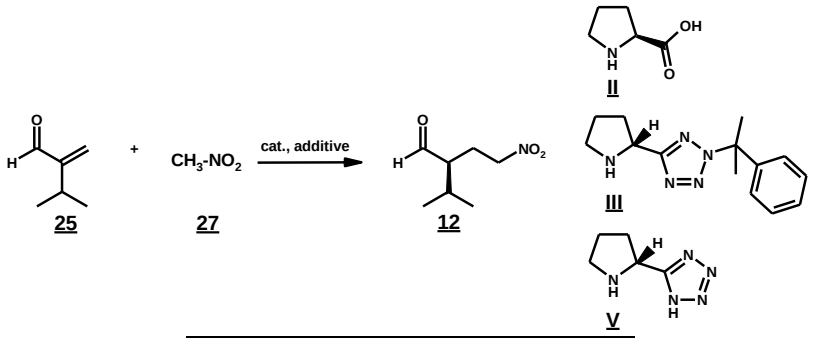
25 **27** **12**

	Catalyst	Additives	Solvent	Temperature	% **12** (%area)	ee (%)
1	-	DBU	DCM	rt	100 (2h)	0
2	-	NaOEt, 21%EtOH	EtOH	rt	degradation	-
3	-	Tetramethylguanidine	THF	rt	100 (2h)	0
4	10%	Benzoic Acid	MeOH	0°C	19 (4d)	64
5	2 eq.	Benzoic Acid	MeOH	0°C	24 (4d)	64
6	10%	LiOAc	MeOH/DCM	rt	17 (4d)	0
7	10%	AcOH	MeOH	0°C	1 (4d)	80
				rt	10 (24h)	66

Table 3: Screening of a selection of additives. Reactions were performed on a 0.5 mmol scale with the desired amount of catalyst **I** at 0°C or 25°C (rt) and 2 equiv. of nitromethane in appropriate solvent. Enantiomeric excesses (ee) were determined by HPLC using a CHIRALPAK AD-H column and compared with literature data. Conversion rate was determined by reverse phase HPLC.

Contrary to the high enantioselectivity observed by Wang[136a], the use of lithium acetate as co-catalyst in a mixture of methanol/dichloromethane performs the Michael addition with low rate and no enantioselectivity was observed (Table 3, Entry 5). Activation of the Michael donor *via* the formation of a more reactive nitronate species was also tested by introduction of a selection of bases (Table 3, Entry 1-4,6) and afforded the nitroaldehyde **12** within a short reaction time, but as racemic mixture (Table 3, Entry 1-4). The utilization of benzoic acid and acetic acid as additives in methanol at 0°C, affords the (S)-Michael product with satisfactory enantioselectivities (ee up to 80%) with low conversion. Subsequent *in situ* reduction of the aldehyde intermediate **12** provides the (S)-Aliskiren precursor **8** with an enantiomeric excesses of 32% up to 70%.

A selection of proline related catalysts was tested to evaluate the influence of the catalyst on the rate and selectivity of the reaction (Table 4). The reactions were performed on a 0.5 mmol scale in MeOH at 0°C and then at 25°C using 10% of the selected catalyst, in the presence of 2 equiv. of nitromethane and 10% of benzoic acid.



	Catalyst	%**12** (%area) (2.5d, 0°C)	%**12** (%area) (24h, 25°C)	ee (%)
1	**I**	-	0.5	-
2	**IV**	-	0.2	-
3	**V**	1.3	1.3	42

Table 4: Screening of a selection of catalysts. Reactions performed on a 0.5 mmol scale with 10% of the selected catalyst at 0°C and then at 25°C, in the presence of 2 equiv. of nitromethane, 10% of benzoic acid in MeOH. Enantiomeric excess (ee) was determined by HPLC using a CHIRALPAK AD-H column and compared with literature data. Conversion rate was determined by reverse phase HPLC.

(S)-proline **I**, and (R)-5-pyrrolidin-2-ylcumyltetrazole **IV** were ineffective in performing the Michael addition of nitromethane to 2-isopropylacroleine **25** affording the aldehyde **12** with unsatisfactory conversion rate (Table 4, Entry 1-2). It should be noted that the (R)-5-pyrrolidine-2-yl tetrazole **V** afforded the nitro aldehyde **12** with a satisfactory enantioselective excess of 42% but with a low conversion rate (Table 4, Entry 3).

III.2.4.2.2. Multicomponent domino aldolization-Michael sequence

An alternative process for the enantioselective preparation of **8** was envisaged using the more reactive nitro-acetic acid methyl ester **21** in a multicomponent domino aldolization-Michael reaction (Figure 68).

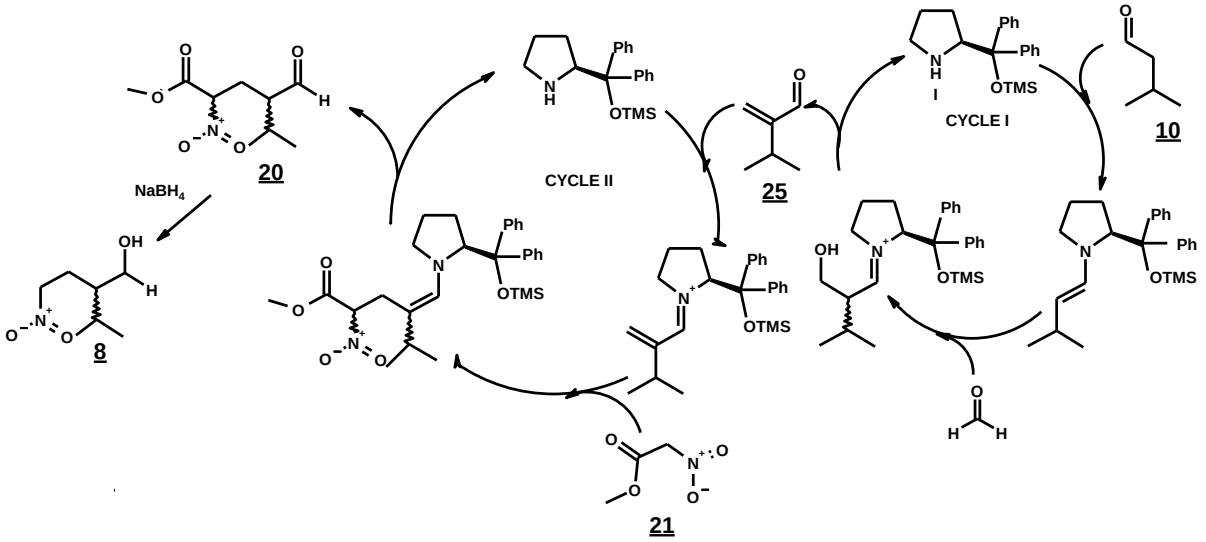


Figure 68: Multicomponent domino aldolization-Michael synthesis of the Aliskiren precursor **8**

^{1}H NMR studies were conducted in $CDCl_3$ in order to evaluate the potential of the sequence. An equimolar ratio of isovaleraldehyde and formaldehyde were mixed in THF at 35°C in the presence of 15% of OTMS diphenyl prolinol ether and 4.9 equivalents of acetic acid (Figure 66).

^{1}H NMR measurement (after 2h45) revealed the presence of the characteristic signals of the isopropyl acroleine derivative **25**: a *singulet* at δ 9.5 ppm attributed to the aldehyde proton and at 6.2 and 5.9 ppm corresponding to vinylic protons. The absence of the signal attributed to the proton of the aldehyde moiety of isovaleraldehyde **10** at 9.7 ppm proved the complete conversion after 2 hours 45 min of **10** to **25** (Figure 69).

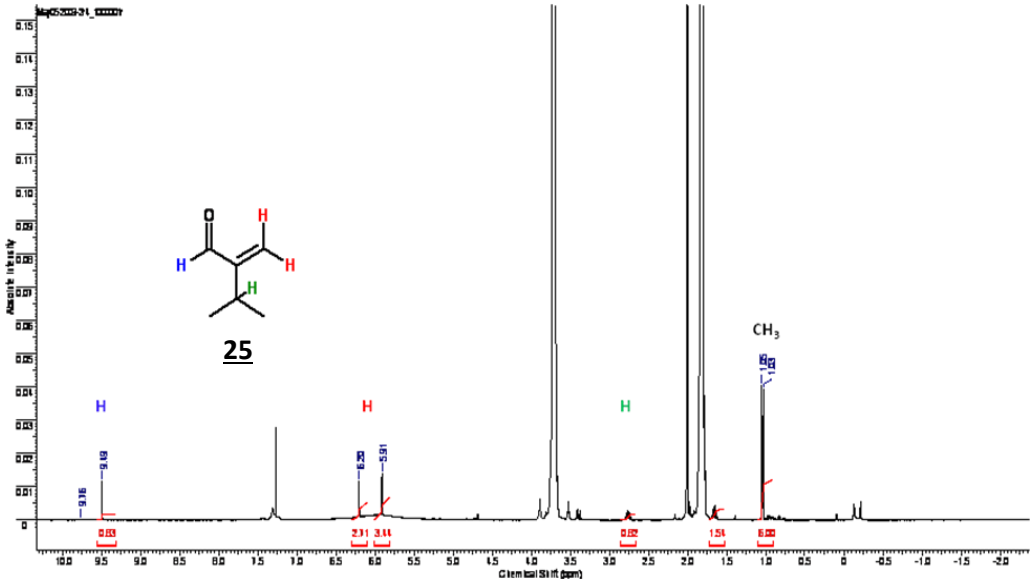


Figure 69: ^{1}H NMR ($CDCl_3$) of the reaction mixture after stirring over 2h45. Reaction performed on a 23 mmol scale with 15% of catalysts, 1 eq. of formalin and 1 eq. of isovaleraldehyde at 35°C in THF in presence of 4.9 eq. of acetic acid.

One equivalent of nitroacetate was then added at 35°C to the reaction mixture. ^{1}H NMR ($CDCl_3$) analysis of the reaction mixture after 2 hours, 18 hours and 48 hours revealed the presence of the characteristic signals of the aldehyde intermediate **20**: at 9.63-9.64 ppm attributed to the aldehyde proton and at 5.17-5.25 ppm for the proton in α-position to the nitro group (Figure 70). Integration of the signals characteristic of **20** and of the starting material **25** revealed the formation of 82% of **20** after two days.

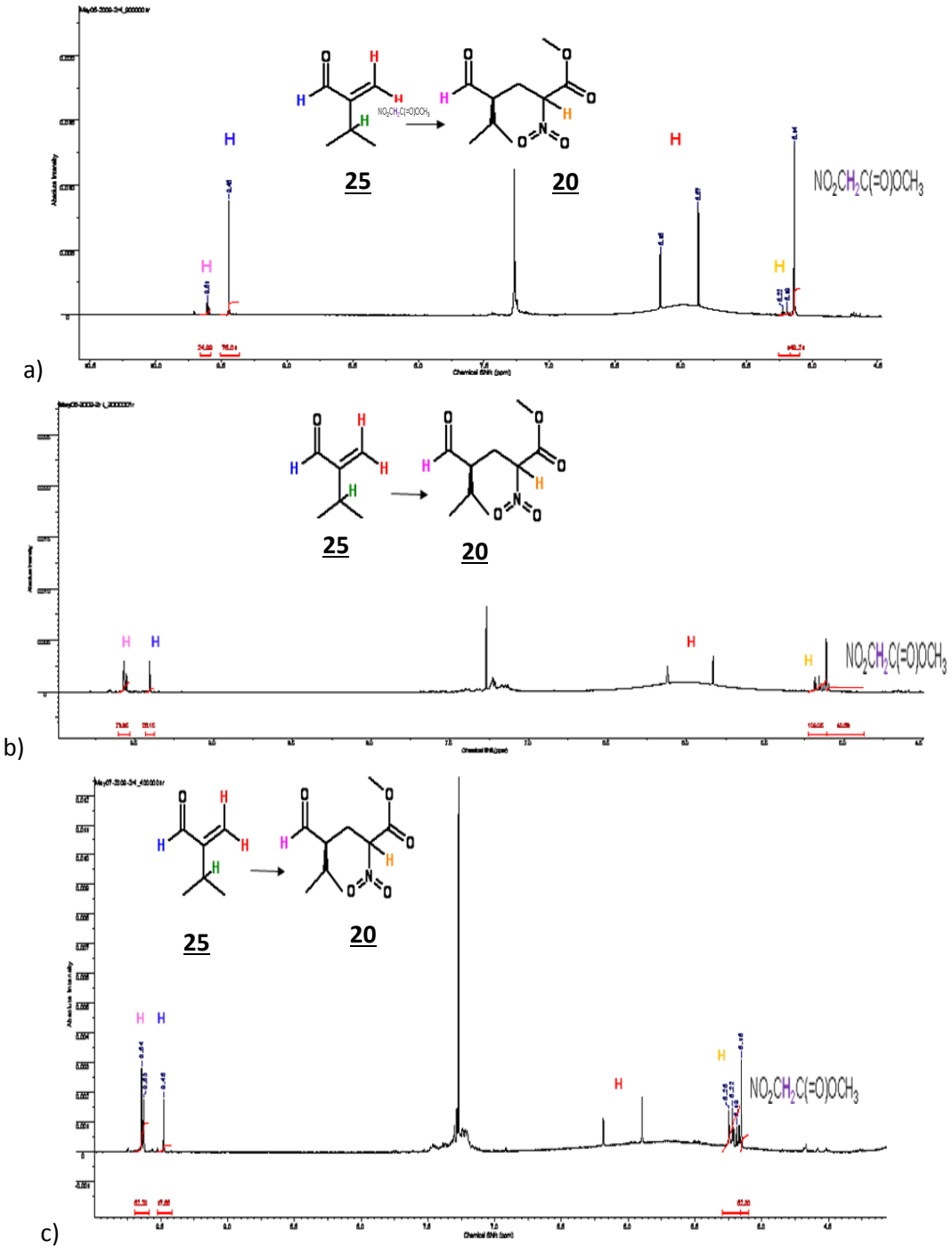


Figure 70: ^{1}H NMR ($CDCl_3$) of the reaction mixture after addition of 1 eq. of nitroacetate. a) after stirring over 2 hours b) after stirring over 18 hours c) after stirring over 48 hours

It is also important to note that the complete conversion of **10** to isopropyl acroleine **25** under the selected reaction conditions (the same as in the case of the preparation of **8** from isovaleraldehyde *via* diphenylprolinol silyl ether **I** catalyzed Michael addition) required the reaction mixture to be stirred over 2 hours 45 min. for the first step. The subsequent Michael addition with nitro-acetic acid methyl ester **21** was a very slow reaction, while the Michael addition of isovaleradehyde to the α-substituted nitroethylene analogue **19** was completed within 30-40 min. The aldolization-Michael pathway is thus not competitive to the enamine process during the 1.4 conjugate addition of

isovaleraldehyde to the *in situ* generated nitroalkene **19**. It only results in the consumption of the starting material.

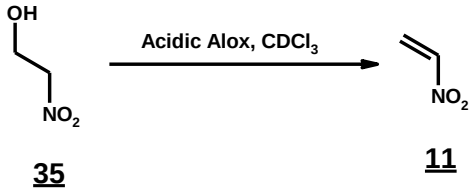
^{1}H NMR ($CDCl_3$) analysis of the reaction mixture revealed also the formation of **20** with a satisfactory (S:S) or (S:R) ratio of 63:37, comparable to the selectivity resulting from the enamine pathway.
The subsequent borohydride reduction of **20** was not performed, but according to the results obtained for the enamine pathway[3], the reaction should afford the (S)-Aliskiren intermediate **8** with moderate to good enantioselectivity.

III.2.4.3. Conclusion

The first reported results relative to diphenylprolinol silyl ether catalyzed 1.4 conjugate addition of nitromethane and of its α-substituted analogue to the α-substituted enal **25** allow us to envisage the possibility of an alternative enantioselective procedure for preparation of the (S)-Aliskiren precursor **8**, involving the activation of **25** *via* the formation of an iminium ion. A multi component domino approach, involving aldolization and Michael addition steps can also be regarded as a potential sequence leading to the desired precursor **8**, although the optimization of the reaction conditions is still required for its application to large scale production. We proved the possibility to produce the C4 nitro intermediate **8** *via* a new safe process.

III.2.5. Alternative procedure for the preparation of nitroethylene

In 1992 Ballini[138] reported the utilization of acidic Alox (Brockmann Activity I) for the dehydration of β-hydroxyl nitro compound into nitro olefin. Using the same reaction conditions, we envisaged to prepare nitroethylene by dehydration of nitroethanol **35** (Figure 71) and studied the reaction with the help of ^{1}H NMR analysis in $CDCl_3$.



35 **11**

Figure 71: Synthesis of **11** from nitroethanol **35**

One equivalent of nitroethanol **35** (0.9 mmol scale) was added in a sealed tube to a suspension of acidic Alox (Brockmann Activity I) and anhydrous magnesium sulfate in $CDCl_3$ and heated to 70°C. ^{1}H NMR ($CDCl_3$) analysis of the reaction mixture after 35 min and 1 hour 30 min. (Figure 72) revealed the presence of the characteristic signals of nitroethylene, at 5.6-5.9 ppm attributed to the vinylic proton in α-position to the nitro group, at 6.5-6.6 ppm and 7.0-7.2 ppm corresponding to the vinylic protons in β position.

[3] see Chapter 2, III.2.3

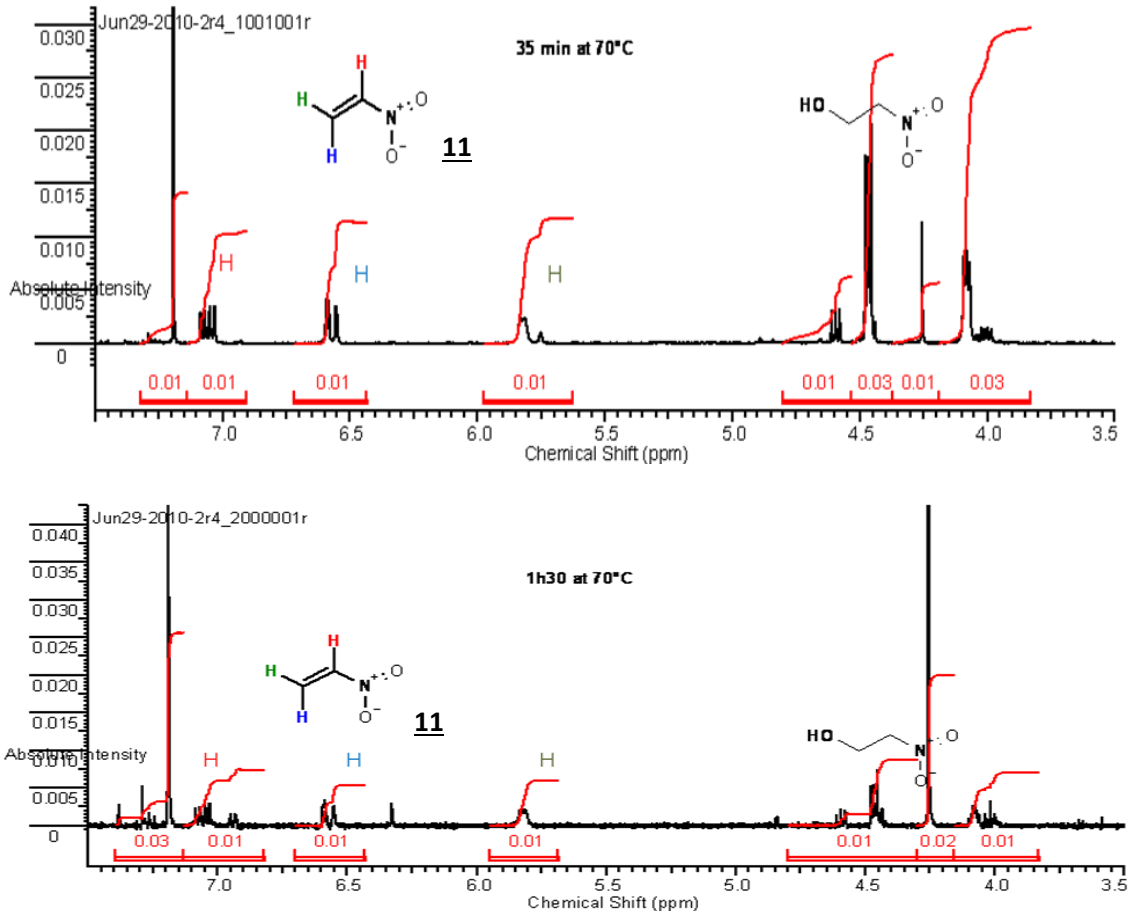
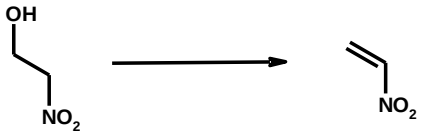


Figure 72: NMR study (^{1}H, $CDCl_3$) of the preparation of nitroethylene from nitroethanol. Reaction performed on 0.9 mmol scale; 1 equivalent of nitroethanol was added in a sealed tube to a suspension of 13 equivalents of acidic Alox and 11 equivalents of anhydrous magnesium sulfate in 4 mL $CDCl_3$ and heated to 70°C

A selection of dehydrating agents, solvents and temperature were screened to accelerate the formation of **11** (Table 5).



35 **11**

	(mmol)	Alox (eq.)	$MgSO_4$ (eq.)	SiO_2	Cellfloc	Solvent (4mL/mmol)	Tempe -rature	Conversion (NMR)	Conversion (%area, LC)
1	0.9	12	10	-	-	$Cl(CH_2)_2Cl$	40°C	11% (45min)	54% (4h30)
2	1.1	9	8	-	-	$Cl(CH_2)_2Cl$	70°C	22% (35min)	85% (4h30)
3	5	6	-	-	-	$Cl(CH_2)_2Cl$	80°C	-	76% (4h00)
4	0.9	13	11		-	$CDCl_3$	70°C	40% (35min) 88% (1h30)	-
5	1.1	9	-	-	-	$Cl(CH_2)_2Cl$	70°C	18% (35min)	-

6	1.1	-	8	-	-	$Cl(CH_2)_2Cl$	70°C	No conversion (35min)	-
7	1.1	-	-	15	-	$Cl(CH_2)_2Cl$	70°C	2% (1h30)	-
8	1.0	-	-	-	1.0676 g	$Cl(CH_2)_2Cl$	70°C	-	1%(1h30)

Table 5: Dehydration of nitroethanol to nitroethylene**.** Reactions were performed in sealed tube under the conditions described in table. [a]SM= starting material

Cellfloc and magnesium sulfate were ineffective in performing the dehydration (Table 5, Entries 6,8). The utilization of silica gel and acidic Alox (Brockmann Activity I) afforded the desired product but the reaction proceeded 10 times faster in the case of Alox in comparison to silica gel (Table 5, Entries 5,7). The best results were obtained when acidic Alox (Brockmann Activity I) was used in combination with magnesium sulfate at 70 to 80°C, the increase of the temperature accelerating the dehydration (Table 5, Entries 1-4).

Distillation under reduced pressure at 49°C (bath temperature) at 100 mbar of the 1,2-dichloroethane solution containing a mixture of nitroethanol and nitroethylene resulting from the utilization of Alox as dehydrating agent at 80°C (Table 5, Entry 3) afforded at a boiling point of 30° C a pure solution nitroethylene in 1,2-dichloroethane . ^{1}H NMR ($CDCl_3$) analysis of the distillation fraction revealed the presence of the characteristic signals of nitroethylene (Figure 73). The signals corresponding to nitroethanol (4.05-4.15 ppm and 4.4-4.5 ppm) were not detected.

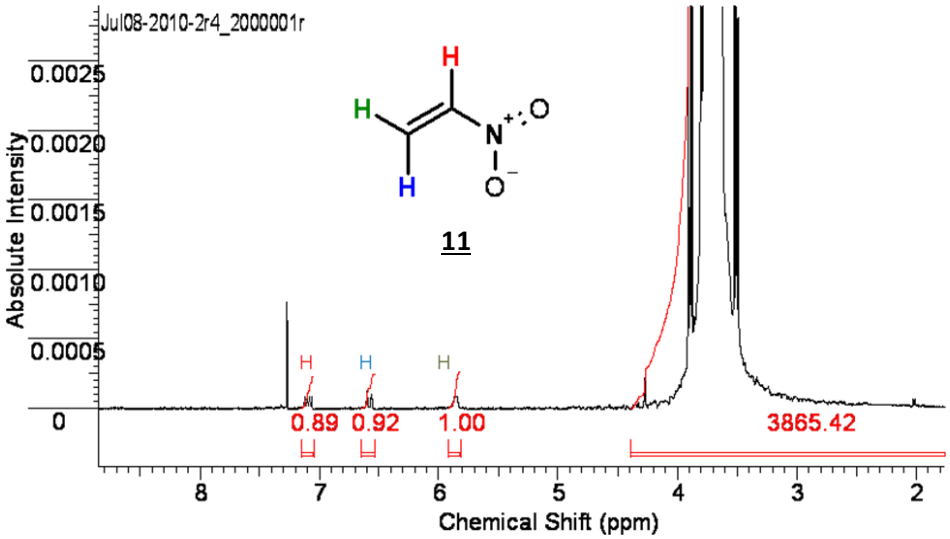


Figure 73: ^{1}H NMR ($CDCl_3$) of the purest destillation fraction of nitroethylene in solution in 1,2-dichloroethane

An heterogeneous phase process for preparation of nitroethylene can be envisaged using Alox (Brockmann Activity I) in 1,2-dichloroethane in the presence of magnesium sulfate. Destillation under reduced pressure affords the nitroalkene derivative as a diluted solution in 1,2-dichloroethane. By replacing 1,2-dichloroethane by toluene and after optimization of the reaction conditions, we could produce the adequate nitroethylene solution for the OTMS diphenylprolinol ether catalyzed enantioselective synthesis of the Aliskiren precursor **8**, from isovaleraldehyde.

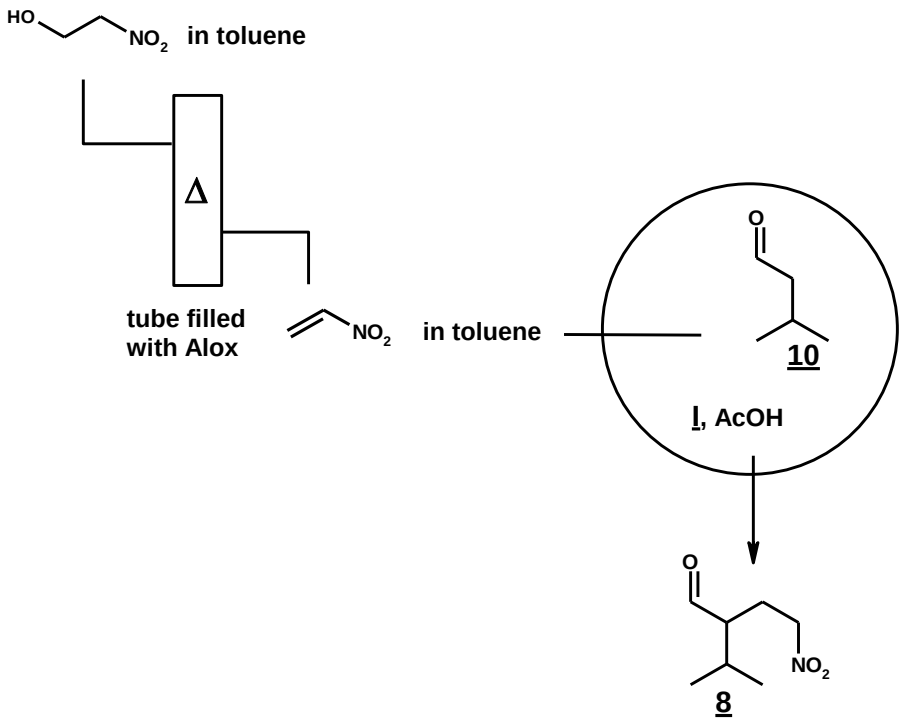


Figure 74: Hypothetical representation of a process for the preparation of Aliskiren precursor **8**, involving acidic Alox (Brockmann Activity I)

In the future, according to the publications of Ballini in 1992[138] and 2006[139], a one-pot sequence, starting from formaldehyde and nitromethane under basic Alox conditions could also be envisaged for the synthesis of Aliskiren precursor **8**.

III.2.6. Conclusion

The 3rd generation synthesis of Aliskiren **1** requires the preparation of the (S)-precursor **8** with excellent enantioselectivity and yield. We envisaged to introduce the chirality by performing enantioselective organocatalyzed Michael addition, involving respectively activation of the substrate by the reversible formation of an enamine or iminium ion.

In the first approach, we performed the OTMS diphenyl prolinol ether **I** catalyzed Michael addition of an *in situ* generated α-substituted analogue of nitroethylene to isovaleraldehyde affording in the presence of acetic acid, (and after *in situ* reduction of the Michael adduct) compound **8** with satisfactory yield (58%) and enantioselectivity (ee up to 84%). The α-substituted analogue **19**, formed *in situ* by Knoevenagel condensation of commercially available nitro-acetic acid methyl ester **21** and formaldehyde was never detected in the reaction mixture, reacting immediately with the *in situ* generated enamine **22**.
Under the similar reaction conditions **22** performed also an aldolization reaction with formaldehyde to provide the α-substituted α,β unsaturated aldehyde **25**. Nitromethane or nitroalkane analogues reacted slowly with **25** under the conditions studied, to yield the Aliskiren precursor with the desired (S)-configuration with moderate conversations. Good enantioselectivity of the reaction was observed using the organocatalyst **I** in methanol in the presence of benzoic acid or acetic acid as co-catalyst. A

one-pot multi-component domino aldolization-Michael addition cascade was evaluated for the synthesis of **8**, involving isovaleraldehyde, formaldehyde and nitro-acetic acid methyl ester **19**.
Starting from the same reactants (isovaleraldehyde, formaldehyde and nitro-acetic acid methyl ester **19**), we were able to prepare the Aliskiren precursor **8** with good to high enantioselectivity *via* two different pathways.

III.3. From C4-nitro alcohol intermediate to C8-lactam-lactone intermediate 15

III.3.1. Introduction

The chemical structure of Aliskiren **1** requires the introduction of four adjacent *syn*-stereocenters. A convergent strategy was envisaged, involving a *syn*-enantioselective Henry reaction to prepare the eight-carbons-chain precursor **9** bearing all the *syn*-configurated substituent of Aliskiren.
The general synthetic route we employed for this strategy was based on the approach patented by Sedelmeier[131j], who reported the effective and elegant preparation of Aliskiren **1** *via* the preparation of the lactam-lacton intermediate **15** from the *syn*-Henry product of nitro compound **8** and its aldehyde analogue **28** (Figure 75).

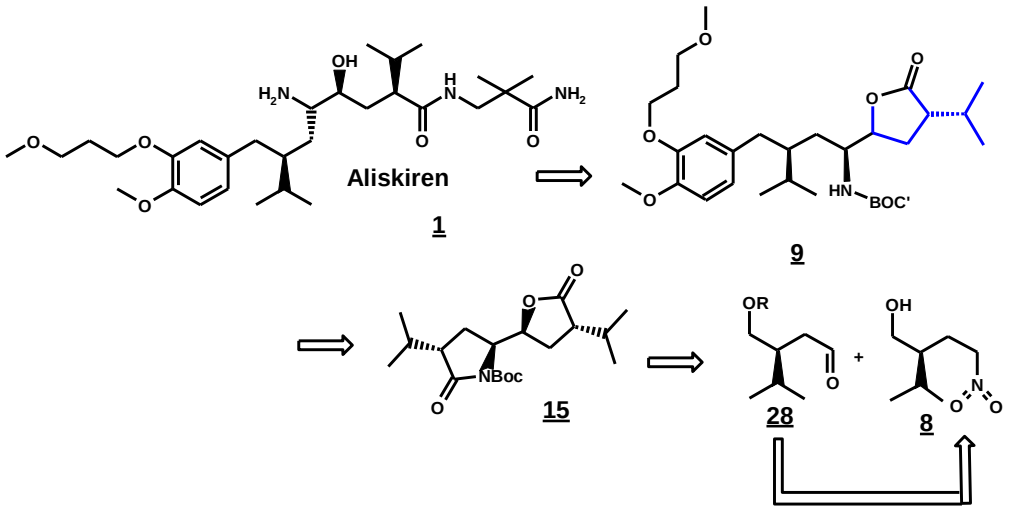


Figure 75: Strategy for the enantioselective synthesis of Akiskiren **1**

The scale up of the process developed by Sedelmeier required the optimization of all the steps of the synthesis to prepare all of the intermediates with excellent yields, enantioselectivities and under "production safe" conditions, in particularly the key intermediates **15**, **28** and **8**.

Sedelmeier[131j] proposed to synthesize the *O*-benzyl protected aldehyde **28** from **8**: 1) by introducing the benzyl protective group with 2,2,2-trichloroacetamidate and trifluoromethane sulfonic acid in dichloromethane and by performing the subsequent Nef reaction under classical methods or with sodium percarbonate; 2) in two steps from the (S)-2-chloromethyl-3-methyl-butoxymethyl-benzene **31** *via* substitution with cyanide, and subsequent reduction of generated nitrile group with DIBAH.

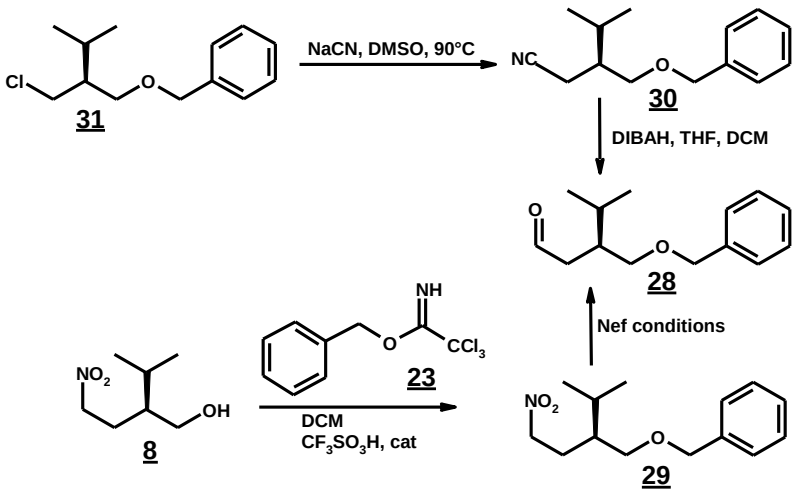


Figure 76: Reported preparation[131j] of the aldehyde **28**

The major drawbacks of the reported processes for their applications on large scale remain:

- the toxicity of cyanide (handling on multi-ton scale)

- the removal of Pd/C and its cost

- the cost of the benzyl-trichloroacetimidate reactant

- the recovery of triflic acid.

By replacing the protective group on the alcohol moiety of **29**, we hoped to develop a practical and cost-efficient synthesis of Aliskiren base **1**.

III.3.2. From the (S)-Aliskiren precursor 8 to its aldehyde analogues

A selection of protective groups was installed including ethers, esters and carbamate derivatives (Figure 77).

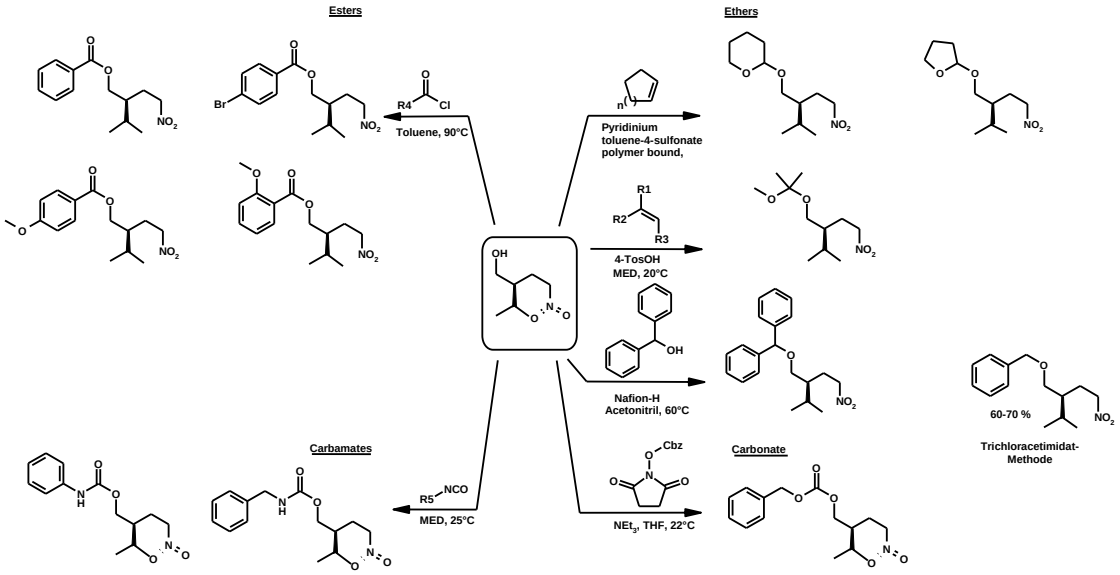


Figure 77: Selection of protective groups introduced to nitro compound **8**

III.3.2.1. Ether derivatives

Ethers are among the most used and well documented protective groups in organic synthesis. They involve simple methyl ether to elaborated substituted trityl ether. They are prepared and removed under various conditions[140]. We introduced the following THP, THF, MIP and benzhydryl groups (Figure 78).

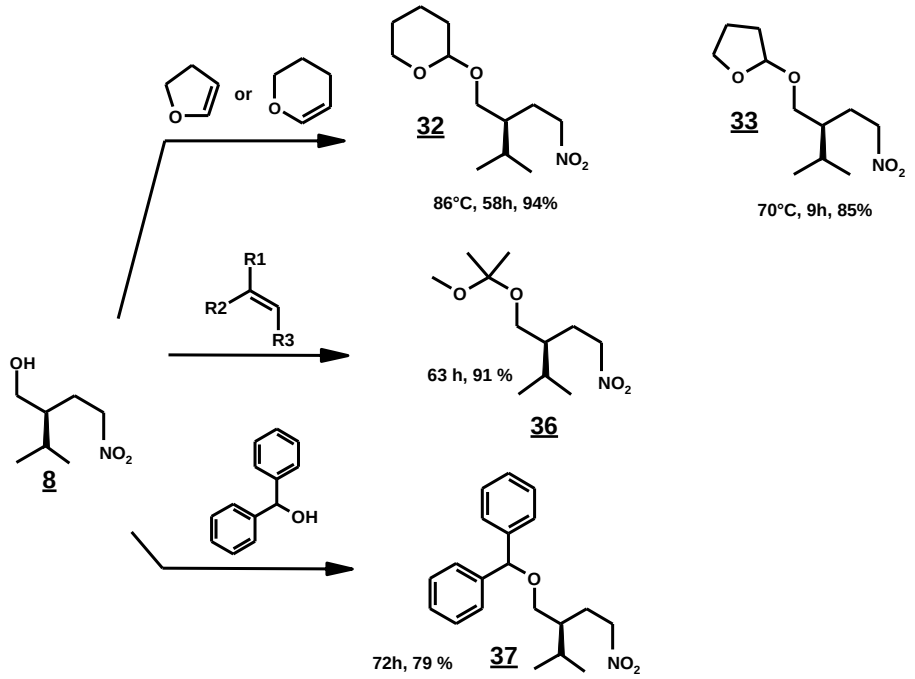


Figure 78: Preparation of a selection of ether derivatives from nitro compound **8**

One drawback of the installation of the THP and THF onto the Aliskiren precursor **8** is the introduction of an additional stereocenter due to the presence of a stereogenic center on the tetrahydrofuran and tetrahydropyran ring. Nevertheless it didn't have any negative influence on the

rest of the synthesis. These protective groups did not complicate the interpretation of the spectroscopic data.

In the practical route, we prepared **32** and **33** by refluxing the corresponding dihydrofuran and dihydropyran starting materials at respective 88°C and 70°C over 58 and 9 hours in the presence of polymer bound pyridinium *p*-toluene sulfonate. A simple filtration and evaporation of the excess of reactants allowed the isolation of the products with respectively 94% and 85% yield.

In a same way, the derivative **36** was synthesized according to the procedure of Mori *et al*[141] from the corresponding ethylene derivative in presence of catalytic amounts of *p*-toluene sulfonic acid in dichloromethane at room temperature (addition of the reactants occurred at 0°C). After 63 hours, an aqueous basic work up led to the isolation of the desired protected nitro compounds **36**, with 91% yield.

The benzhydryl (diphenylmethyl) group is a relatively inexpensive protective group, stable towards a variety of reagents. The benzhydryl ethers are usually prepared by treatment of an alcohol with diphenylmethanol under acid conditions[142] , including acid ion exchange resins[142] and silica gel-supported acid. We selected a perfluorinated sulfonic acid resin (Nafion-H)[142] as catalyst for the DPM etherification of nitro compound **8**. In a practical way, nitro compound **8** was warmed to 90°C in presence of diphenylmethanol and catalytic amounts of Nafion-H in acetonitrile. After 72 hours, removing of Nafion-H by filtration and evaporation of the solvent yielded crude material that was purified by column chromatography to give **37** with 79% yield.

III.3.2.2. Ester derivatives

The ester protective groups can be introduced under basic or acid conditions, by transesterification or biotransformation[140].

In a general procedure, nitro compound **8** and the selected acyl chloride derivatives were warmed to 90°C in toluene. Evaporation of the solvent and purification by column chromatography on silica gel, yielded **38**-**41** with 48-69% yields (Figure 79).

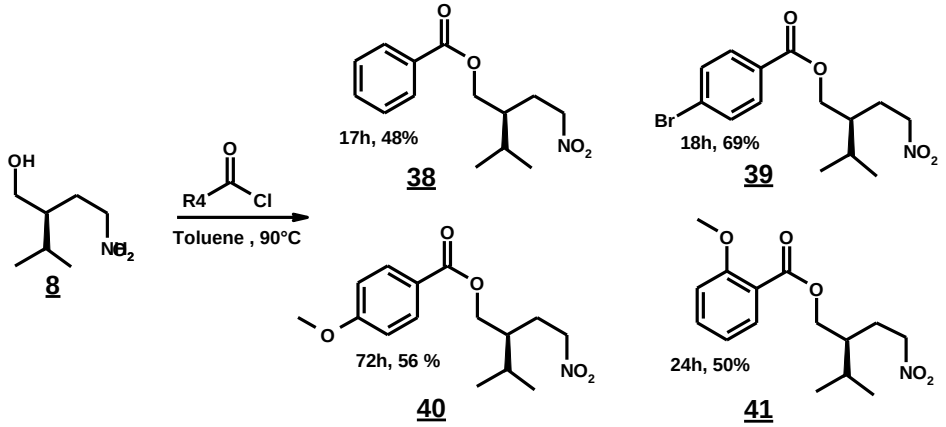


Figure 79: Preparation of the ester derivatives **38**-**41**

III.3.2.3. Carbamate derivatives

Carbamate derivatives can be prepared from their corresponding isocyanate derivatives in presence of an anhydrous organic base (pyridine) at room temperature[143]. The alkyl N-phenyl and N-benzyl carbamates **42** and **43** have been synthesized without treatment with a base, by addition of phenyl or benzyl isocyanate in dichloromethane at room temperature. After 18 hours or 72 hours, purification by chromatography on silica gel yielded the phenyl and benzyl carbamate derivatives **42** and **43** with respectively 40% and 48% yields (Figure 80).

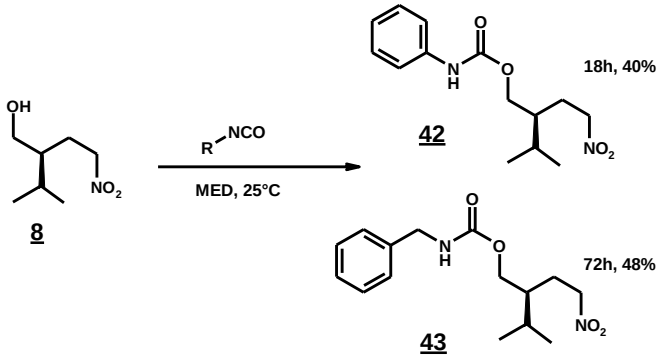


Figure 80: Preparation of the carbamate derivatives **42** and **43**

III.3.2.4. Carbonate derivative

Carbonates, like esters, can be cleaved by hydrolysis under basic conditions. They are nevertheless more stable towards hydrolysis because of the resonance effect of the second oxygen[140]. That is why we tried to introduce a carbonate protective group to the alcohol moiety of the key C4-nitro alcohol. Benzyl carbonates can be prepared by treatment with benzylchloroformate in presence of a base, such as TMEDA at low temperature[144].

In our study, nitro compound **8** was converted in 48% yield to its carbonate derivative by treatment with the Z-succinimidyl derivative **88** in THF at room temperature in presence of triethylamine.

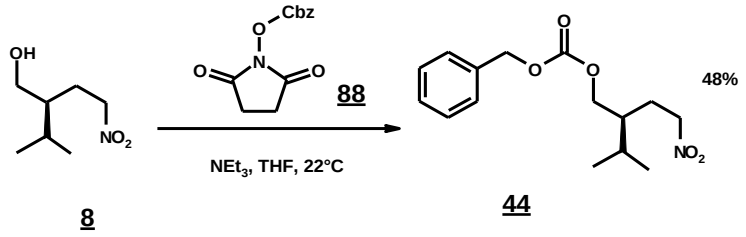


Figure 81: Preparation of the carbonate derivative **44**

Eleven new derivatives have been prepared with moderate to good yields and some of them have been converted to their aldehyde analogues *via* a Nef reaction.

III.3.3. Preparation of the aldehyde intermediates *via* a Nef reaction

One of the first transformations involving the nitro group is its conversion into carbonyl unit, discovered by Nef[145] in 1894. Since Nef reported[145] that primary and secondary nitro compounds can upon treatment with mineral acids be transformed into aldehydes and ketones, several variations of the reaction conditions have been published[146,147].

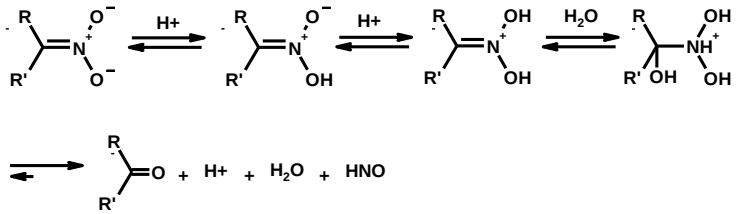


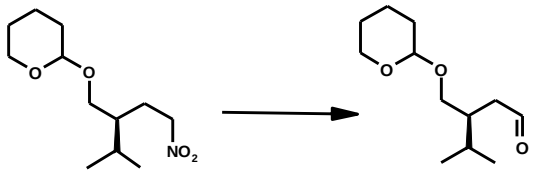
Figure 82: Mechanism of the original Nef reaction[147]

A limited number of reductive methodologies have also been published. The most important procedure (McMurry method) uses $TiCl_3$ to reduce nitronate salts into aldehydes or ketones via the formation of an oxime or nitroso intermediate[148]. Aluminium powder in the presence of $NiCl_2{\cdot}6H_2O$[149], zinc dust- trifluoroacetic acid[150] or magnesium powder-$CdCl_2$-water in THF[151], such as treatment of primary nitroalkanes with $SnCl_2{\cdot}2H_2O$ in the presence of thiophenol and triethylamine, (followed by addition $SnCl_2{\cdot}2H_2O$ and tartaric acid–$NaHSO_3$) allow the formation of an imine intermediate, which is rapidly hydrolysed to the corresponding aldehyde unit[151]. Various metal nitronates of secondary nitroalkanes can also be converted into the corresponding oximes by treatment with hexamethyldisilane[152].

At the opposite, many procedures in the literature employ oxidative conditions to convert the salts of nitroalkanes, obtained by their treatment with bases. The most widely employed oxidant for this conversion is the $Mn0_4^-$ ion which has been used under various conditions[146,163,163]. But other oxidizing reagents such as sodium chlorite[153], MoOPH[154], t-BuOOH[155], m-iodoxybenzoic acid[156], singlet oxygen[157], dimethyldioxirane[158] (prepared by the reaction of oxone with acetone) or other peroxide-based systems, bis(trimethylsilyl)-peroxide[159] or sodium percarbonate ($Na_2CO_3{\cdot}1.5H_2O_2$)[160], tetrapropylammonium perruthenate (TPAP) with N-methylmorpholine-N-oxide[161] can also be used. Copper salts in mixtures with acetic acid in methanol[162] are also able to oxidize nitro aldol to α-keto acids.

Among them the promising works of Kornblum *et al* [146b] and Shechter and later of Steliou and Poupart[163], (who reported an oxidative procedure using $KMnO_4$) seem to be a general, efficient, practical simple way to prepare of carbonyl derivatives from their nitro precursors. After modification of the previous procedures, Steliou and Poupart[163] published that treatment of nitro derivatives with methanolic potassium hydroxide, in methanol at 0°C produces the corresponding potassium salts, that are *in-situ* oxidized into the corresponding carbonyl units by addition of a concentrated aqueous solution of $KMn0_4$ and $MgSO_4$. (The principal function of the magnesium sulfate is to maintain the neutrality of the oxidation mixture by precipitating hydroxide ion as magnesium hydroxide[146]).

We prepared the THP protected aldehyde **45** applying a selection of conditions adapted from the literature (Ballini and Petrini[153], Pinnick *et al* [164] and Steliou and Poupart[163]). In a general procedure, the nitronate intermediate was generated at 0°C by addition of the selected base. After stirring a few minutes, the oxidizing agent was added dropwise to the reaction mixture.



32 **45**

Entry	Base	Oxidizing agent	Solvent	Additives	Temperature	% area (GC)[f]
1	$NaOH^{a}_{aq.}$ (3 eq.)	$NaClO_{2aq.}$ (0.15 equiv.)	DCM [d]	$nBuNHSO_4$ (0.1 eq.)	RT	8% (30 min) 43% (27h)
2	$NaOH^{a}_{aq.}$ (3 eq.)	$NaClO_{2aq.}$ (0.15 equiv.)	DCM [d]	-	RT	No conversion
3	$NaOH^{a}_{aq.}$ (3 equiv.)	$NaClO_{2aq.}$ (0.15 equiv.)	tBuOH [d]	Mebutene (0.04 equiv.)	RT	2% (30 min) 14% (25h)
4	NEt_3[b] (1.0 equiv.)	$KMnO_{4\ aq.}$ (1.0 equiv.)	DCM[d]	$nBuNHSO_4$ (0.1 equiv.)	0-5°C	0.3% (10 min) 0.8% (23h)
5	NaOH/MeOH (1.2 equiv.)	$KMnO_4$[b] $_{aq.}$ (0.35 equiv.)	$MeOH/H_2O$[e]	$MgSO_4$ (0.07 equiv.)	0-5°C	88% (30 min) 97% (3h) 97% (23h)
6	NaOH/MeOH (1.2 equiv.)	$KMnO_4$[b] $_{aq.}$ (0.45 equiv.)	$MeOH/H_2O$[e]	$MgSO_4$ (0.07 equiv.)	0-5°C	95% (t_0)
7	NaOH/MeOH (1.2 equiv.)	$KMnO_4$[b] $_{aq.}$ (0.6 equiv.)	$MeOH/H_2O$[e]	$MgSO_4$ (0.07 equiv.)	5-10°C	100% (t_0)
8	NaOH/MeOH (1.2 equiv.)	$KMnO_4$[c] $_{aq.}$ (0.5 equiv.) / $NaIO_{4\ aq.}$ (0.2 equiv.)	$MeOH/H_2O$[e]	$MgSO_4$ (0.07 equiv.)	5-10°C	100% (t_0)
9	NaOH/MeOH (1.2 equiv.)	$KMnO_4$[c] $_{aq.}$ (0.12 equiv.) / $NaIO_{4\ aq.}$ (2.5 equiv.)	$MeOH/H_2O$[e]	$MgSO_4$ (0.07 equiv.)	5-10°C	98.6% (t_0) 99.6% (1h)
10	NaOH/MeOH (1.2 equiv.)	$NaIO_4$[c] $_{aq.}$ (2.5 equiv.)	$MeOH/H_2O$[e]	$MgSO_4$ (0.07 equiv.)	5-10°C	2% (t_0) 2% (1h30)
11	KOH/MeOH (1.2 equiv.)	$KMnO4_{\ aq.}$ (0.7 equiv.)	$MeOH/H_2O$[e]	$MgSO_4$ (0.07 equiv.)	0-5°C	100% (t0)

Table 6: screnning of a selection of conditions for the Nef reaction on 32. [a]1mmol nitro compound scale, [b]4 mmol scale, [c]6 mmol scale**,** [d]3mL/ mmol, [e]32 mL/mmol, [f]ratio measured by Gas Chromatography

We found that the most promising oxidative agent was the ion MnO_4^- alone or in mixture with $NaIO_4$ (Table 6, Entries 5-9,11). The utilization of $NaClO_{2aq}$ as oxidative agent was ineffective to perform the studied Nef reaction (Table 6, Entries 1-3).

When an organic base such as triethylamine was used to depronate **32** to its nitronate analogue, the Nef reaction performed very slowly (Table 6, Entry 4). Methanolic solutions of NaOH or KOH, as described by Steliou, were the most promising methods to generate the nitronate anions (Table 6, Entry 5-11).

We found that 0.6 equiv. of $KMnO_4$ are the minimal required amount. Using a combination of $KMnO_4$ and $NaIO_4$ might allow to reduce the quantity of MnO_2 produced.

Using the modified procedure of Steliou *et al* [162] we prepared the following ether protected aldehydes **34**, **45**-**48**, from their corresponding nitro derivatives (Figure 83). In a general procedure, treatment of the nitro derivatives with a methanolic solution of potassium hydroxide (1.2 equiv.) at 0°C and the subsequent additions of $MgSO_4$ (0.07 equiv.) and dropwise of a concentrated aqueous solution of $KMn0_4$ (0.7 equiv.) afforded after filtration of the generated MnO_2, the desired aldehydes **34**, **45** to **48** with yield from 68% up to 79%. No trace of over oxidation of the nitro compounds was detected at the end of the reaction. Nevertheless in some case, an inefficient work up (traces of MnO_4^-, and base) can promote the conversion of the aldehyde intermediates into its carboxylic acid analogue during storage.

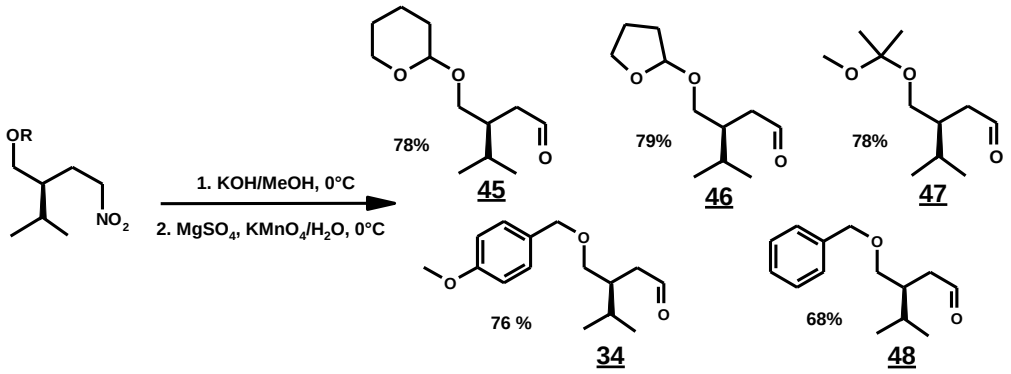


Figure 83: Oxidative Nef reaction under Steliou *et al* conditions[162]

Treatment of the nitro compounds **38** to **41** and **43** with a methanolic solution of KOH did not afford the desired aldehyde derivatives **49**-**53** but yielded the cyclic acetal **54** resulting from the removal of the protective group under the reaction conditions. Using a suspension of K_2CO_3 in methanol to generate the nitronates species and subsequent addition of $MgSO_4$ (0.07 equiv.) and an aqueous solution of $KMn0_4$ (0.7 equiv.) at 0°C afforded the aldehydes **49**-**53** with yields of 55% to 84% (Figure 84).

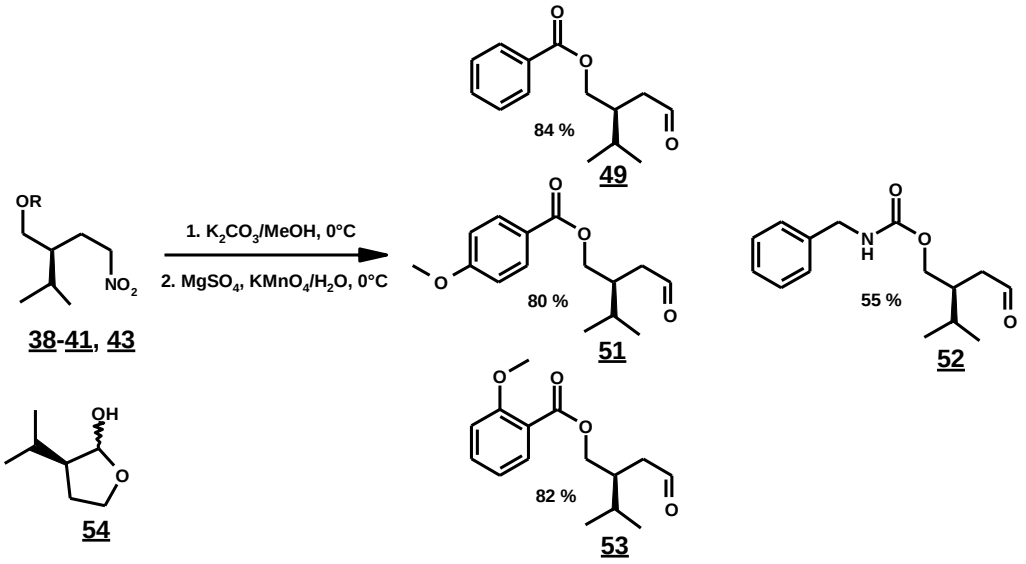


Figure 84: Modified Nef conditions to afford the aldehyde derivatives **49**-**53**

III.3.4. Henry reaction

III.3.4.1 Introduction

A range of interesting organometallic complexes and organocatalytic protocols have been successfully explored and applied to perform *syn*-enantioselective Henry reaction [4]. Among them, the use of complexes genereated from copper (I) and copper (II) salts and chiral ligands have been reported by Woggon[48a-b] *et al* who demonstrated that asymmetric Henry reaction of 4-nitrobenzaldehyde and nitromethane can be catalyzed by copper (II) complexes of various reduced Schiff Base (as for example the ligand **A** in Figure 85) of various aldehydes with nitromethane with high (S)-enantioselectivity. They also demonstrated that 4-nitrobutyrate can react with various prochiral nitroalkanes[48b,49] under similar conditions with high *syn*-enantioselectivity.

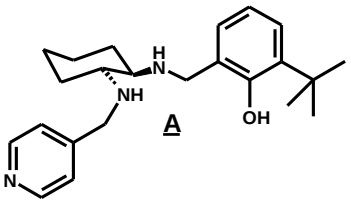


Figure 85: Chiral ligand **A** designed by Woggon *et al.* [48a-b]

Applying similar conditions as Woggon[48], we hoped to be able to convert our protected aldehyde **45** to the corresponding Henry product **54** with high *syn*-diastereoselectivity, affording the (S,S,S,S) configured diastereoisomers as the major products; the *anti*-products (the (S,S,R,S,S) and the (S,S,S,R,S) for example) being theoretically epimerized to their *syn*-analogues (Figure 86). In an other case[5], (using of *O*-benzyl instead of the THP protective group), it could be shown that the epimerization from the *syn*- to the *anti*-products (and vice-versa) occurred with different kinetics, in

[4] for an overview see chapter 1

[5] These results were obtained in the laboratory by A. Litzler and G. Sedelmeier

the presence of catalytic amounts of DBU in THF. Retro-Henry reaction could also be observed after 24h reaction time. For previous analogue Henry reactions with **8** and the benzyl protected aldehyde **28** see patent application cited in Literature 131j.

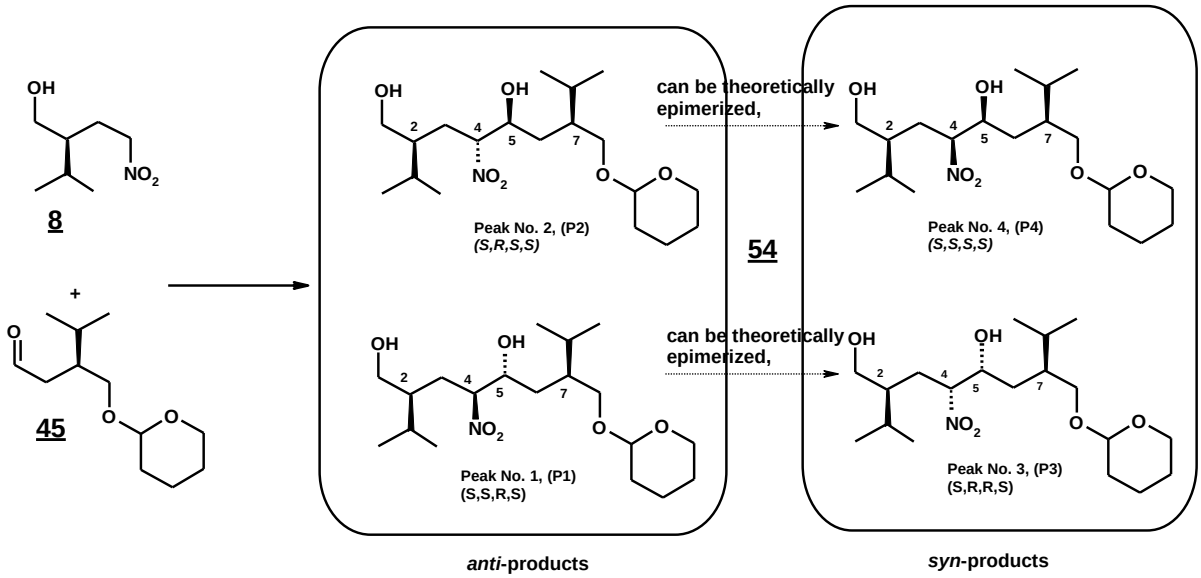


Figure 86: Example of the Henry reaction with THP protected aldehyde **45** and the nitro compound **8**

III.3.4.2. Results and discussion

III.3.4.2.1. Henry reaction catalyzed by formation of a chiral ligand- copper (II) complex

We applied the encouraging results of Woggon *et al*[48a] and performed the reaction of the protected aldehydes **45**, **46** and **49** and the nitro compound **8** using an *in situ* generated complex from $Cu(OAc)_2$ and the chiral ligand **A**.

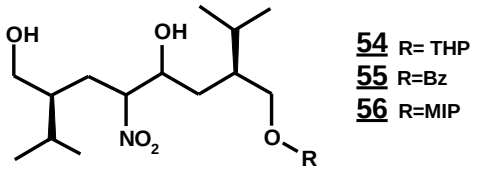
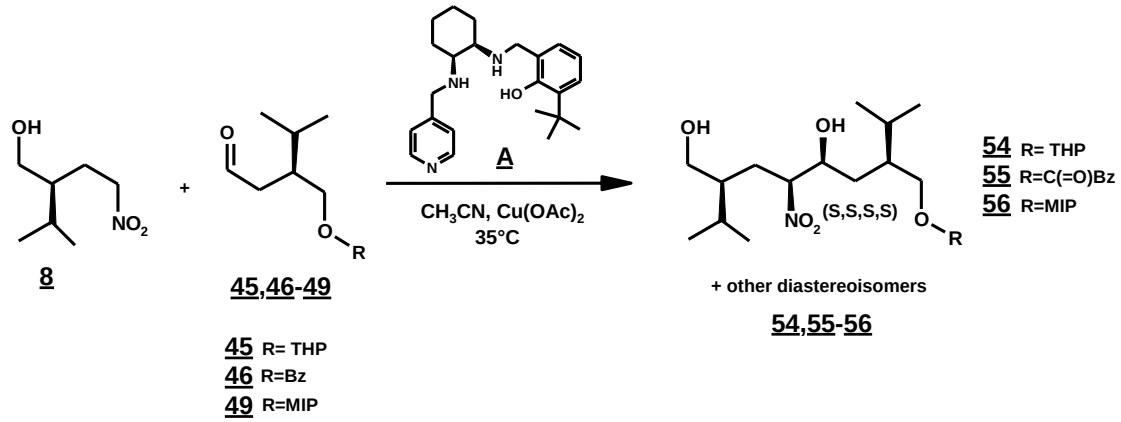


Figure 87: Scaffold of Henry products **54** to **56**

In a general procedure, we prepared the ligand-copper (II) complexes by mixing in a 1:1 ratio of the ligand and $CuOAc_2$ in acetonitrile. After few minutes, the selected aldehyde and the nitro compound **8** were added to the reaction mixture, and stirred at 35°C. Chiral HPLC on CHIRALPAK AD-H (Table 7) of the reaction mixtures revealed the presence of a major signal[6] (from 58 to 64%), characteristic of

[6] As we could show later, the diastereoisomers with opposite absolute configuration at the chiral center of the THP protecting group are not separated under the conditions used for the HPLC chromatography. The proof of the relative and absolute configuration of the major diastereoisomer was obtained by chemical correlation

the (S,S,S,S) diastereoisomer (as demonstrated by X-Ray analysis by Sedelmeier[131j], in the case of R=benzyl). In all cases, the Henry reaction performed slowly and the Henry products **54** to **56** were isolated with moderate diastereoselectivity; the THP protected nitro alcohol **54** being prepared with the best *syn*-diasteroselectivity.



Entry	Product	Time	Conversion	d.r.
1	**54**	7 days	70	6:14:13:**67**
2	**55**	2.5 days	77	7:7:27:**59**
3	**56**	4 days	65 (+ 25% lactol)	25:17:**58**

Table 7: Henry reaction of various aldehydes with nitro compound 8. All reactions were performed with 10% of ligand, 10% of $Cu(OAc)_2$ in acetonitrile at 35°C. Diasteroisomeric ratios (d.r.) were determined by HPLC using CHIRALPAK AD-H column.

Column chromatography on silica gel with a mixture of heptane/ethyl acetate allowed us in all cases to isolate the desired (S,S,S,S) diastereoisomer with a diastereoisomeric ratio > 90%. In the case of the MIP protected aldehyde **49**, deprotection of the corresponding Henry product occurred during the reaction (Table 7, Entry 3).

54 was also prepared with an isomeric ratio of (4:10:11:75) from **8** and **45** on a 6 mmol scale, using the conditions of Table 7. The (S,S,S,S) diastereoisomer was isolated as single isomer with 26% yield.
To explain the *syn*-selectivity observed, we propose, according to the contributions of Evans[39], the hypothesis of Woggon and the calculations done by Cossio[50], the formation of the potential transition state **TS-I**. The nitro component **8** and the selected aldehyde should coordinate to the metal centre, so that it should position the nucleophile perpendicular to the ligand plane, and the electrophile in equatorial position. The nitronate should attack favorably the aldehyde from one of its face, yielding to the formation in preponderance of the Henry Product with the *syn* (S,S,S,S) stereochemistry (Figure 88). The influence of the two stereocenters in the starting materials is not clear at the moment.

with the Aliskiren precursor **9**, during a kilo-lab campaign. The other three pics could be until now characterized in regard of their absolute configuration.

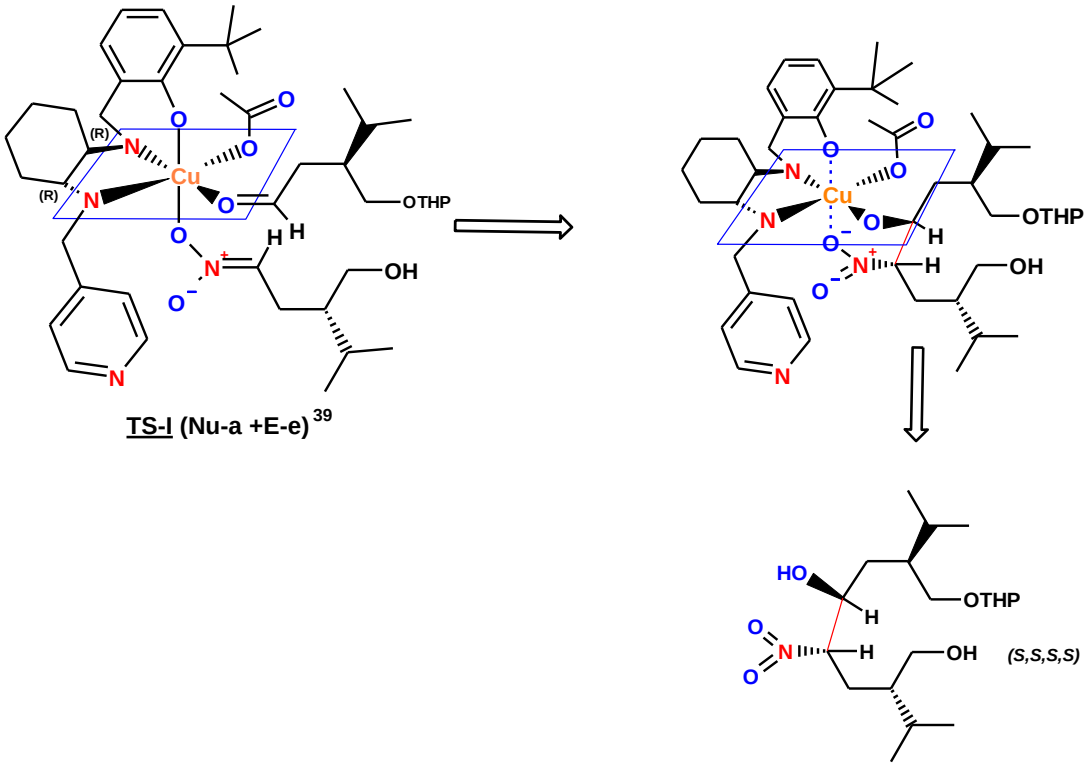


Figure 88: Postulated transition state for the Cu(II) complex catalyzed Henry reaction for the synthesis of the Aliskiren precursors

III.3.4.2.2. New chiral ligands and Cu(I) and Cu(II) salts for the Henry reaction

III.3.4.2.2.1. Introduction

The application on large scale of this strategy for the preparation of Aliskiren required the synthesis of the intermediate **15** with excellent yields and *syn*-enantioselectity. Optimization of the Henry reaction step was required to access better selectivity. The novel[7] ligand[48b] **B** (Figure 89) was exploited in the reaction of nitro compound **8** to the aldehyde **45**.

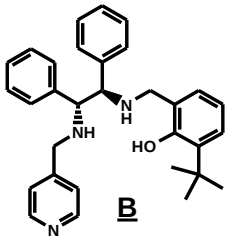


Figure 89: New C_1 symmetrical Ligand **B**

We envisaged the formation of complexes from both, copper (I) and copper (II) salts. Woggon[48b] *et al* had indeed shown that copper (I) system can also be efficient for the Henry reactions using a copper (I) complex of some symmetric ligands.

[7] The ligand **B** was first synthesized by J. Sedelmeier and successful applied in copper catalyzed Henry reactions within CHAD-Novartis.

III.3.4.2.2.2. Results and discussion

Applying the conditions described by Woggon *et al*, we performed the Henry reaction of **8** to the THP protected aldehyde **45** in the presence of copper (I) salt in THF, and of a base additive (Figure 90).

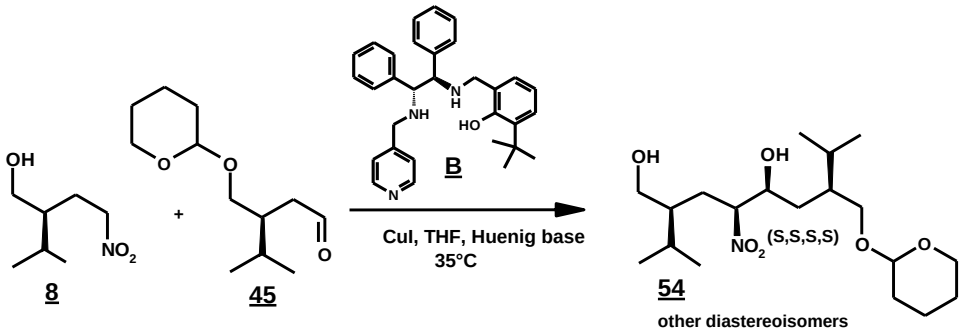


Figure 90: *Syn*-Henry reaction of THP protected aldehyde **45** with nitro compound **8**

We mixed copper (I) iodide (0.10 eq) at room temperature to 0.06 equivalent of the ligand in THF. The suspension was stirred at room temperature, and after a period of 20 min, 0.5 equivalent of Hünig base was added. The mixture was then allowed to stir at 30°C for 30 min before 1 equivalent of aldehyde **45** and 1 equivalent of nitro component **8** were added. The reaction mixture was stirred over a period of 2.5 days. Chiral HPLC on CHIRALPAK AD-H of the reaction mixture revealed the presence of a mixture of diastereoisomers in the ratio of 13:11:19:57. The major diastereoisomer was eluted with a retention time characteristic for the predicted (R/S,S,S,S,S) diastereoisomer, based on the postulated transition state for the Henry reaction.

The crude material was purified in the laboratory of Dr. E. Francotte by chromatography on CHIRALPAK AD-H (30*250 nm) with CO_2/isopropanol (8:2) and a flow of 120 g/min to yield in the pure fractions **54** (yield 12%) as a yellow oil containing the (S,S,S,S) configured **54** (as 50:50 ratio of (R,S,S,S,S) and (S,S,S,S,S) isomers) with a purity of 98%.

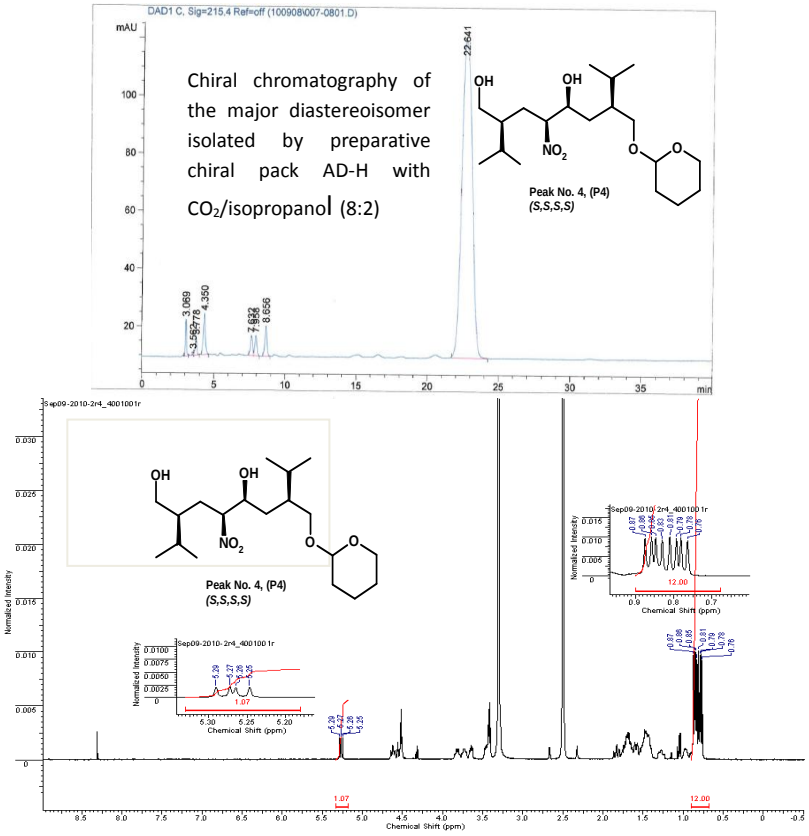


Figure 91: Chiral HPLC analysis of the isolated (R/S,S,S,S) diastereoisomers **54** isolated after chromatography on preparative CHIRALPAK AD-H with CO_2/isopropanol (8:2). HPLC measurements were conducted on CHIRALPAK AD-H with a mixture hexan/isopropanol/methanol/ethanol 973:9:9:9, 1 mL/min, at 40°C and λ=215 nm

The *syn*-selectivity observed can be rationalized based on a similar transition state as the transition state (**TS-I**) proposed in Figure 88, since, as postulated by Woggon *et al*, aerial oxidation of copper (I) to copper (II) can occur within the reaction. The role of the external base is not clear so far: is the nitronate species formed before it enters the "active pocket"? or does the nitro component enter the active specie and is then deprotonated?

Performing the same reaction with copper (II) salts and ligand **B** afforded (S,S,S,S) configurated isomere of **54** with up to 75% purity.

III.3.4.2.2.3. Conclusion

Using catalytic systems involving the C1 symmetric ligand **A** and copper (II) salts, we were able to convert the THP, MIP and benzoate protected aldehydes **45**, **46** and **49** into their respective β-hydroxyl nitro analogues **54** to **56** with moderate to satisfactory yields (21% to 56%) and purities.

Using catalytic system involving a novel DPEN (diphenylethylenediamine)-Salan ligand **B** and copper (I) or (II) salts, we were also able to form the required (S,S,S,S) configured nitro aldol product **54** as major stereoisomer. It could be isolated by column chromatography with a purity of up to 90% .

The reported strategy could be applied successfully after optimization of the Henry reaction for a kilo-lab campaign of Aliskiren intermediate **15**.

III.3.5. Towards the synthesis of Aliskiren precursor 14

The THP protected (S,S,S,S) nitroaldol **14** can be easily hydrolyzed under acidic conditions in presence of p-toluene-sulfonic acid in methanol at 0°C affording the desired new nitrodiol compound **14** with 86% yield (Figure 92).

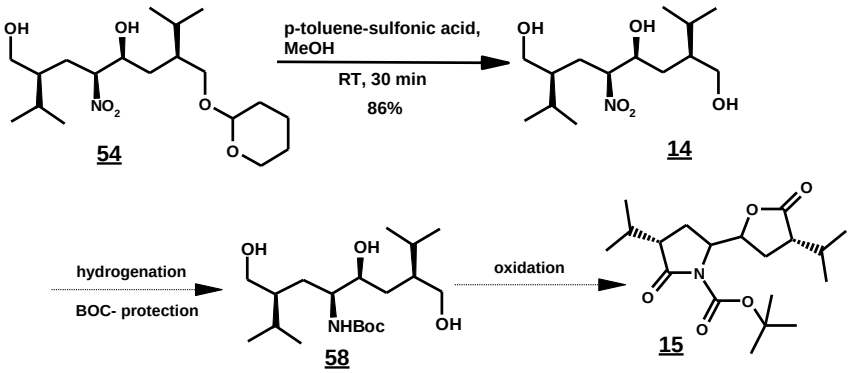


Figure 92: Towards the synthesis of Alikiren precursor **15**

The conditions described by Sedelmeier[131j] could then be applied to the novel β-hydroxynitro intermediate **14**. The nitro group can be hydrogenated with Ni-Ra at normal pressure in ethanol in the presence of Boc_2O. The key Aliskiren precursor **15** could be generated from **58** by oxidation with catalytic amount of tetrapropylammonium perruthenate TPAP and N-Methyl-morpholine N-Oxide or in the presence of TEMPO and bleach as oxidant. The preparation of **15** from **14** was not studied in the course of this Ph.D.

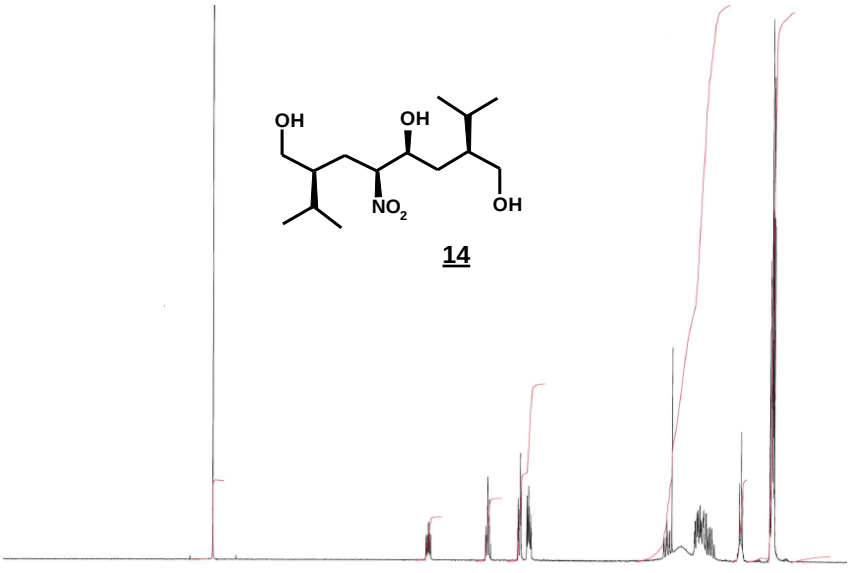


Figure 93: ^{1}HNMR ($CDCl_3$, 400 MHz) of **14**

III.3.6. Conclusion

While many ways of preparation of the renin inhibitor Aliskiren **1** have been published in the literature, a short, safe, diastereoselective process remains a challenge. We described the possibility to improve the promising manufacturing procedure published in 2008 by Sedelmeier[131j]:

1) by replacing the risky nitroethylene reagent by its more safe *in situ* generated α-ester analogue **19**, which reacts with isovaleraldehyde via enamine catalysis to form the desired (S)-Aliskiren precursor **8**

2) *via* a new multi-component aldolization-Michael addition sequence, undergoing *via* the iminium catalytic Michael addition of nitromethane or related derivatives to (*in situ* generated) isopropylacroleine **25**

3) by modifying the protective group on the terminal hydroxyl group of **8** and by the subsequent preparation of the related aldehyde intermediates

4) by performing copper salts and chiral ligand **B** complexes catalyzed Henry reactions, the β hydroxynitro intermediate can be prepared with moderate to satisfactory yield, depending on the protective group used and the reaction conditions.

We were also able to isolate, thanks to standard silicagel column chromatography, the desired (S,S,S,S) Henry product **54** and so the new related intermediate **14** with good yield (86%) and enantiomeric purity (ee > 96%).

These modifications in the current process allowed the convergent, elegant, economic and safer preparation of the highly advanced precursor **8** of Aliskiren drug **1** with moderate to good yield and stereoselectivity *via* key asymmetric Michael and Henry reactions.

In the future, because of the short reaction times of the multi component domino enamine catalytic Michael addition, a continous flow process could be possible. The following protection and oxidative Nef steps could also be adequate for a continous process[165].

III.4. A new atom-economy strategy for the preparation of Aliskiren 1

III.4.1. Introduction

The concerns of the pharmaceutical companies have always been to find the best way in term of yields, selectivities, safety and ecology to produce quickly a drug. To that extend, we turned our attention to the development of alternative efficient approaches for the synthesis of Aliskiren **1**. Using metal catalyzed and organocatalytic procedures, we proposed to prepare the drug substance in a shorter 4+4 approach, involving novel key intermediate **59** (Figure 94).

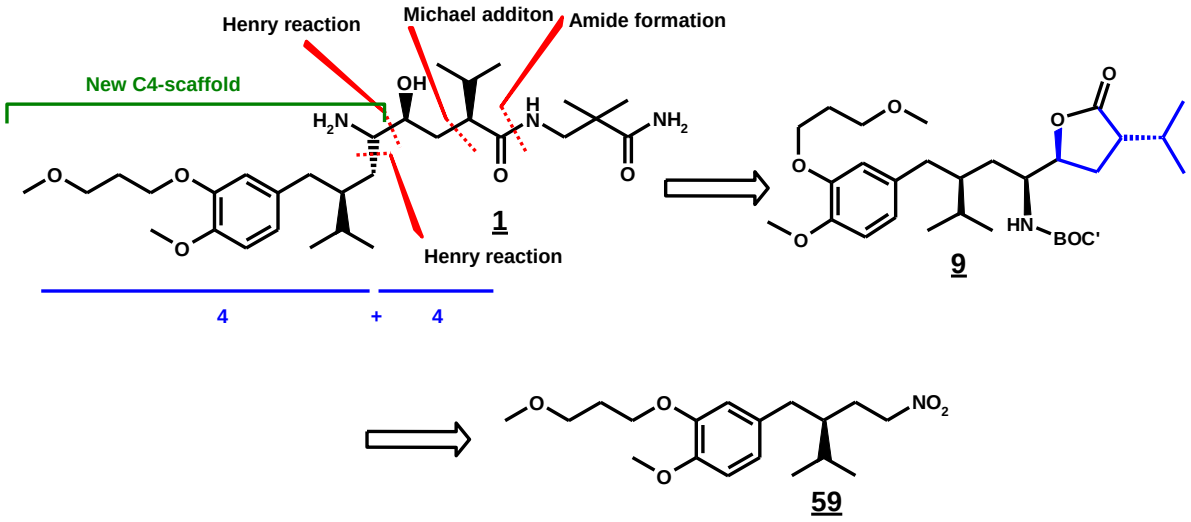


Figure 94: Retrosynthetic study for an alternative preparation of Aliskiren base **1**

A shown on Figure 95, the API intermediate **9** could be prepared in 10 (or 11) steps from the commercially available alcohol **62** (first described in the literature[131a] in 2000 by Maibaum *et al*). Aliskiren base **1** would be available in 11 or 12 steps.

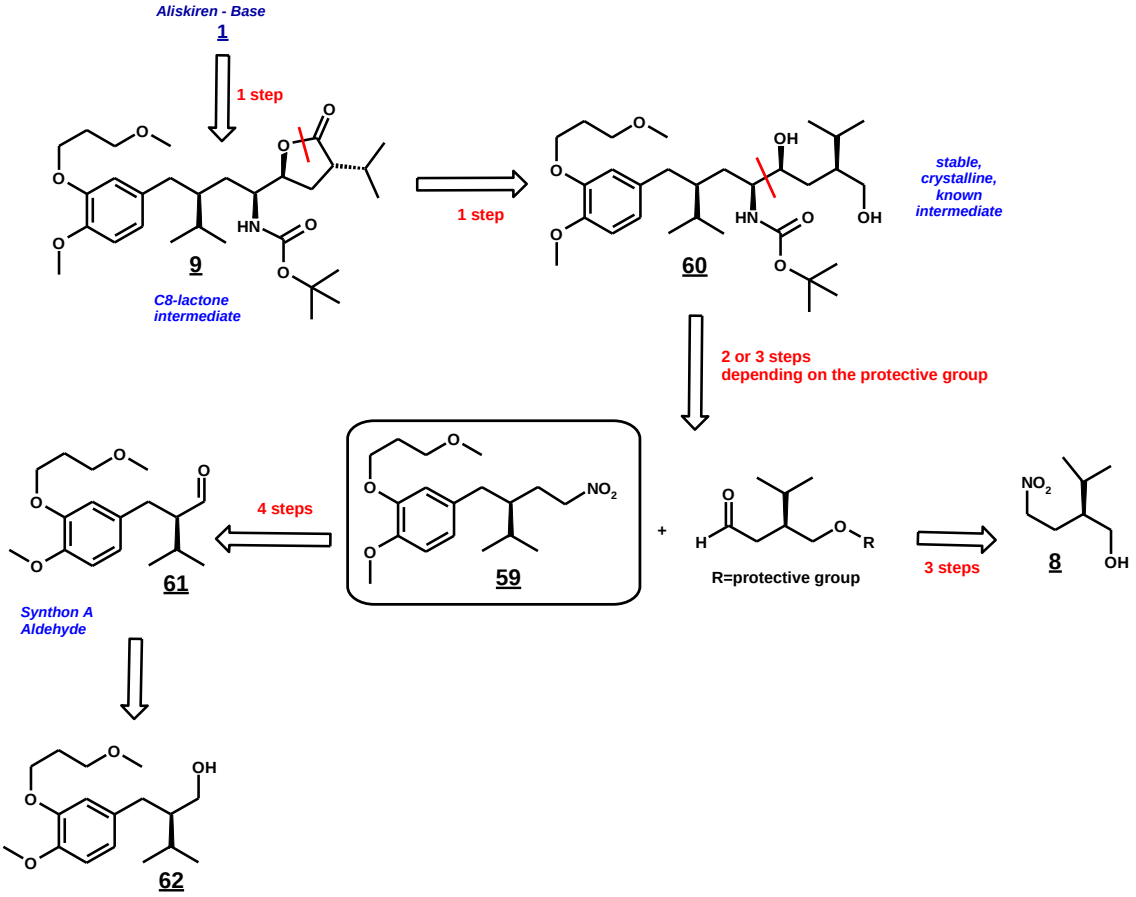


Figure 95: Retrosynthetic analysis of key intermediates in the synthesis of Aliskiren **1**

The challenges of this novel approach for the preparation of Aliskiren **1** are: developping an efficient synthesis of the novel nitro intermediate **59** in excellent yield and enantiomeric purity. Subsequent

copper catalyzed *syn*-enantioselective Henry reaction of **59** with the THP protected aldehyde **45** should allow the introduction of the required (S,S,S,S) configuration of Aliskiren **1** (Figure 95).

III.4.2. Synthesis of the novel key (S)-nitro compound 59

A wide range of strategies was available for the preparation of **59** (Figure 96). It was successfully synthesized from the aldehyde intermediate **61** in 3 steps *via* consecutive Henry reaction/dehydration step/reduction of the nitro olefin sequence. As depicted in Figure 96, **59** is also available from the chloride analogue **16** in 3 steps[8] (conversion into the nitrile derivative **65**, reduction, and oxidation steps). Both aldehyde **61** and chloride **16** derivatives can be prepared from the common commercially available intermediate **62**. Alkylation of nitromethane or nitroacetate with the chloride derivative **16** was also envisaged. All the proposed routes were tested in the laboratory with more or less success. **59** was also prepared as racemic mixture.

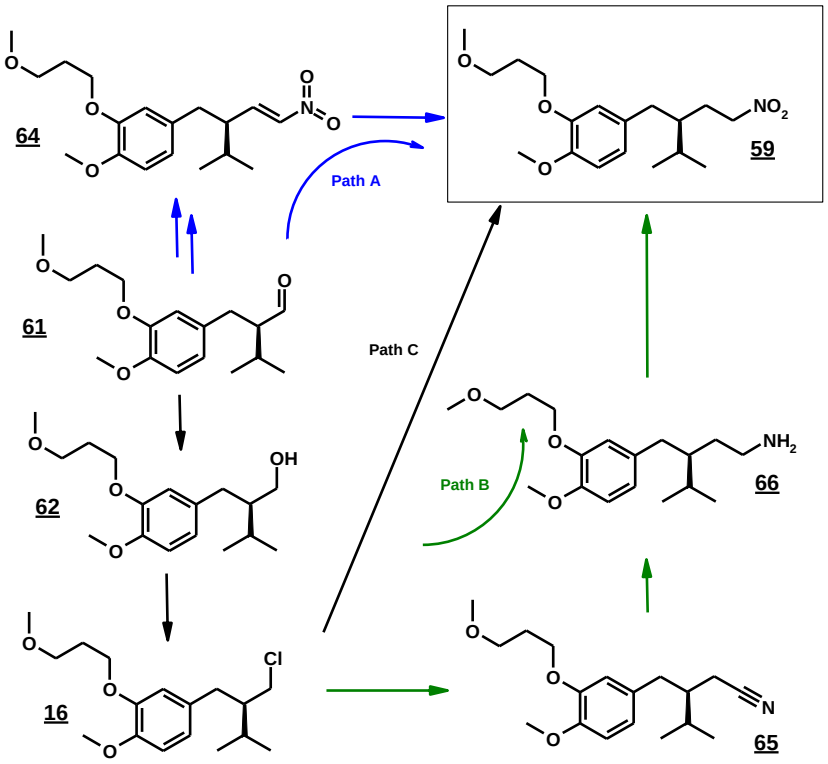


Figure 96: Selected ways for the preparation of **59**

[8] This approach was successfully applied by D. Grimler in the laboratory.

III.4.2.1. Preparation of the Aliskiren precursor 59 as a racemic mixture

59 was obtained in reasonably good yield (47%) via a three steps procedure (Figure 97).

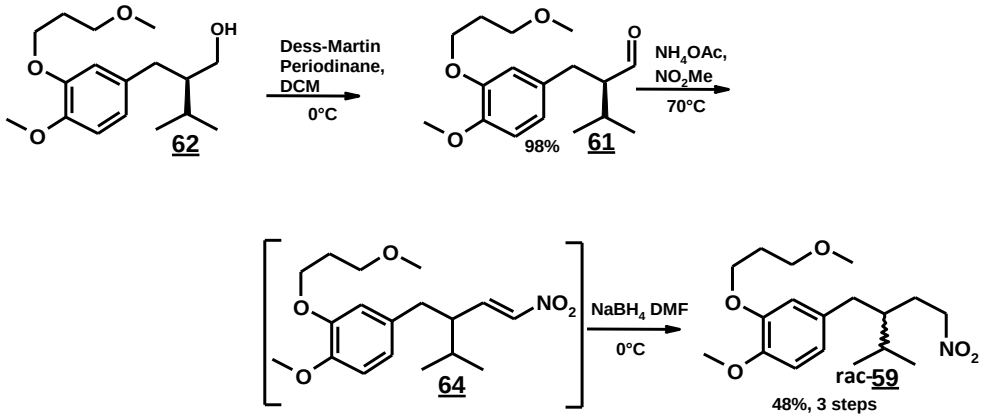


Figure 97: Preparation of **59** as a racemic mixture

The oxidation of the alcohol derivative **62** preceeded smoothly using Dess-Martin oxidation conditions[166] affording **61** with 98% yield. HPLC measurements on CHIRALCEL OD-H proved, that no racemization on the α-position of the aldehyde occurred during the reaction and revealed the presence of 98% of the (R)-enantiomer and *ca* 2% of the (S)-enantiomer.

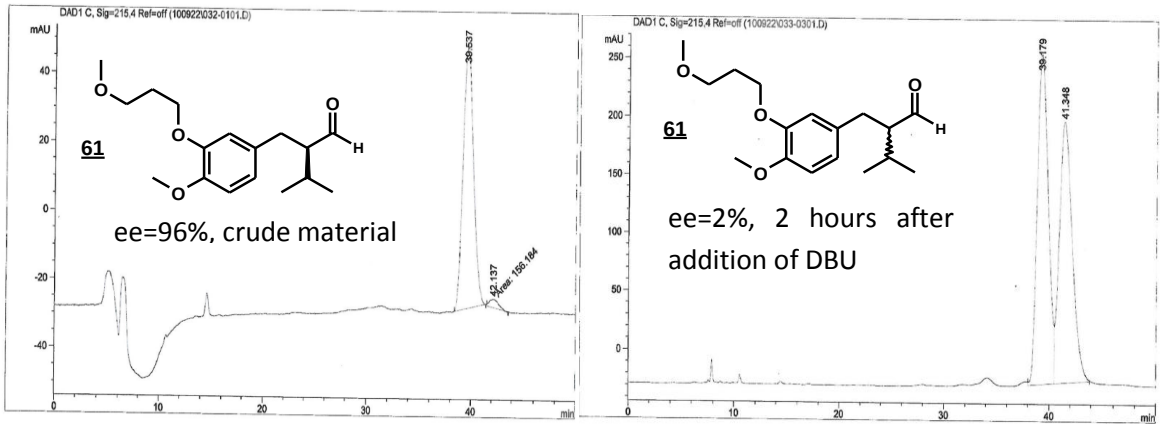


Figure 98: Chiral HPLC of crude **61** and comparison with the racemic mixture. The racemic version of **61** was prepared by addition of a few drops of DBU to the analysis vials. HPLC measurements were conducted on CHIRALCEL OD-H, hexane/isopropanol 9:1, 20°C, 0.5 mL/min, λ=215 nm

It was important for the synthesis of the nitro compound **59** to find out under which conditions, racemization of the aldehyde **61** occurred. That's why racemization studies were carried out by addition of a few drops of DBU and followed by chiral HPLC on CHIRALCEL OD-H, as depicted in Figure 98. It is worth to mention that the addition of sparteine and triethylamine (26 mg/0.09 mmol of **61**) don't affect the stereochemistry of **61**.

Using the procedure of Pedras and Okinyo[168] we prepared the nitro olefine **64**, as racemic mixture, by treatment of **61** with ammonium acetate in nitromethane at 70°C. The chiral HPLC analysis (Figure

99) revealed the presence of the signals of the (S)-enantiomer at 10.5 min and of the (R)-enantiomer at 11.4 min.

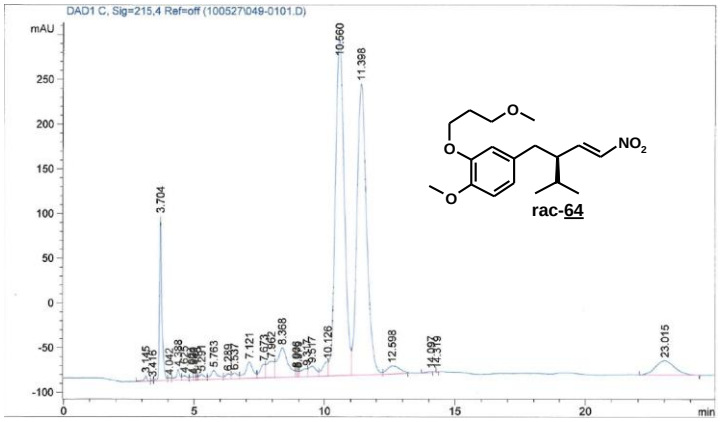


Figure 99: Chiral HLC rac-**64**, CHIRALCEL OD-H, hexane/isopropanol 97:3, 20°C,1 mL/min, λ=215 nm

The subsequent reduction[167] with sodium borohydride yielded **59** as a racemic mixture in 48% yield over 2 steps[168].

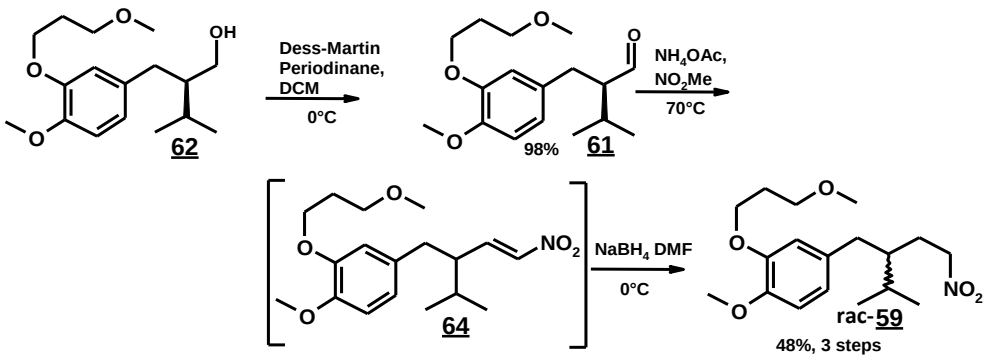


Figure 100: Preparation of rac-**59**

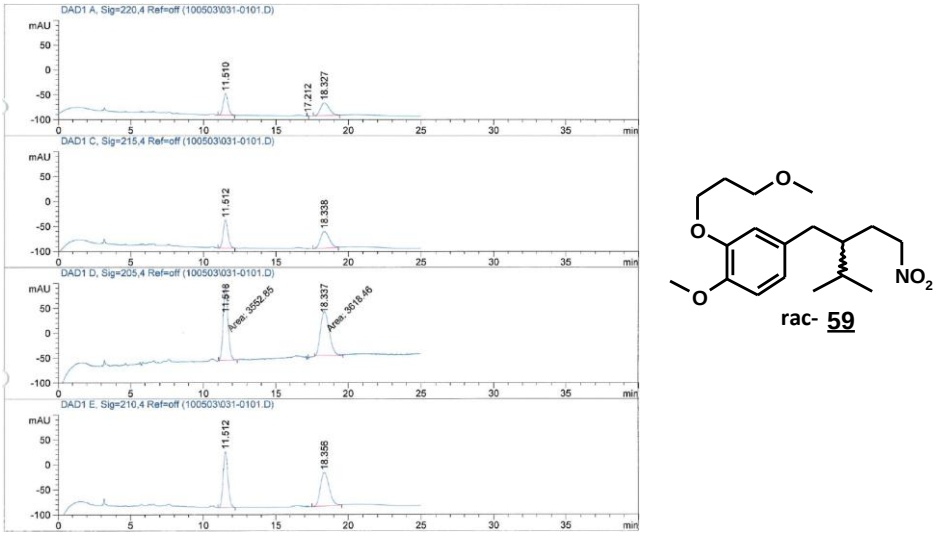


Figure 101: Chiral HPLC of rac-**59** on CHIRALCEL OD-H, hexane/isopropanol 93:7, 20°C,1 mL/min, λ=205, 210, 215 and 220 nm

III.4.2.2. Asymmetric synthesis of Aliskiren precursor 59

The Aliskiren precursor **59** was obtained from **62** with high enantioselectivity (ee 96%) and moderate yield (44%) via a four steps procedure, involving Dess-Martin oxidation, Henry reaction, dehydration and subsequent reduction with sodium borohydride.

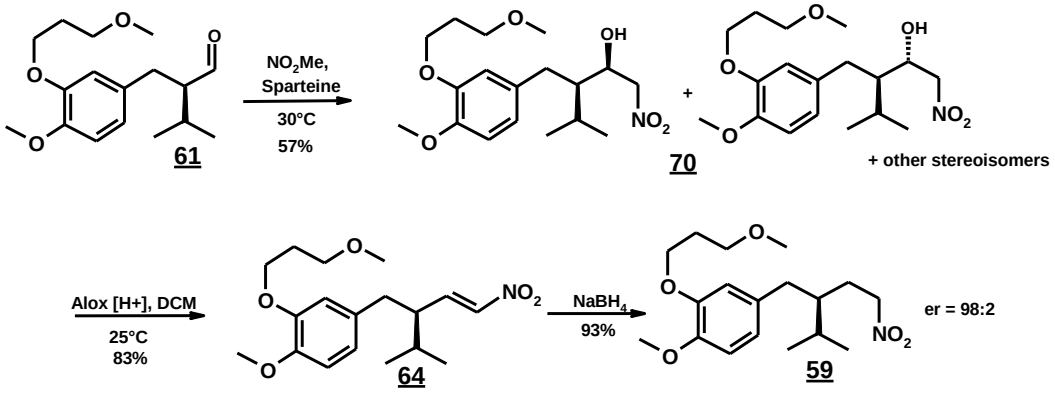
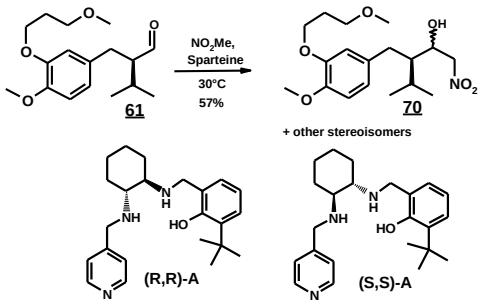


Figure 102: Asymmetric synthesis of nitro-compound **59**

Henry reaction of (R)-**61** with nitromethane (6 equivalents) was performed at room temperature in presence of 0.3 equivalent of sparteine to give the desired β-hydroxy nitro compound **70** with 67% yield with a diastereoisomeric excess of 60%.
A selection of catalysts has also been tested for the Henry reaction of **61** with nitromethane, yielding or not 70 as a mixture of diastereoisomers **P1**/**P2**/**P3**/**P4**.



Entry	Ligand	Ligand /mol%	Metal salt	Metal /mol%	Solvent	Tempe-rature	(**P1**:**P2**):**P3**:**P4** (%)[b]	ee (new stereocenter) (%)[b]
1	(R,R)-**A**	5	$CuOAc_2$	5	EtOH	35°C	(1):1:89	96
2	(S,S)-**A**	5	$CuOAc_2$	5	EtOH	35°C	(7):77:6	66
3	(S,S)-**A**	5	$CuOAc_2$	5	DCM	35°C	no conversion	no conversion
4[a]	Sparteine	30%	-	-	-	35°C	(5:1):26:68	44
5[a]	Sparteine	30%	-	-	-	30°C	(3):19:78	60

Table 8: Enantioselective Henry reactions of CH_3NO_2 with aldehyde 61 under various conditions. All reactions were performed on a 1 mmol scale with 1 equiv. of aldehyde **61** and 2 equiv. of nitromethane in the solvent. [a] reaction performed with 6 equiv. of nitromethane [b] determined by chiral HPLC using a CHIRALCEL OD-H column hexane/isopropanol 97:3, 20°C, 1 mL/min, λ=215 nm

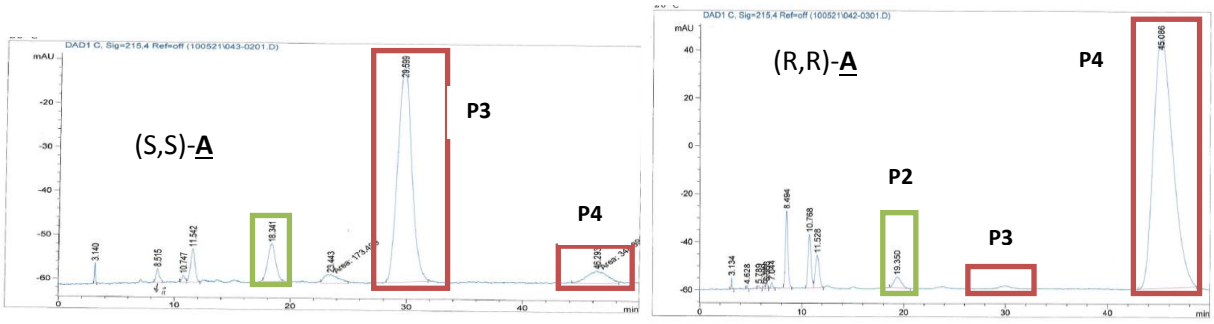


Figure 103: Chiral HPLC chromatograms of **70**, under the tested conditions of Table 8, CHIRALCEL OD-H,

Performing the Henry reaction of **61** with nitromethane in the presence of sparteine afforded the β-hydroxyl compound **70** with a moderate enantioselectivity (Table 8, Entry 4,5), the temperature of the reaction influencing the selectivity. Better selectivities (ee up to 96%), as represented on the chromatograms of Figure 103, were obtained in the presence of *in situ* generated complexes from the chiral ligands (R,R)-**A** and (S,S)-**A** and copper (II) salts in ethanol (Table 8, Entry 1-2). No reaction occurred when the reaction was performed in dichloromethane (Table 8, Entry 3).

It was not important to find out the absolute configuration of the alcohol moiety, since this group will be eliminated. What is important is that the (R) configuration of the isopropyl group is not affected during the reaction.

The diastereoisomers **P3** and **P4** were separated on preparative chiral column AD (Hept/EtOH/MeOH 90:5:5, 400 mL/min) to yield both diastereoisomers with up to 93% purity for the diastereoisomer **P3** and up to 98% purity for the diastereoisomer **P4**.

^{1}H NMR analysis (DMSO-d^{6}) revealed also the presence of both new (S) and (R) configured stereocentres: *doublet* at 5.41 ppm corresponding to proton of the **P3** alcohol moiety, and at 5.30 ppm attributed to proton of the alcohol moiety of the **P4** isomer. A shift in the signal attributed to the proton of the generated stereocenter is also observed between **P3** and **P4**. Both diastereoisomers can also been differentiated, since a schift is observed in region δ= 15-2.6 ppm.

Subsequent Alox (Brockmann Activity I)[138] dehydration afforded at room temperature the nitro olefine **64** in 83% yield and with 96% ee (Figure 105). It was important here to know if racemization occurred during the reaction.

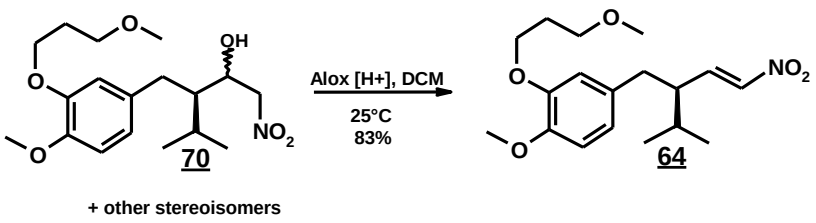


Figure 104: Preparation of **64**

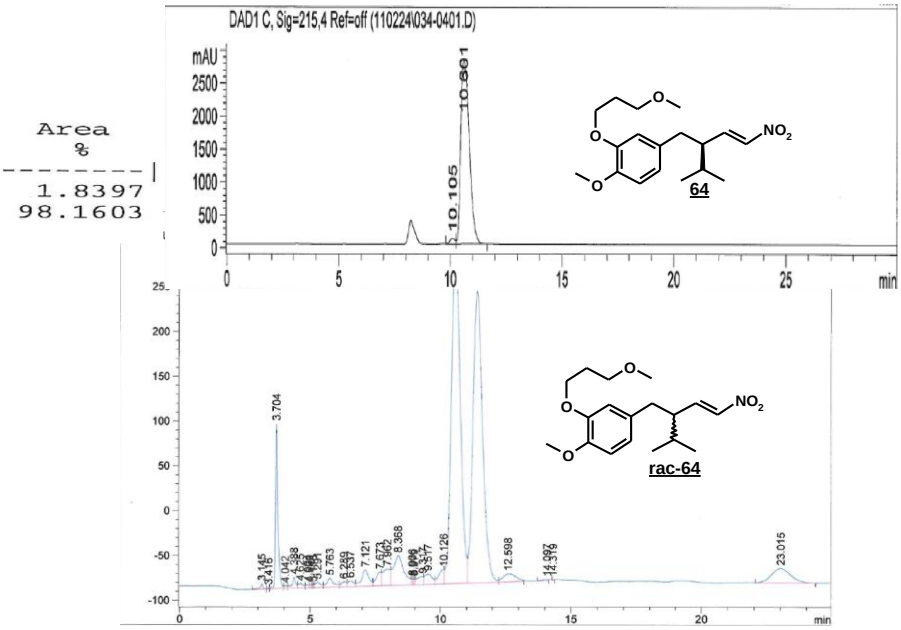


Figure 105: Chiral HPLC of **64** and rac-**64**, CHIRALCEL OD-H, hexane/isopropanol 97:3, 20°C, 1 mL/min, λ=205, 215, 230 nm

A selection of dehydrating agents, solvents and temperature has been investigated for the preparation of **64**. An attractive conversion rate was achieved using Alox (Brockmann Activity I) at 60°C in 1,2 dichloroethane (Table 9, Entry 3).

Entry	Dehydrating agent	Solvent	Temperature	Reaction time (hours)	% **64** formed (%area)[c]
1[a]	Alox	DCM	25°C	17h	77
2[a]	Alox	1,2-dichloroethan	40°C	18h	100
3[a]	Alox	1,2-dichloroethan	60°C	1h45min.	100
4[a]	$KHSO_4$ (3.7 equiv.)	DCM	25°C	18h	-
5[a]	$KHSO_4$ (7.5 equiv.)	1,2-dichloroethan	25°C	18h	1
6[a]	SiO_2	1,2-dichloroethan	25°C	18h	1
7[b]	Ac_20	DMSO	25°C	16h	12

Table 9: Selection of conditions tested for the preparation of 64. [a] The reactions were performed on a 0.3 mmol scale in 1 mL of the selected solvent, in the presence of 150 mg of the dehydrating agent. [b] The reaction was performed on a 0.4 mmol scale in 3.5mL DMSO in the presence of 5.5 equiv. of Ac_20 [c]determined by reverse phase HPLC, column INERTSIL, 40°C, λ=220 nm

The subsequent reduction of **64** with sodium borohydride at 10°C in ethanol afforded the desired (S)-intermediate **59** with 93% yield. HPLC analysis on CHIRALCEL OD-H revealed the presence of 98% of the (R)-enantiomer and 2% of the (S) enantiomer, no racemization occurring during the synthesis.

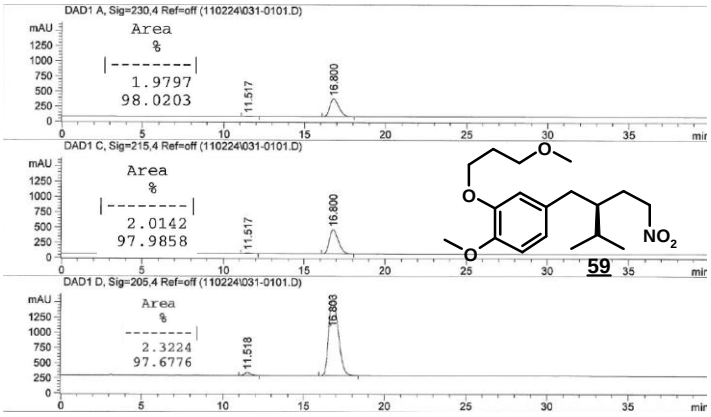


Figure 106: Chiral HPLC of (S)-**59**, CHIRALCEL OD-H, hexane/isopropanol 93:7, 20°C,1 mL/min, λ=215, 205 and 230 nm

III.4.3. Synthesis of Aliskiren precursor 60: proof of concept

The general synthetic approach for the preparation of the known[169,131e,h] and crystalline (S,S,S,S)-Aliskiren precursor **60** from **59** involves a sequence of four chemical transformations, which can be performed within two or three synthetic operations, depending on the protective group introduced on the nitro compound **8**. The key step in the synthesis of **60** remains the chiral ligand-copper-based catalysed *syn*-Henry reaction of **59** with the (S)-aldehydes **45** or **28** (Figure 107).

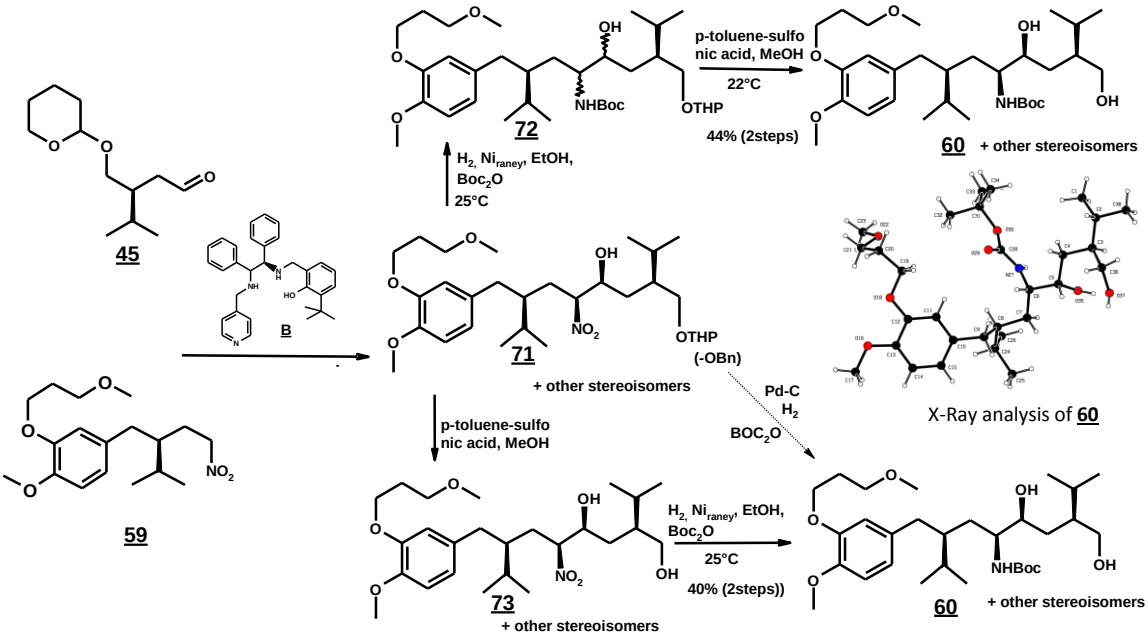


Figure 107: The preparation of the (S,S,S,S)-precursor **60** *via* copper catalyzed asymmetric Henry reaction of nitro compound **59** and aldehyde **45**

III.4.3.1. Copper catalyzed asymmetric Henry reaction

The slow diastereoselective Henry reaction of the nitro compound **59** with the THP protected aldehyde **45** was carried out *via* the *in situ* pre-formation of a complex from copper salts and the chiral ligand **B**.

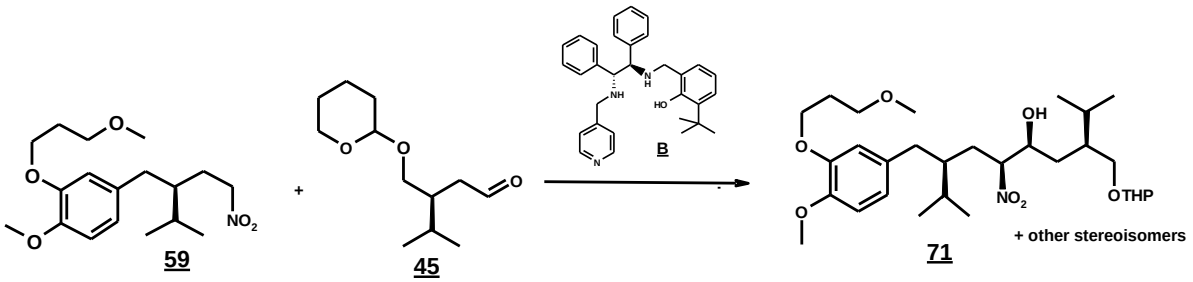
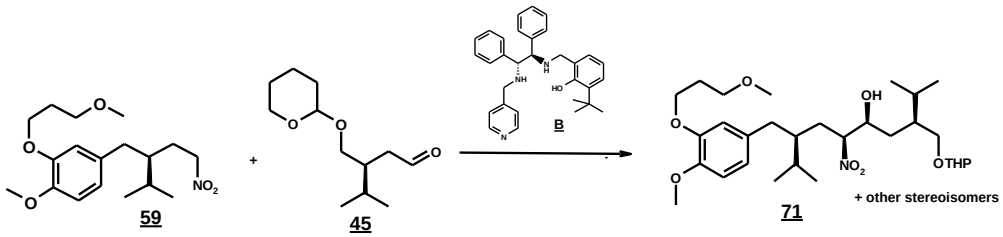


Figure 108: Henry reaction of the nitro compound **59** with the THP protected aldehyde **45**

First, the reaction was carried out using copper (I) salt and the chiral ligand **B**, in the presence of an external base. In a general procedure, the **B**-copper complex was pre-formed by mixing in THF 0.1 equivalent of Cu(I)I salt with 0.04 equivalent of the C_1 symmetric Ligand **B** (in a 1:2 ratio) at room temperature (Figure 89) and subsequent addition of Hünig base (0.8 equivalent). After 45 min, 1 equivalent of the nitro compound **59** and 1.3 equivalent of the THP protected aldehyde **45** were added at 30°C. The desired derivative **71** was isolated in moderate yield (40% yield) as a mixture of diastereoisomers containing 66% of the major stereoisomer (chiral HPLC analysis on CHIRALCEL OD-H).

A selection of conditions (copper (II) salts, additives) has then been investigated for the preparation of (S,S,S,S) **71**. In a general procedure, the **B**- copper (II) complex was generated at a 0.1 equivalent scale by mixing an equimolar ratio of the Cu(II) salt and the C_1 symmetric Ligand **B** (in a 1:2 ratio) at room temperature (Figure 89). After stirring at room temperature for a few minutes, one equivalent of the nitro compound **59** and 1.5 equivalent of the aldehyde **45** were added. The reactions were followed by CHIRALCEL OD-H, with hexane/isopropanol 97:3, 20°C, 1 mL/min, and λ=215 nm.



Entry	Ligand	Ligand /mol%	Metal salt	Metal /mol%	Additives	Solvent	Tempe-rature	**P1**/**P2**/**P3** ratio[a]
1	(R,R)-**B**	10	$Cu(OTf_2)$	10	Hünig Base	Dioxan	25°C	**72**:12:15
2	-	30%	-		Sparteine	EtOH	25°C	**50**:26:24
3	(R,R)-**B**	5	$CuOAc_2$	5	Hünig Base	THF	30°C	**67**:17:16

Table 10: Henry reactions of 59 with aldehyde 45. All reactions were performed with 1.3 equiv. of aldehyde **45** and 1 equiv. of **59** in the selected solvent. [a] determined by chiral HPLC using a CHIRALCEL OD-H column; **P2** and **P3** contained mixture of isomers.

Performing the reaction in ethanol at 25°C in the presence of sparteine afforded the major stereoisomer with a percentage of 50% (Table 10, Entry 2). As illustrated in Figure 109 and Table 10 (Entry 1), $CuOTf_2$ can be employed in dioxane as copper source to perform the Henry reaction of **59** with the aldehyde **45**, since it allowed the formation of the major stereoisomer with the highest ratio. A combination of $CuOAc_2$ and Hünig base in THF allowed also the formation of **71** with a comparable isomeric ratio (Table 10, Entry 3).

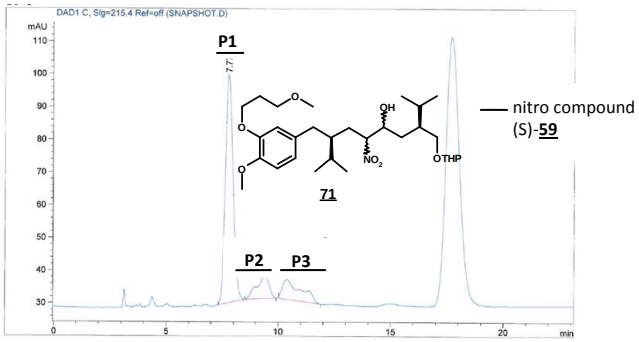


Figure 109: Chiral HPLC of the reaction mixture during the preparation of (S)-**71**, using the conditions described in Table 10, Entry 1, CHIRALCEL OD-H, hexane/isopropanol 97:3, 20°C,1 mL/min, λ=215 nm

The complexes formed by coordination of a chiral ligand type **B** with copper(II) salts are reported to mediate *syn*-selective Henry reactions[9]. According to our previous investigations, the major stereoisomer obtained would/should be the one with the desired (S,S,S,S) configuration. As depicted in Figure 110, the formation of the transition states **TS-I,** where both reactants coordinate the metal centre, driving the reaction to the formation of the *syn* (S,S,S,S) product, could be postulated to explain the stereoselectivity of the reaction.

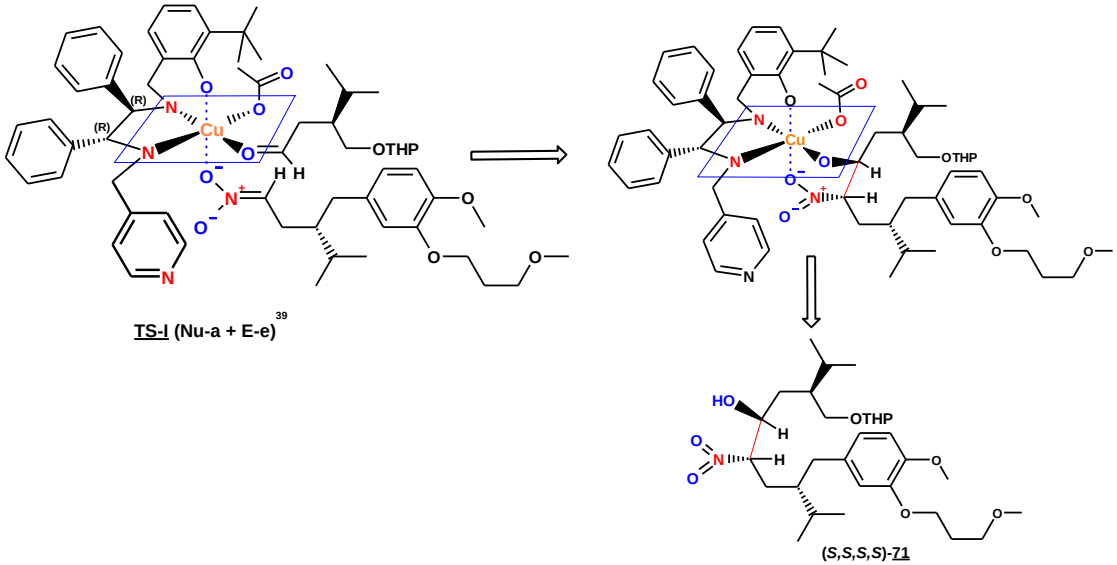


Figure 110: Speculative transition state for the formation of the (*S,S,S,S*) Henry product **71** in the presence of the ligand **B** and $Cu(OAc)_2$

[9] About *syn*-selective Henry reactions: Chapter 1 and references cited

III.4.3.2. Preparation of the (S,S,S,S) Aliskiren precursor 60

Two non optimized routes were tested for the preparation of the crystalline amino-Boc-diol derivative **60** from **71**. The analytical data of **60** are presented in Figure 111.

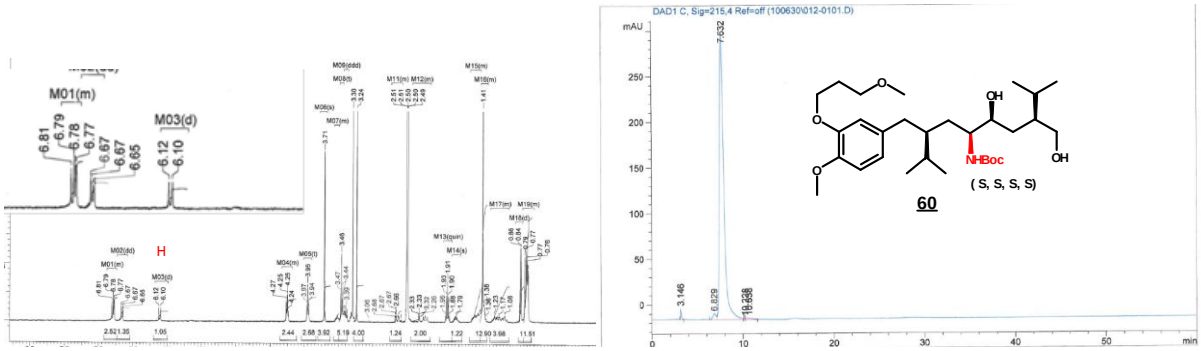


Figure 111: ^{1}HNMR (DMSO-d6) and chiral HPLC (CHIRALCEL OD-H) of the (S,S,S,S) configured isomer of **60**. It was prepared in the laboratory by B. Berod from the API- intermediate **9** by $LiBH_4$-reduction

In the first one-pot approach, the removal of the tetrahydropuranyl protective group of **71** (containing 58% of the major isomer) was carried out by treatment with catalytic amounts of p-toluene sulfonic acid in methanol at room temperature. The successive hydrogenation of the nitro moiety of **73** and protection of the generated amino group, in presence of Raney-Ni and Boc_2O in ethanol under a hydrogen atmosphere afforded the desired derivative **60** containing the desired (S,S,S,S) diastereoisomer as major stereoisomer.

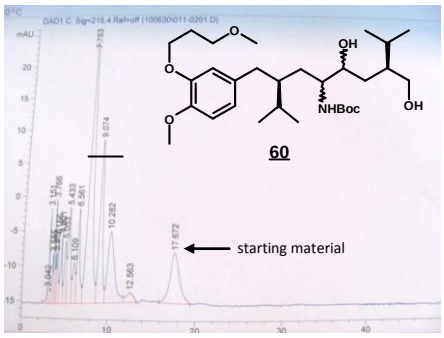


Figure 112: Chiral HPLC of the **60**-crude material, CHIRALCEL OD-H, hexane/isopropanol 97:3, 20°C,1 mL/min, λ=215 nm

Filtration on silicagel of the crude material afforded **60** with (S,S,S,S) isomer as major isomer with an overall yield of 17%, over 3 steps, and four chemical transformations. ^{1}H NMR (DMSO-d^6) analysis of **60** revealed indeed the presence of the characteristic signals of compound **60**: *doublet* at 6.07-6.14 ppm attributed to the NH(-Boc) proton of the (S)-configured Boc amino group and at 6.43-6.47 corresponding to the proton of the (R)-configured Boc amino group in a ratio of ca. 76:24 (Figure 113). Chiral HPLC analysis (CHIRALCEL OD-H) revealed the presence of the signal corresponding to the (S,S,S,S) configured Aliskiren precursor **60** as major one (Figure 113). Since the Henry reaction was expected to afford *syn*-selectivity, and according to the reported analysis, we assume the major diastereoisomer obtained being the (S,S,S,S) configured one.

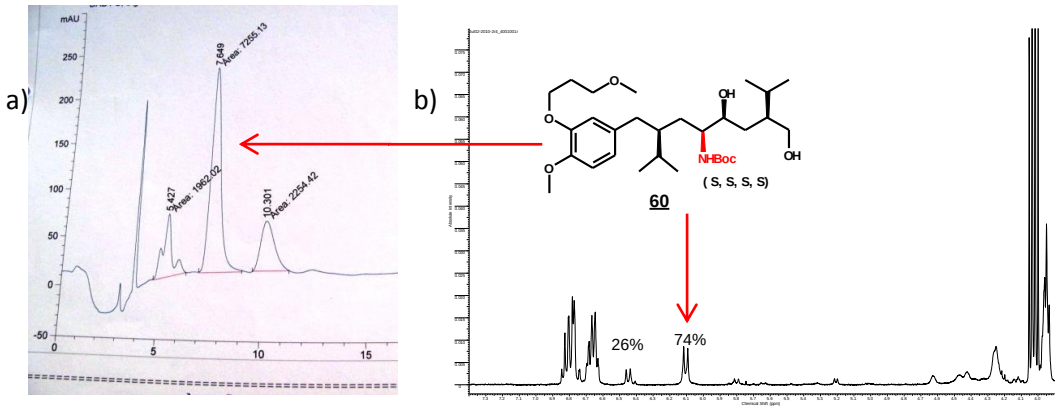


Figure 113: a) Chiral HPLC (CHIRALCEL OD-H) of **60** b) ^{1}H NMR (DMSO-d_6) of **60**

The hydrogenation of **71** containing the major stereoisomer as an isomeric mixture with a ratio of 60:20:20, and the concomitant protection of the generated amino group under hydrogen atmosphere in presence of Raney-Ni and Boc_2O in ethanol at room temperature afforded the amino Boc derivative **72**. Subsequent removal of the THP protective group at room temperature with catalytic amounts of p-toluene sulfonic acid in methanol providing **60** as a mixture of stereoisomers and a moderate overall yield of 41%, over 2 steps, and three chemical transformations.

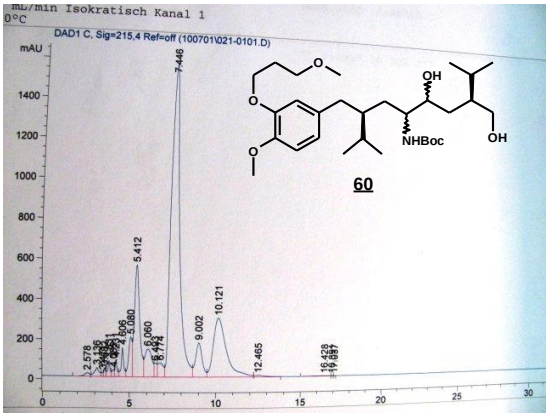


Figure 114: Chiral HPLC of the **60**-crude material, CHIRALCEL OD-H, hexane/isopropanol 97:3, 20°C,1 mL/min, λ=215 nm

Purification on silicagel of the crude material afforded **60** with (S,S,S,S) isomer as major isomer with an overall yield of 44%, over 2 steps, and three chemical transformations. ^{1}H NMR (DMSO-d^{6}) analysis of crude material **60** revealed the presence of the characteristic signals of compound **60**: *doublet* at 6.07-6.14 ppm attributed to the NH(-Boc) proton of the (S)-configured Boc amino group and at 6.43-6.47 corresponding to the proton of the (R)-configured Boc amino group in a ratio of ca. 75:25 (Figure 115). Chiral HPLC analysis (OD-H) revealed the presence of the signal corresponding to the (S,S,S,S) configured Aliskiren precursor **60** as major one (Figure 115). Since the Henry reaction was expected to afford *syn*-selectivity, and according to the reported analysis, we assume the major diastereoisomer obtained being (S,S,S,S) configured.

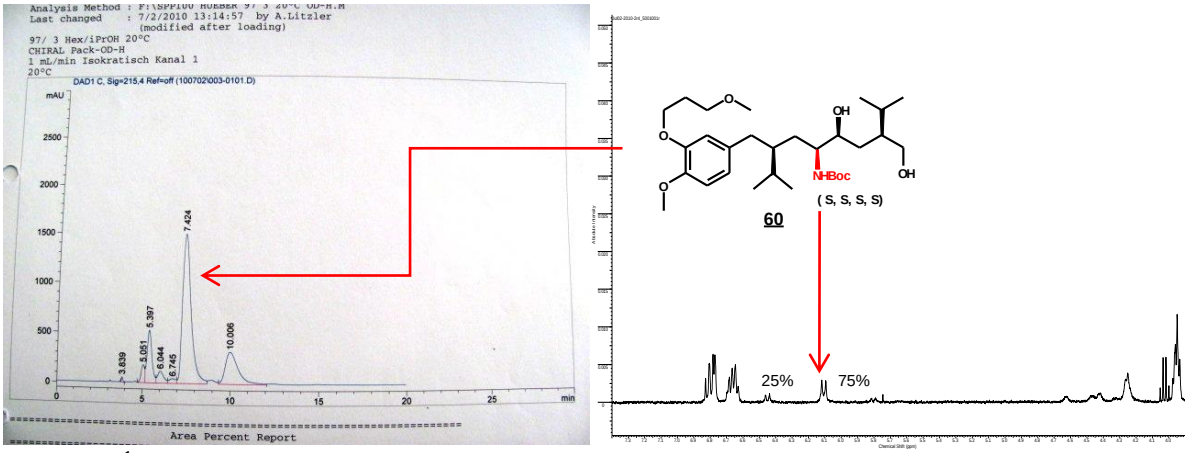


Figure 115: ^{1}HNMR (DMSO-d6) and chiral HPLC (CHIRALCEL OD-H) of the **60**.

III.4.3.3. Conclusion

We reported there a new short route for the total synthesis of (S,S,S,S)-Aliskiren precursor **60**, involving the enantiopure preparation of the two novel precursors **59** and **45**. This strategy includes the use of a chiral ligand-copper catalytic system for the key asymmetric Henry reaction step, which afforded the novel intermediate **71**. The (S,S,S,S)-Aliskiren precursor **60** was isolated from **71**, without any optimization of the reaction steps. We have shown that the described synthetic route could be a practical route for the synthesis of Aliskiren in large scale.
Experiments to isolate the major diastereoisomer of **60** are currently performed in the laboratory. Until now, crystallization assays failed.

IV. New less successful alternative synthesis

IV.1. Introduction

Since the preparation of Aliskiren remains a challenge, we tested some other alternatives to access the precursor **9** from the nitro alcohol derivative **8** (Figure 116).

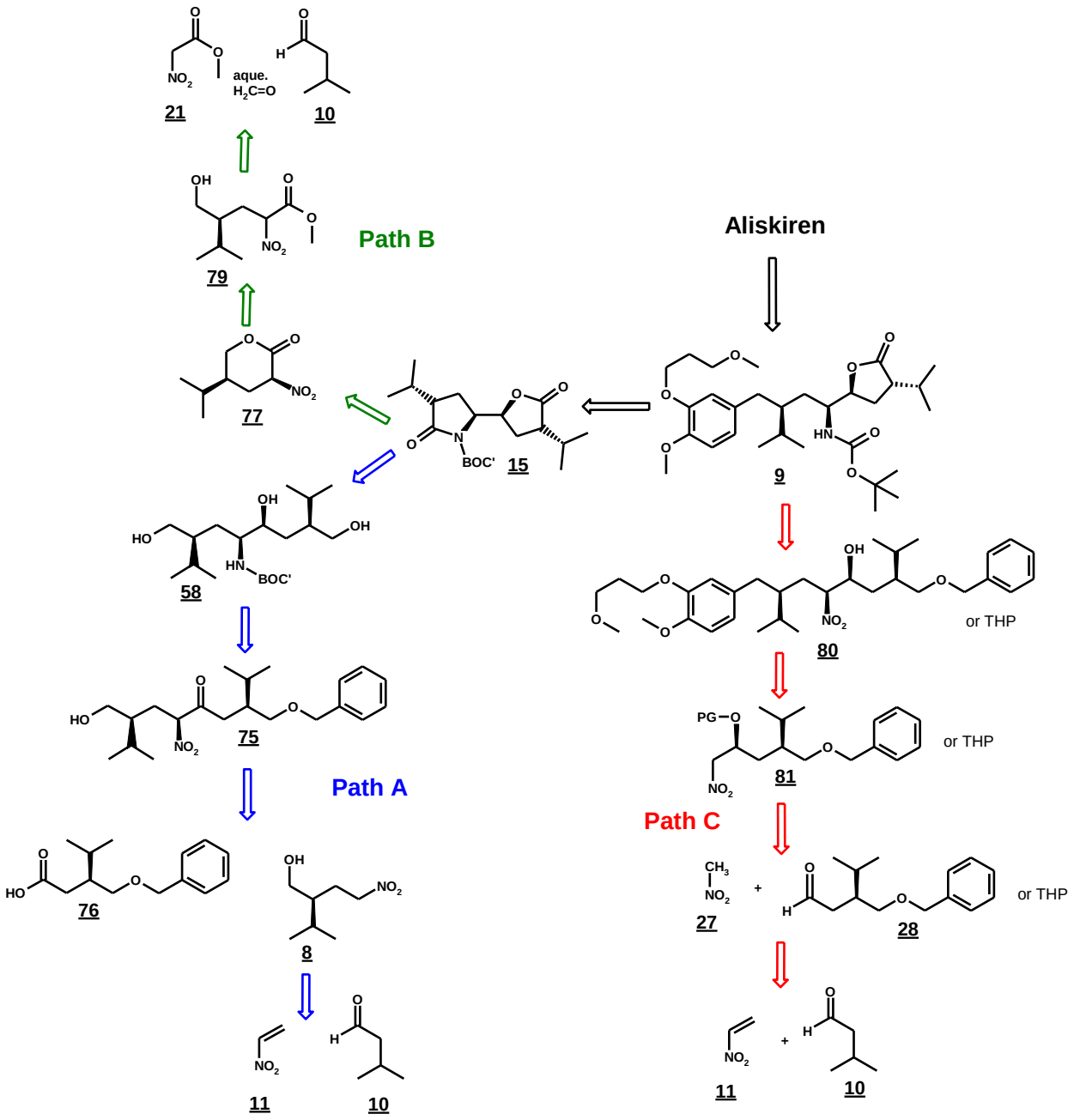


Figure 116: Novel strategies for the total synthesis of Aliskiren **1**

IV.2. Towards the synthesis of Aliskiren *via* pathway A

IV.2.1. Introduction

We proposed to prepare Aliskiren base **1** *via* a "4+4 approach" involving the synthesis of the new nitroketone building block **75**, bearing three of the required (S,S,S) configured substituents of Aliskiren (Figure 117).

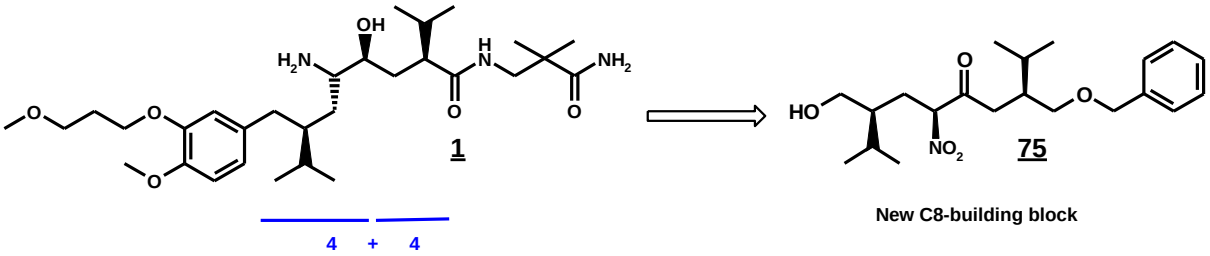


Figure 117: New retrosynthetic study for the preparation of Aliskiren **1** *via* a 4+4 strategy, involving the novel C8 building block **75**

Nitro ketone intermediates are widely used for the synthesis of different classes of compounds, and many methods for their preparation are available in the literature: 1) nitration of enol acetates, potassium enolates, and enol silyl ethers, 2) oxidation of olefins, 3) Henry reaction followed by oxidation, 4) C-α-acylation of the nitro compounds[170] (Figure 118).

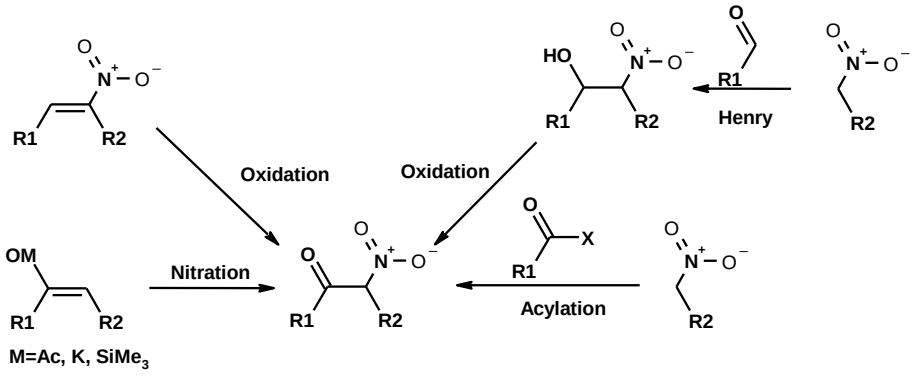


Figure 118: Selected methods for the preparation of nitro ketone derivatives

As illustrated in Figure 119, the preparation of the novel nitroketone derivative **75** was based on the intramolecular acylation of the ester intermediate **82**. We expected that the reaction would be driven by the formation of preferred six carbons ring intermediate *via* a "favoured 6-endo-trig" ring closure[171] and hoped that no *O*-acylation will occur[172].

The lactam-lactone intermediate **15** could be obtained by successive: 1) enantioselective reduction of the nitro ketone **75** to the corresponding β-hydroxyl amino intermediate **58**, 2) protection of the amino moiety by a Boc protective group, and 3) oxidation to the lactam-lactone intermediate **15** (Figure 119).

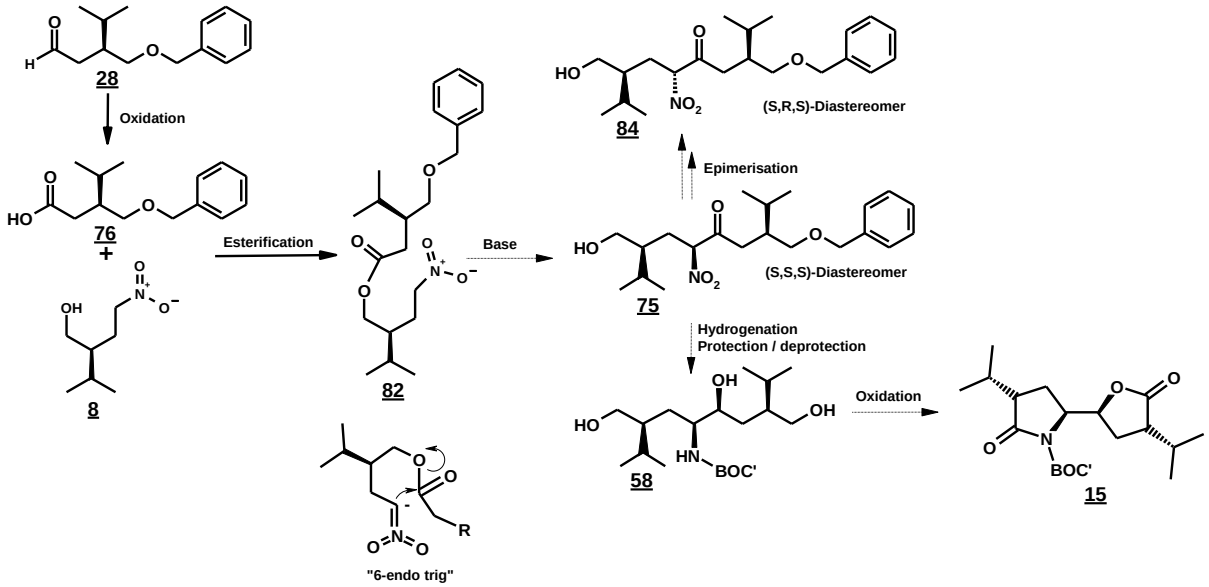


Figure 119: Pathway A for the preparation of C8-lactam lactone intermediate **15**

IV.2.2. Preparation of the novel (S,S) Aliskiren intermediate 82 and intramolecular acylation assays

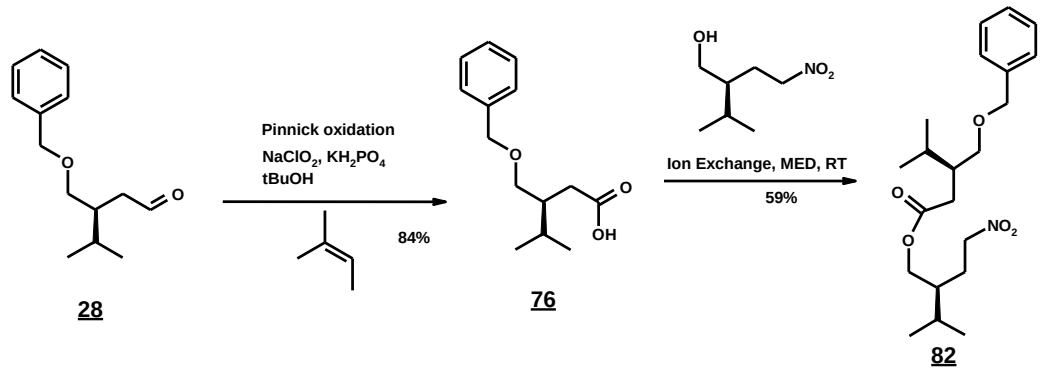


Figure 120: Preparation of the novel (S,S) Aliskiren intermediate **82**

Oxidation of the aldehyde derivative **28** into **76**[10] was performed with 84% yield according Pinnick oxidation conditions by addition of an aqueous solution of $NaClO_2$ and KH_2PO_4 to a mixture of aldehyde and 2-methyl butene in *t*-butanol. **76** was converted to its novel ester analogue **82** with moderate yield 48%, using Amberlist 15[173] in methylene chloride; the same esterification step performed by treatment with DCC/DMAP in dichloromethane at room temperature afforded only 24% of the desired ester **82** after 4.5 days.

The reaction sequence could be applied to a selection of protected aldehyde derivatives. The THP protected derivative **86** for example was prepared with 69% yield from its related nitro compound **32** by treatment of **32** with an aqueous solution of KOH (0.5M) and K_2HPO_4 (1.25M) in *t*-butanol and successive oxidation by an aqueous solution of $KMnO_4$ (Figure 121).

[10] **76** was first isolated in our group by D. Grimler

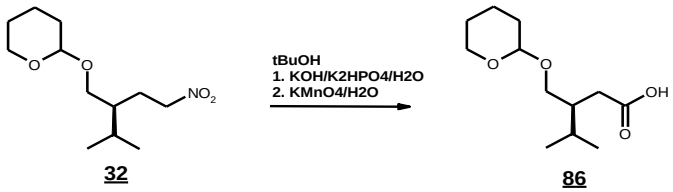


Figure 121: Oxidation of **32** to acid carboxylic acid intermediate **86**

Three different procedures have been tested to prepare the nitro ketone derivative **75** (Figure 122):

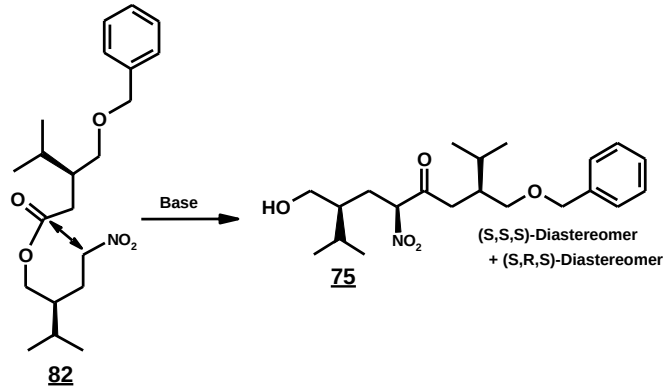


Figure 122: Unsuccessful preparation of the nitro ketone intermediate **75**

1) applying the procedures of Katritzky *et al* (related to the synthesis of nitro ketones using *N*-Acylbenzotriaoles[174]) and Jaeger *et al* [174b], we tried to deprotonate the nitro compound **32** to its nitronate analogue by treatment with two equivalents of *t*-BuOK in dimethyl sulfoxide at 10°C

2) by addition of KF in DMSO

3) by addition of triethylamine in THF.

In all cases, the HPLC and ^{1}H NMR (d_6-DMSO) analysis confirmed the presence of the starting material **32**.

IV.2.3. Conclusion

The reported strategy was based on the synthesis of the nitro ketone intermediate **76**, via the intramolecular acylation of the novel ester derivative **82**. As no systematic screening has been performed, the potential preparation of **75** *via* the formation of the nitronate analogue of **82**, remains possible. Applying for example, the procedures of Seebach[175a] *et al*, who reported the preparation of silyl nitronates from primary and secondary nitroalkanes and the increase of the C-nitronate nucleophily via the formation α,α-doubly deprotonated nitroalkane using a combination of nBuLi and HMPT in THF[175b]. KF or chiral quaternary ammonium salt fluorides[176], LDA, or KHMBS could also be promoters of choice.

IV.3. Towards the synthesis of Aliskiren *via* the pathway B

We envisaged the preparation of Aliskiren via a 3+5 strategy, involving the diastereoselective synthesis of the novel (S,S) lactone intermediate **77** (Figure 123).

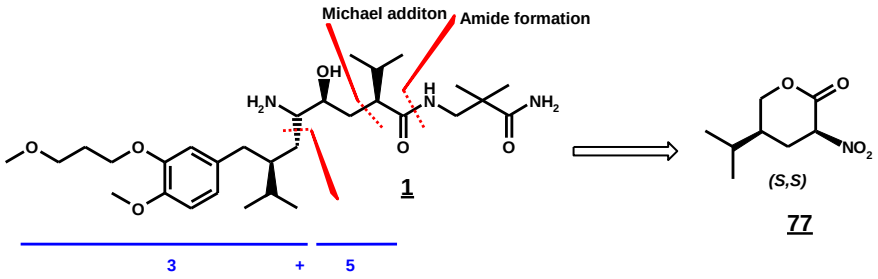


Figure 123: Retrosynthesis proposed for the preparation of Aliskiren base **1** and novel (S,S) lactone intermediate **77**

We exploited the results we obtained for the Michael addition of α-nitroacrylate **22** to isovaleraldehyde, *via in situ* formation of an enamine intermediate with a proline derived catalyst[11]. Performing the *in situ* reduction of the intermediate **20** under acidic conditions provided the lactone intermediate **77** (Figure 124).
The strategy for the multi-step synthesis of **9** or **15** from **77** would involve the preparation of **78** (Figure 124).

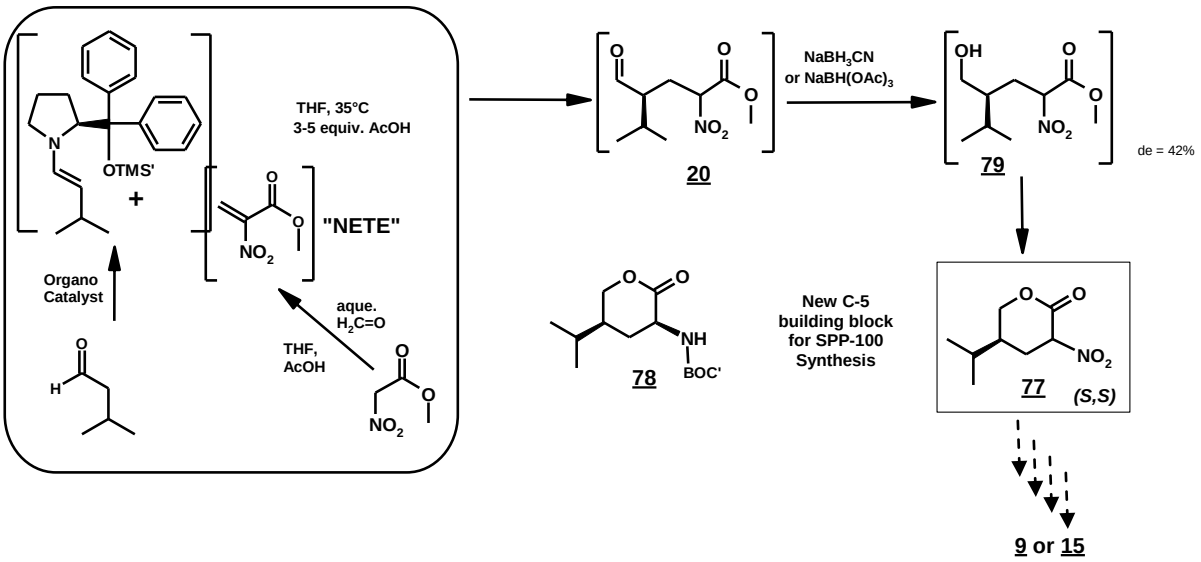


Figure 124: 3+5 strategy for the preparation of Aliskiren base **1**

The Michael addition of the *in situ* generated α-nitro acrylate **22** to isovaleraldehyde was performed as reported in Chapter 2, III.2.3.2.3. The expected Michael product was obtained with a diastereoisomeric excess of *ca*. 50%. Subsequent *in situ* reduction under acidic conditions using an excess of $NaBH_3CN$ (7.7 equiv.) provided the desired lactone **77** in mixture with its alcohol precursor **79** with a diastereoisomeric excess of 42% and 72% yield. Purification by columm chromatography on

[11] see chapter 2, III.2.3

silicagel with heptane/ethyl acetate (3:1) afforded in the pure fractions the desired lactone **77** as an oil and the alcohol precursor **79**. Addition of trifluoracetic acid to a mixture of the derivatives **79** and **77** drives to the formation of pure lactone **77**.

Determination of the diastereoisomeric ratio by ^{1}H NMR ($CDCl_3$, 400 MHz) revealed the presence of 71% of the diastereoisomer **A** and 29% of the diastereoisomer **B** (*syn/anti* stereoisomers) of the alcohol intermediate **79**. ^{1}H NMR (DMSO-d^6, 400 MHz) analysis showed the presence of the characteristic signals of *cis* and *trans* configured intermediate **77** with 1:1 ratio: *dd* at 5.98 ppm attributed to the *cis*-proton in α-position of the nitro group and a *triplet* at 6.04 ppm (J_1=9 Hz) corresponding to the *trans*-proton in α-position.

The preparation of **77** as a 50:50 mixture of the *cis* and *trans* isomers is not satisfactory for the application of the strategy to the synthesis of Aliskiren in large scale. We didn't perform the subsequent reaction steps.

IV.4. Towards the synthesis of Aliskiren *via* the pathway C

We envisaged preparing Aliskiren **1** *via* a 3+5 strategy, involving the novel C5 (S,S)-β hydroxyl nitro intermediate **81** (Figure 125).

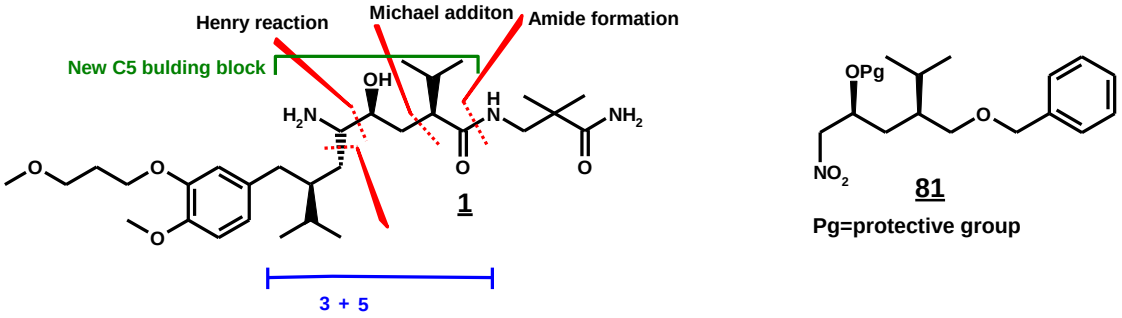


Figure 125: Retrosynthetic study for the preparation of Aliskiren base **1**, involving the novel intermediate **81**

We envisaged to prepare the (S,S) configured derivative **81** *via* a chiral ligand-copper based catalyzed asymmetric Henry reaction. Subsequent alkylation of **81** with the chloride derivative **63** should afford the Aliskiren precursor **80**, bearing the 4 substituents in the C-8 chain of Aliskiren in an all *syn*-configuration (Figure 126).

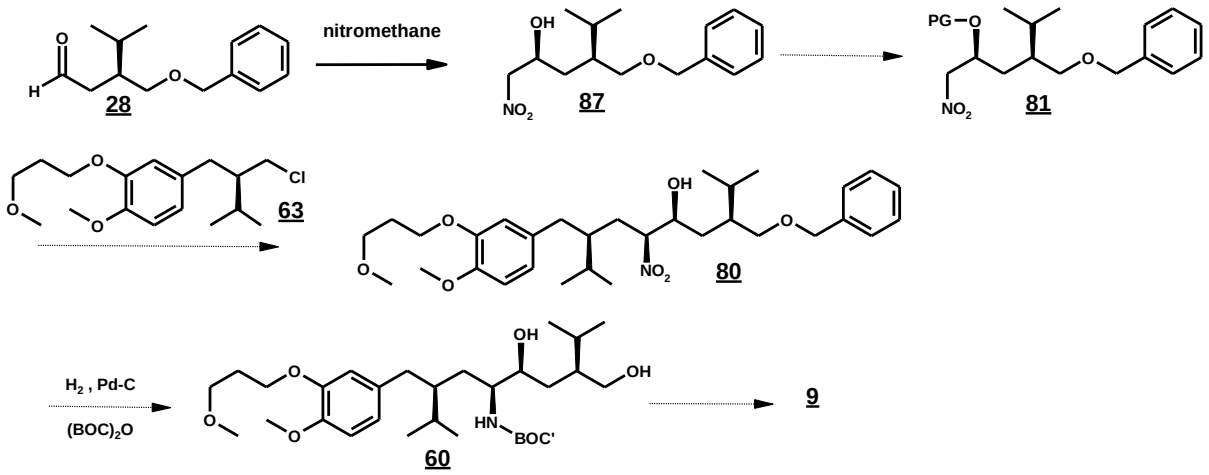
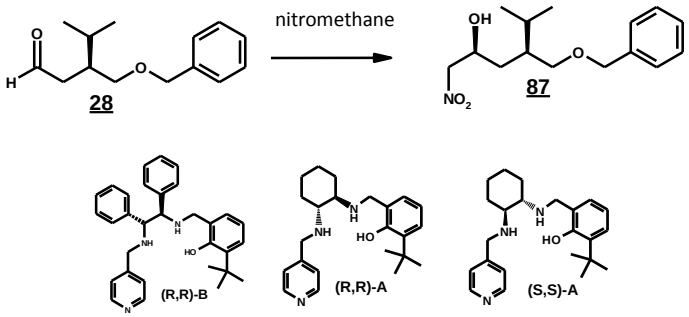


Figure 126: New 5+3 strategy for the preparation of (S,S,S,S) Aliskiren precursor **60**

IV.4.1. Copper catalyzed asymmetric Henry reaction of 28

A selection of conditions were investigated to prepare the (S,S) derivative **87**, involving the formation of complexes from the chiral ligands (R,R)-**B**, (R,R)-**A** and (S,S)-**A** and copper (I) and (II) salts or in the presence of sparteine (Table 11). The reactions were performed on a 1 mmol scale with 1 equiv. of aldehyde and 1.4 equiv. of nitromethane in the selected solvent. The enantiomeric ratios were determined by chiral HPLC using a CHIRALCEL OD-H column.



Entry	Ligand	Ligand/mol%	Metal salt	Metal/mol%	Solvent	Time/h	er (%)[a]	ee (%)[a]
1	(R,R)-**A**	5	$CuOAc_2$	5	MeCN	14h30	2:98	96
2	(S,S)-**A**	5	$CuOAc_2$	5	MeCN	14h30	98:2	96
3[b]	(R,R)-**A**	10	CuI	10	THF	14h30	2:98	96
4[b]	(R,R)-**B**	10	CuI	10	THF	2.5 days	1:99	98
5	sparteine	30	-	-	-	15h	40:60	20

Table 11: Enantioselective Henry reactions of CH_3NO_2 with benzyl protected aldehyde in the presence of various ligands. All reactions were performed on a 1 mmol scale with 1 equiv. of aldehyde and 1.4 equiv. of nitromethane in the solvent. [a] determined by HPLC using a CHIRALCEL OD-H column [b] 5 mol% iPr_2EtN was added

Performing the Henry reaction of **28** with nitromethane in the presence of sparteine afforded the β-hydroxyl compound **87** with a moderate enantioselectivity (ee=20%, Table 11, Entry 5). Excellent enantioselectivities (ee up to 98%) were obtained in the presence of *in situ* generated complexes from the chiral ligands (R,R)-**A** and (S,S)-**A** and copper (II) salt (Table 11, Entries 1-2) and in the

presence of in-situ generated complexes from the chiral ligands (R,R)-**A** and (R,R)-**B** and copper (I) salt and of an external base (Table 11, Entry 3-4). It is interesting to note that the (R,R)-**B** and copper (I) salt system don't perform the reaction as fast as the other tested systems.

The (R,R)-**A** and (R,R)-**B** ligands afforded the diastereoisomer **87-A** as the major isomer, while the (S,S)-**A** ligand provided the diastereoisomer **87-B** as the major one. According to the literature speculations and our own results, we suppose the diastereoisomer **87-A** to be the (S,S) configured isomer, and **87-B** the (S,R) configured isomer. We propose to explain, for example, the formation of **87-A**, the formation of the transition state presented in Figure 127; the coordination of the nitro component and of the aldehyde to the catalytic system driving the stereochemistry of the formed product.

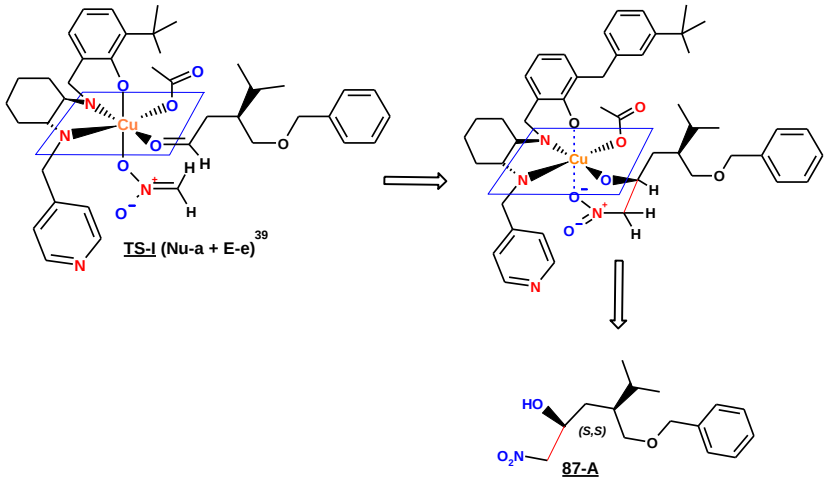


Figure 127: Proposed transition states for the formation of the **87-A**

The Henry reaction of **28** with nitromethane in the presence of (R,R)-A was performed on a 54 mmol scale, using (R,R)-**A** and $Cu(OAc)_2$ in ethanol. After 24 hours, the β-hydroxyl compound **87** was isolated with an excellent enantiomeric excess of 96%.

IV.4.2. Preparation of the C5 β-hydroxyl nitro intermediate 81 and α-alkylation

The alkylation step required the protection of the β-hydroxyl group of **87**. We selected the MIP protective group. The protective group was introduced with 78% yield (after chromatography) under standard conditions by stirring **87** in a large excess of 2-methoxy propene at 36°C in the presence of catalytic amount of polymer bound pyridinium toluene-4-sulfonate.

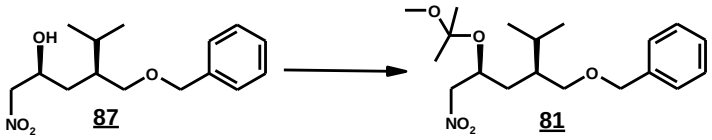


Figure 128: MIP protection of the β-hydroxyl nitro intermediate **87**

The α-alkylation of **81** was performed 1) by applying the conditions described by Seebach *et al*[177] (additon of 6 equivalents of HMPA and 2 equivalents of *n*BuLi in THF to a solution of nitro derivative **81** at low temperature) 2) by generating the nitronate analogue of **81** by addition of organic base, such as triethylamine. None of the selected conditions yielded the desired Aliskiren precursor **80** (Figure 116).
An alternative procedure might be tested, consisting in the α-alkylation of the nitro ketone **84** using for example the procedures of Stach *et al*, Ono *et al* or Ballini *et al*[178] (Figure 129).

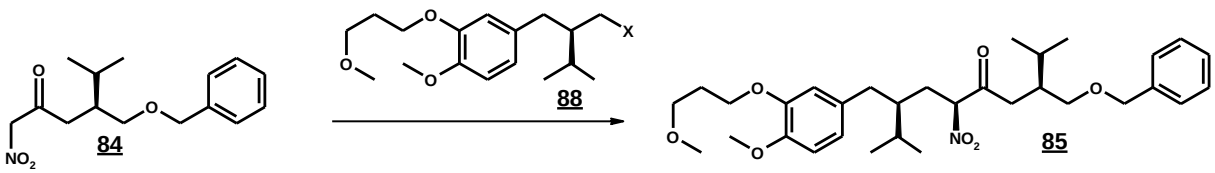


Figure 129: α-alkylation of the β-nitro ketone intermediate **84**

V. Conclusion

Our interest in the development of new asymmetric alternative routes to the renin inhibitor Aliskiren base **1** led us to develop five different approaches for the synthesis of different advanced precursors of Aliskiren **1**.

During our investigations using the chemistry of the nitro group, we focused our attention on the asymmetric preparation of β-and δ-hydroxyl nitro compounds, *via* different catalytic asymmetric strategies:

- *via* a multi-component Knoevenagel-Michael sequence, involving the Michael addition of commercially available aldehyde **10** and the *in-situ* generated α-substituted nitroethylene **19** derivative via the formation of enamine intermediate with proline related organocatalysts,

- *via* a multi-component aldolization-Michael sequence, involving the Michael addition of the *in situ* generated acrolein derivative **25** and nitroalkanes *via* the formation of iminium intermediates with proline related organocatalysts,

- *via* copper catalyzed *syn*-Henry reactions, involving the *in situ* formation of complexes of chiral Salan ligands and copper (I) and (II) salts.

Among the synthetic routes we have tested, the first one (the so-called III generation) was successfully applied after optimization to a kilo-lab campaign.

The novel approach based on the preparation of the novel nitro derivative **59**, has been patented in 2011. At this stage the other alternative routes would need a major optimization effort to be applied for the preparation of Aliskiren.

CHAPTER 3: ASYMMETRIC SYNTHESIS OF A POTENTIAL DRUG FOR THE TREATMENT OF PARKINSON: AFQ056

I. Pharmacological properties

In the second part of this Ph.D. we worked on the preparation of another Novartis drug candidate: AFQ056 **90**, the (3aR, 4S, 7aR)-4-hydroxy-4-*m*-tolylethynyl-octahydro-indole-I-carboxylic acid methyl ester represented in Figure 130.

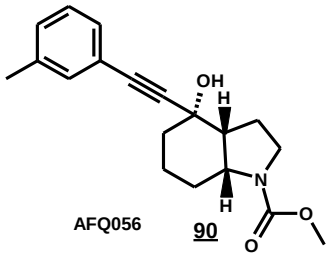


Figure 130: Novartis drug candidate AFQ056 **90**

It belongs to the therapeutic class of glutamate (mGluR5 - metabotropic receptor subtype 5) antagonists. These compounds, selective for mGlu receptors, particularly $mGlu_{2/3}$ and/or $mGlu_5$, have proven their efficacy in the treatment of disorders associated to irregularities of glutamatergic signal transmission and of central nervous disorders mediated by $mGluR_5$ causing many diseases.

Glutamate is the major neurotransmitter in mammalian central nervous system. It is released by nerve cells in the brain (about 70 % of all excitatory synapses in the central nervous system are stimulated by glutamate) and is responsible for sending signals between neurons, and so plays an important role in learning and memory. Glutamate mediates and regulates neurotransmission by its interactions with families of receptors and transporters, such as metabotropic G-protein-coupled glutamate (mGlu) receptors. Dysfunction of glutamatergic neurotransmission (overconcentration of glutamate or over sensibility of nerve cells to glutamate) can generate nerve cell damage or death, causing many diseases such as pain, anxiety[179], psychiatric diseases, dementia, epilepsy, ischemic diseases, Parkinson's disease and disorders associated, Alzheimer, Huntington Chorea, and multiple sclerosis[184].

As specific mGluR5 antagonist, AFQ056 has the potential to become the first treatment of Parkinson's disease levodopa[12]-induced dyskinesia[13,180]. The Parkinson's disease is caused by a progressive loss of neurons in the *nigratum stratum*, the part of the brain that produces dopamine

[12] Levodopa: L-3.4 dihydroxyphenylalanine was discovered by Hoffmann La Roche in 1973, and is marketed under the name of Modopar. It was the first antagonist shown to be selective of the $mGlu_5$ and $mGlu_1$ receptor and it is used for the treatment of Parkinson's disease.

[13] Levodopa-induced dyskinesia is the major problem in the treatment of Parkinson's disease. It results from the chronic Levodopa treatment, yielding in the occurrence of abnormal involuntary movements.

and controls the movement; resulting in the decrease of production of dopamine and in abnormal and involuntary movements. AFQ056 proved positive results *in vitro*, *in vivo* [180] and in clinical study[181] and will be enrolled in a Phase IIb trial.

AFQ056 showed also promising results in the treatment of other diseases, such as of behavioral symptoms linked to brain disorder, or autism. A recent study[182] showed promising effects in the treatment of patients suffering from Fragile X syndrome (FXS). This syndrome is an X-linked damage that affects one per 5000 boys and one per 9000 girls and causes intellectual disability and behavior problems including anxiety, aggression, hyperactivity, impulsivity, shyness, attention deficit disorder, and autism. AFQ056 as specific glutamate mGluR5 antagonist blocks the expression of the FMR1 gene (responsible of the over activation of mGluR5 pathways and of Fragile X Syndrome), and is a potential treatment of FragileX Syndrome.

II. Preparation

The preparation of the AFQ056 **90** structure was first published in 2003 by Gasparini *et al* [183]. In 2010, Kuesters *et al* [184] (and co-workers) patented an alternative process for the preparation of the 1,5,6,7-tetrahydroindol-4-one building block (**91**, Figure 131) in four steps from the commercially available cyclohexenone **93**.

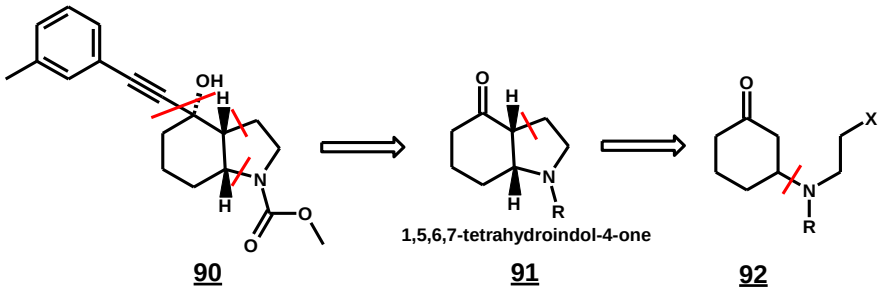


Figure 131: Reported strategy for the preparation of AFQ056 **90**

The first step of the synthesis involves, such as described by Dolfini and Dolfini in their paper[185], the Michael addition of aziridine to cyclohexenone **93** affording the substituted cyclohexanone **94**. The resulting tertiary aziridine ring of **94** is then cleaved by addition of methyl chloroformate providing the halogenated intermediate named **92**.

Dolfini and Dolfini have indeed proved that alkyl chloroformate can convert the aziridine derivatives. The opening of the aziridine ring is due to release of the ring strain of the aziridinium salt (Figure 132).

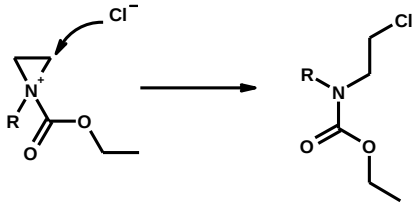


Figure 132: Aziridine ring opening

The cyclisation step is performed *via* the *in situ* formation of an enamine intermediate from a secondary amino base and **95**, and affords as major compounds the both *syn* (R,R) and (S,S) stereoisomers **96**, being separable on preparative chiral column chromatography.
Addition 1-ethynyl-3-methyl-benzene in THF in the presence of nBuLi to **97** provides the desired drug product **90** with high enantioselectivity.

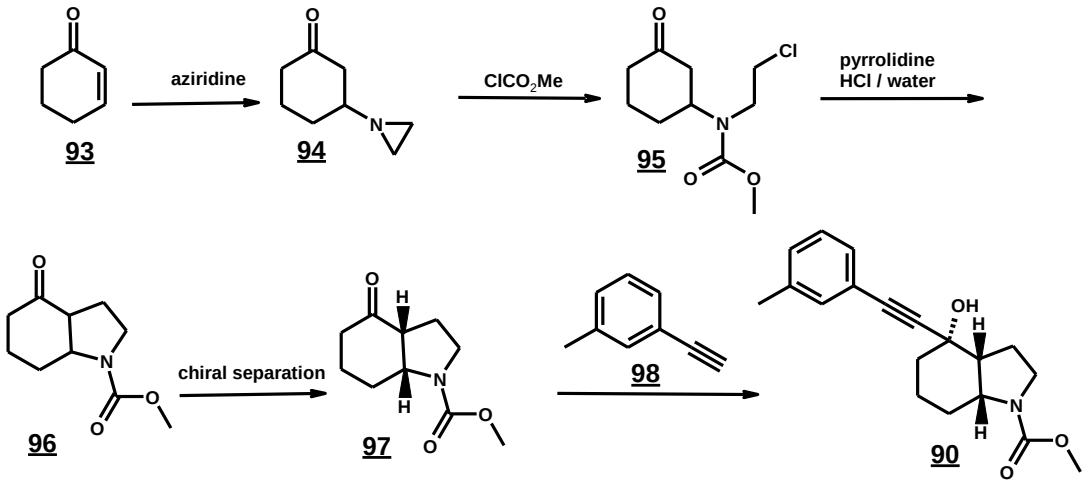


Figure 133: Patented process for the preparation of AFQ056 **90**[184]

One drawback of this process is clearly the preparation of compound **96** as racemic mixture, resulting in the loss of at least 50 % of the product. Therefore the development of an alternative asymmetric process is of great importance.

III. New asymmetric strategy

III.1. Introduction

The challenge in the preparation of AFQ056 **90** remains the introduction of the chirality on the early stage of the synthesis.

To that purpose, we focus our attention on an organocatalytic asymmetric version of the current aza-Michael addition, involving aziridine or more reactive nucleophiles (bearing or not the required two-carbons side chain) and proceeding *via* iminium activation (Figure 134).

Very few organocatalytic asymmetric aza-Michael addition of amino nucleophiles to cyclohexenone are available in the literature (Jorgensen *et al*[186]), whereas many publications report efficient racemic versions, using for example Lewis acid[187], ionic liquid[188] or copper complexes immobilized in ionic liquid[189], copper salts[190], $FeCl_3/Me_3SiCl$ systems[191], phase transfer catalysts[192].

We based also our approach on the fact that the cyclisation step could be achieved *via* enamine **99** activation (Figure 134), according to work published by List *et al* [193] relative to the catalytic asymmetric intramolecular α-alkylation of aldehydes using proline related catalysts.

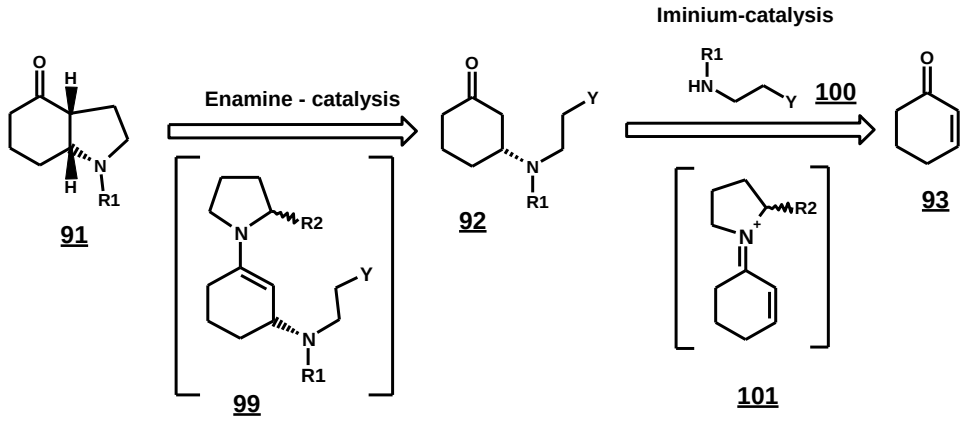


Figure 134: Proposed new asymmetric approach for the preparation of AFQ056 intermediates

This strategy offers the possibility to prepare of the enantiopure or enriched 1,5,6,7-tetrahydroindol-4-one building block of AFQ056 (**90**) in a one pot sequence of a domino process, based on an iminium-enamine activation (**101**, **99**) cascade (using the same organocatalyst for both steps). Moreover the amino ketone derivatives type **92** could be prepared *via* two different pathways (Figure 135):

1) In one step: using an activated aza-nucleophile bearing the required side chain and leaving group

2) In two steps: *via* Michael addition of an activated secondary amino nucleophile to cyclohexenone **93**, and subsequent alkylation of the resulting amino derivative.

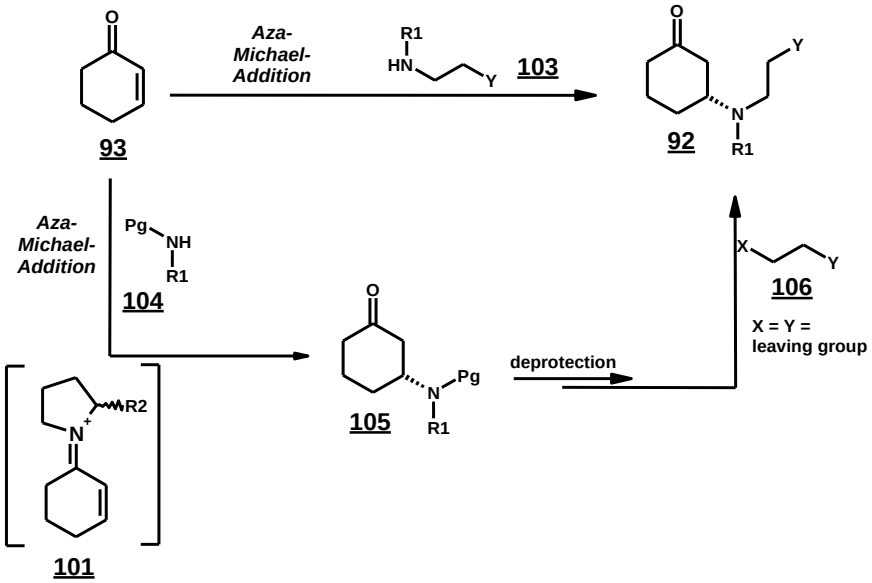


Figure 135: Asymmetric strategies for the preparation of intermediate **92**

III.1.1. Design of the nucleophiles

The major concern relative to the design of an efficient aza-nucleophile is that, it has to be nucleophilic enough to undergo the Michael addition, but should not react with the α,β unsaturated enone to form an iminium ion.

To that extend, we based our design on the work of MacMillan *et al* [194] , Codorva *et al* [195] and Ricci *et al* [196] , who reported the addition of *N*-silylcarbamates to crotonaldehyde (MacMillan *et al*), catalytic asymmetric aziridination of α,β-unsaturated aldehydes (Cordova *et al*), and *O*-benzyl hydroxyl amine to chalcones (Ricci *et al*). We tried to increase the nucleophilicity of the amino center *via* α-effect[197] generated by the introduction of a N-O functionality.

The type of the substituents at the nitrogen atom of the nucleophile plays a role in the selectivity of the reaction. Indeed, as reported in 2011[195b] by Cordova *et al*, completely different chemoselectivity can be obtained depending on the substituents on the N-atom of the nucleophiles, affecting its pKa.

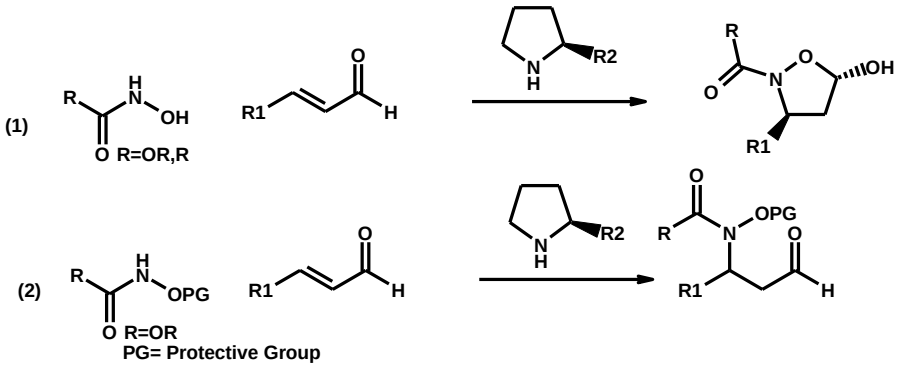


Figure 136[195b]**:** Influence of the N-substituents on the type of product formed by Michael additions

For example, secondary hydroxylamines containing an electron-withdrawing substituent (carbamate or acyl group) at the N atom leads to a tandem aza-Michael/hemiacetal sequence to furnish 5-hydroxyoxazolidines (Eq. 1, Figure 136). In contrast, having a protective group on the oxygen atom (trimethylsilyl (TMS), tert-butyldimethylsilyl (TBS), Me, or Bn) of a carbamate-protected hydroxylamine affords the desired aza-conjugate adduct if the enal is aliphatic (Eq. 2, Figure 136). However, reacting an O-protected N-aryl- or -alkyl-substituted hydroxylamine with an enal drives the reaction to the formation of an iminium ion[195b].

According to the considerations above, we selected the following *O*-benzylhyroxylamines as potential adequate nucleophiles (Figure 137).

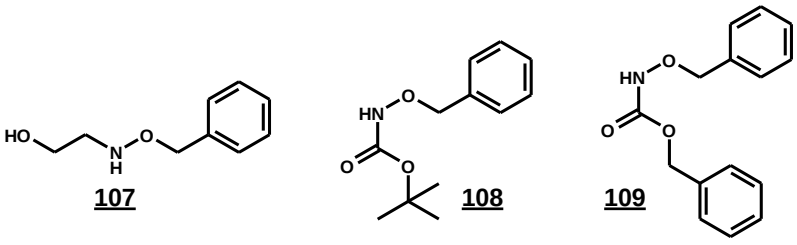


Figure 137: Selected nucleophiles for aza-Michael additions

In addition, we imagined the use of hydrazone derivatives, which are described by Jorgensen *et al* [186] to be effective nucleophiles in aza-Michael addition to cyclic enones using cinchona alkaloids as catalysts (Figure 138).

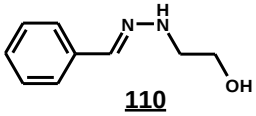


Figure 138: Selected hydrazone nucleophile **110**

III.1.2. Selection of the organocatalysts for the investigated aza-Michael additions to cyclohexenone

The right catalysts[194] should be able to form an iminium intermediate with the α-β unsaturated enone, but should not perform any 1,4 conjugate additions to the cyclohexenone **93**, resulting in catalyst consumption.
We selected proline related catalysts[198a-b,195c], that are known to participate in asymmetric Michael addition *via* the formation of iminium species with acyclic or cyclic α-β unsaturated enones[98b].

III.2. Results and discussion

III.2.1. Synthesis of the *N*-benzylhydoxylamine derivatives 107 and 109

The *N*-benzylhydroxyl amines **107** and **109** were prepared according to the literature procedures.
Many methods are available for the CBz- protection of amino groups[140]. The Z- protected *N*-hyroxylbenzyl amine **109** was prepared (Figure 139) in 89% yield from the commercially available benzyl hydroxylamine hydrochloride **111** by addition of a solution of Z-succinimidyl **88** (1.0 equivalent) and DMAP (0.1 equivalent) in tetrahydrofuran at room temperature.

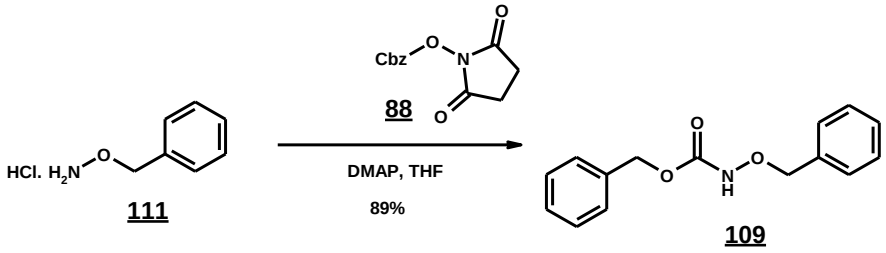


Figure 139: Synthesis of Z- protected *N*-hyroxylbenzyl amine **109**

The nucleophile **107** was prepared from the commercially available Boc protected benzyl hydroxylamine **108** in 2 steps (Figure 140) according to the procedure of Slusky and Demers[199]. In the first step, the alkylation of 1.0 equivalent of **108** with 1.0 equivalent of 2-bromo-1-tert-butvldimethylsilyloxy-ethane in the presence of 1.1 equivalent of NaH in DMF at 60°C afforded the novel tertiary amine **113** with 83% yield. Concomitant hydrolysis of the TBDMS and Boc protective groups was performed in dry dichloromethane at 0°C to room temperature in presence of trifluoroacetic acid. The base was generated in ethyl acetate by addition of potassium carbonate, yielding the nucleophile **107** in 96% yield.

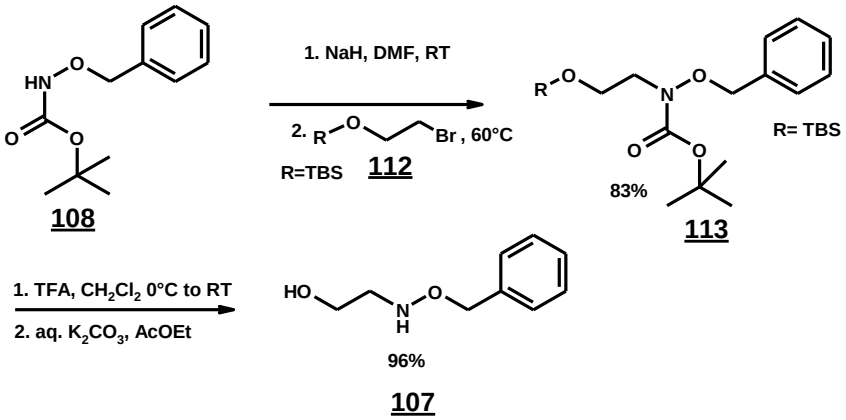


Figure 140: Preparation of **107**

The commercially available bromo ethanol **114** was protected according to the procedure of Vader[200], by addition of 1.0 equivalent of TBDMS triflate and 1.3 equivalent of imidazole at 0°C to a solution of 1.0 equivalent of bromoethanol in DMF at 0°C (Figure 141).

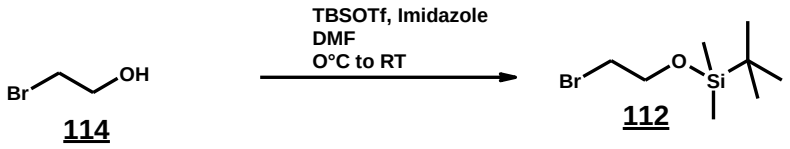


Figure 141: *Tert*-butyldimethylsilyloxy protection of bromoethanol **114**

III.2.2. Iminium catalysis

We turned our attention to the racemic preparation of the following β-amino hexanone intermediates **115** and **116** (Figure 142).

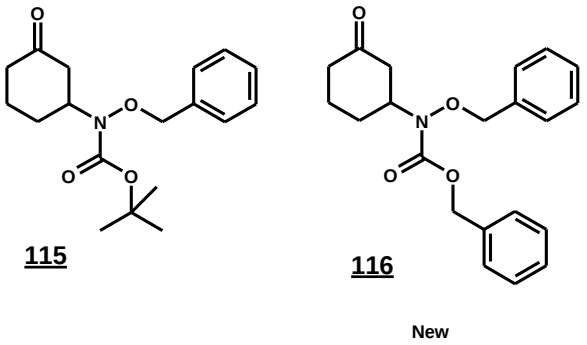


Figure 142: β-amino cyclohexanone intermediates **115** and **116**

The Michael adducts **115** and **116** (Figure 142) were prepared using the procedures of Park and Jeong[192], related to the aza-Michael addition of tert-butyl benzyloxycarbamates to a wide range of electron deficient olefins using potassium hydroxide (50%w/w, 1.2 equivalent) in the presence of 10 mol% of tetrabutylammonium bromide (TBAB) as phase-transfer catalyst in toluene phase. Mixing 2.0 equivalents of the Boc-protected benzylhydroxyl amine derivative **106** and 0.1 equivalent of TBAB in toluene a room temperature and consecutive addition of an aqueous solution of potassium hydroxide and of 1.0 equivalent of cyclohexenone **93**, afforded after 50 min at room temperature

and aqueous work-up, the desired Michael adduct **115** as racemic mixture with 30% isolated yield. With this material in hand, we were able to develop a analytical methods for the separation of the enantiomers.

Using the same procedure for the Michael addition of benzyl benzyloxycarbamate **109**, afforded after 6 days the novel Michael adduct **116** in 77%.

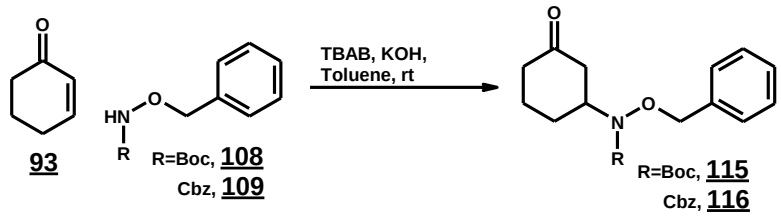


Figure 143: Racemic aza-Michael addition of *tert*-butyl- and benzyl- benzyloxycarbamates **108** and **109** to cyclohexenone **93** using TBAB as phase transfert catalysts

III.2.2.1. First studies on the *tert*-butyl benzyloxycarbamate nucleophile 108

With the analytical characterizations of the racemic mixture of the Michael adduct **115** in hand, we performed the screening of a selection of catalysts, solvents, additives, temperatures, to prepare them in an enantiomeric pure or enriched way. In the first studies we used the commercially available Boc protected hydroxyl amine **108** as nucleophile and screened the following catalysts **I-VI** (Figure 144).

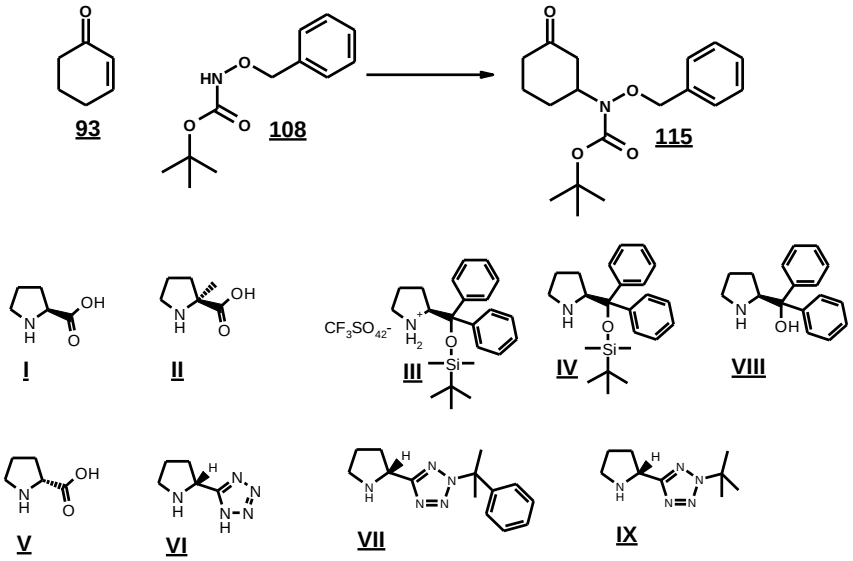


Figure 144: Proline and related organocatalysts screened in the Michael addition of **108** to cyclohexenone **93**

The following tables compile some results, which were obtained during our investigations.

-Table 12, influence of the catalyst

-Table 15, influence of the base

- Table 14, influence of the temperature

First, we applied the promising conditions reported by Ley *et al*[201] in 2008 for the organocatalytic enantioselective synthesis of nitrocyclopropanes from bromonitromethane and cyclic and acyclic

enones, using organocatalyst **VI** in the presence of morpholine in chloroform. We therefore screened the organocatalysts presented in Figure 144.

It is first noteworthy to report that no reaction occured during the tested reaction time when no base additive was used. Only the R-tetrazole derivative **VI** and α-L-methyl proline **II** afforded the desired product with poor yields and enantioselectivity (Table 12, Entries 2 and 5). In the case of the OTBMS diphenyl prolinol ethers **II** and **III** without addition of a base, no conversion occurred (Table 12, Entries 3 and 4). The L- and D- proline catalysts **I** and **V** did not provide any enantioselectivity (Table 12, Entries 1 and 6), but we observed better conversion rate.

Entry	Catalyst	Temperature	Base	Solvent	Reaction time	% **115** (%area)	ee (%)
1	**I**	Room temperature	Morpholine	$CHCl_3$	2 days	32	11
2	**II**	Room temperature	Morpholine	$CHCl_3$	2 days	28	28
3	**III**	Room temperature	-	$CHCl_3$	2 days	-	-
4	**IV**	Room temperature	-	$CHCl_3$	16 hours	-	-
5	**VI**	Room temperature	Morpholine	$CHCl_3$	2 days	28	28
6	**V**	Room temperature	Morpholine	$CHCl_3$	2 days	70	4
7	**VI**	Room temperature	-	$CHCl_3$	2 days	-	-

Table 12: Iminium catalysis, screening of catalysts Reactions were performed on 1 mmol scale at a concentration of 4 mL/mmol with 15% of catalyst in the presence of 1 equivalent of base, 1 equivalent of cyclohexenone and 1.5 equivalent of nucleophile. Conversion rate and enantiomeric excess were determined by chiral phase HPLC (CHIRALPAK AD-H).

With the moderate effective organocatalyst **VI** in hand, optimization of the reaction conditions was undertaken by screening different solvents (acetonitrile, chloroform, dichloromethane, dimethylformamide, toluene, dimethylsulfoxide, diethyl ether), the best one being chloroform in term of both yields and enantioselectivities. Performing the reaction under solvent-free conditions resulted in the increase of the reaction rate, but yielded in the decrease of the enantioselectivity (Table 13). The same trend was obtained using L-proline **I** and triethylamine as base.

Entry	Catalyst	Temperature	Base	Solvent	Reaction time	Conversion (%area)	ee (%)
1	**VI**	O°C	Morpholine	-	3 days	36%	36
2	**VI**	room temperature	Morpholine	-	3 days	76%	24

Table 13: Iminium catalysis, Reactions were performed on 1 mmol scale with 15% of catalyst in the presence of 1 equivalent of base, 3 equivalents of cyclohexenone and 1.0 equivalent of nucleophile. Conversion rate and enantiomeric excess were determined by chiral phase HPLC (CHIRALPAK AD-H).

A similar trend was obtained (faster reaction, but lower enantioselectivity) by increasing the temperature (Table 14, Entries 1-3 and 4-6). The use of 15% of organocatalyst **VI** at 0°C or 10°C was found to be the best conditions, yielding the desired product with an enantiomeric excess of 54% (Table 14, Entries 2-3).

Entry	Catalyst	Temperature	Reaction time	Conversion (%area)	ee (%)
1	**VI**	Room temperature	20h	16%	28
2	**VI**	10°C	15h	7.5%	54
3	**VI**	0°C	48h	8%	54
4	**I**	Room temperature	48h	32%	11
5	**I**	10°C	15h	11%	28
6	**I**	0°C	48h	13%	28

Table 14: Iminium catalysis, impact of temperature Reactions were performed on 1 mmol scale at a concentration of 4 mL/mmol in chloroform with 15% of catalyst in the presence of 1 equivalent of morpholine. Conversion rate and enantiomeric excess were determined by chiral phase HPLC (CHIRALPAK AD-H).

We then examined the impact of the base additives on the rate and enantioselectivity of the reaction. Increasing the pKa of the base additive drives the reaction to the racemic process, affording inferior enantioselectivity (Table 15, Entries 1-4). Addition of 1 equivalent of piperazine as additive in the presence of **VI** in chloroform at room temperature could be an appropriate combination according to Ley *et al* [98b]. It accelerated indeed significantly the reaction (Table 15, Entry 7) until almost complete conversion, but we also observed lower enantiomeric excesses.

Entry	Catalyst	temperature	Base	Reaction time (hours)	Conversion (%area)	ee (%)
1	**VI**	0°C	triethylamine	24h	18%	28
2	**VI**	0°C	morpholine	48h	2%	54
3	**VI**	0°C	N-methyl morpholine	48h	-	-
4	**VI**	0°C	Hünig Base	24h	15	10
5	**VI**	0°C	Immobilized morpholine	48h	-	-
6	**VI**	0°C	Immobilized Diisopropyl-(4-methyl-benzyl)-amine	48h	-	-
7	**VI**	19°C	*trans*-2,5- dimethylpiperazine	17h	89%	20
8	**I**	0°C	morpholine	48h	13%	28
9	**I**	0°C	Immobilized morpholine	48h	-	-
10	**I**	0°C	Immobilized Diisopropyl-(4-methyl-benzyl)-amine	48h	-	-

Table 15: Iminium catalysis, impact of additives. Reactions were performed on 1 mmol scale at a concentration of 4 mL/mmol in chloroform with 15% of catalyst, in the presence of 1 equivalent of base. Conversion rate and enantiomeric excess were determined by chiral phase HPLC (CHIRALPAK AD-H).

We then screened again some bases using dichloromethane as solvent.

Without any catalyst but in the presence of a base, no reaction and also no side reaction occurred when triethylamine and Hünig base were used as additives (Table 16, Entries 1-2). ***This proves the mechanism of reaction, which is working via the formation of an iminium intermediate***.

Nevertheless increasing the pKa of the base afforded the Michael adduct (Table 16, Entry 4) via a racemic pathway. Utilizing one equivalent of DBU yielded, for example, the formation of 47% conversion of the racemic desired product within 18 hours (Table 16, Entry 4).

Adding the organocatalyst **I** or **VI** resulted in the formation of the desired product with all of the bases we tested with improved conversion rate but no enantioselectivity was observed. Nevertheless only the utilization of *trans*-2,5- dimethylpiperazine allows the formation of the Michael adduct with moderate enantioselectivity.

Entry	Catalyst	Temperature	Base	Base equivalents	Reaction time (hours)	Conversion (%area)	ee (%)
1	-	19°C	triethylamine	6	17h	-	-
2	-	19°C	Hünig Base	1	18h	-	-
3	-	19°C	sparteine	1	18h	3	-
4	-	19°C	DBU	1	18h	47	-
5	**VI**	19°C	DBU	1	17h	57	18
6	**VI**	19°C	*trans*-2,5-dimethylpiperazine	1	17h	89	20
7	**VI**	0°C	DBU	1	17h	51	18
8	**VI**	0°C	Hünig Base	1	24h	15	10
9	**I**	19°C	triethylamine	1.1	8h	11	6
10	**I**	19°C	triethylamine	2	8h	16	4
11	**I**	19°C	triethylamine	6	8h	24	4
12	**I**	19°C	Hünig Base	0.4	18h	13	4
13	**I**	19°C	sparteine	0.4	18h	28	2
14	**I**	19°C	DBU	1	17h	56	2
15	**I**	19°C	DBU	0.4	17h	59	6
16	**I**	0°C	DBU	0.4	17h	52	6

Table 16: Iminium catalysis, impact of additives. Reactions were performed on 1 mmol scale at a concentration of 4 mL/mmol in dichloromethane with 15% of catalyst or without catalyst. Conversion rate and enantiomeric excess were determined by chiral phase HPLC (CHIRALPAK AD-H).

All the conditions we tried, didn't allow us to isolate the Michael adduct with significant enantioselectivity and good conversion rate. The best conditions we obtained were the use of the organocatalyst **VI** and addition of one equivalent of morpholine at 0°C in chloroform or under solvent-free conditions (Table 13, Entry 1; Table 14, Entry 3; Table 15, Entry 3).

The Michael addition of **108** to cyclohexenone **93** was performed on a representative 1.0 mmol scale, by adding at room temperature to a solution of 1.0 equivalent of cyclohexenone in chloroforme, 0.16 equivalent of 5-pyrrolidin-2-yltetrazole **VI**, 1.5 equivalents of nucleophile **108** and one equivalent of morpholine. The desired Michael product **115** was isolated after two days with 19% yield and an enantiomeric excess of 32%.

Having the "best" conditions in hand, we extended our studies to the Michael addition of the Z-protected N-hydroxylbenzyl amine **109**, the N-hydroxylbenzyl amine **107** bearing the required ethanol side chain, and aziridine **102** to cyclohexenone **93**.

III.2.2.2. First studies on the O-benzyl- benzyloxycarbamate nucleophile 109

Applying the same conditions as for the derivative **115**, we prepared the Z-protected analogue **116** with moderate yield and enantioselectivity (Figure 145).

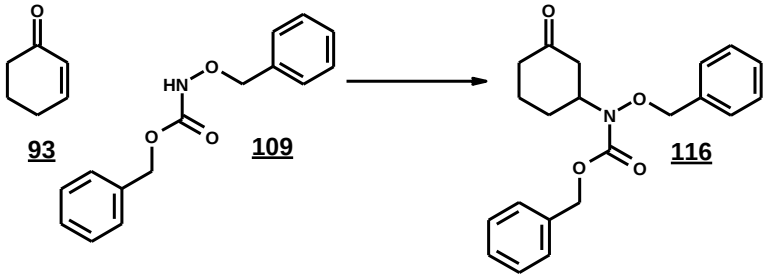


Figure 145: Michael addition of the Benzyl benzyloxy carbamate **109** to cyclohexenone **93**

Utilizing the tetrazole organocatalyst **VI** in presence of one equivalent of morpholine or *trans*-2, 5-dimethylpiperazine in chloroform at room temperature or at 0°C yielded the best conversion rate (Table 17, Entries 4,6). Nevertheless only in the case of organocatalyst **VI**, in presence of morpholine in chloroform at 0°C, we observed significant enantiomeric excesses (Table 17, Entry 3). Conducting the same reaction at room temperature or under solvent free conditions resulted in the decrease of e.e. (Table 17, Entry 2). When the reaction was performed under solvent-free conditions, we observed a complete conversion (Table 17, Entries 4, 5). Utilizing L-proline **I** as catalysts did not improve the reaction in terms of conversion and enantioselectivity (Table 17, Entry 1).

Entry	Catalyst	temperature	Base	solvent	Reaction time (hours)	Conversion (%area)	ee (%)
1[a]	**I**	19°C	morpholine	chloroform	72h	41	4
2[a]	**VI**	19°C	morpholine	chloroform	72h	40	8
3[b]	**VI**	0°C	morpholine	chloroform	72h	15	44
4[c]	**VI**	0°C	morpholine	-	72h	100	20
5[c]	**VI**	19°C	morpholine	-	6h	12	26
6[b]	**VI**	19°C	*trans*-2,5-dimethylpiperazine	chloroform	18h	98	8

Table 17: Iminium catalysis. [a]Reactions were performed on 1 mmol scale at a concentration of 4 mL/mmol in chloroform with 15% of catalyst, 1 equivalent of cyclohexenone, 1.5 equivalents of the amine, 1 equivalent of base [b] Reactions were performed on 1 mmol scale at a concentration of 4 mL/mmol in chloroform with 15% of catalyst, 3 equivalents of cyclohexenone, 1 equivalent of the amine, 1 equivalent of base [c]Reactions were performed on 1 mmol scale with 15% of catalyst, 3 equivalents of cyclohexenone, 1 equivalent of the amine, 1 equivalent of base. Conversion rate and enantiomeric excess were determined by chiral phase HPLC (CHIRALPAK AD-H).

In the course of our investigations, we also observed degradation and retro-michael addition of the formed product at higher temperature.

The Michael product **116** was also prepared on a 1 mmol scale, by adding to a solution of three equivalent of cyclohexenone, 0.16 equivalent of 5-pyrrolidin-2-yltetrazole **VI**, 1.5 equivalents of

nucleophile **109** and one equivalent of morpholine at room temperature. The desired Michael product **116** was isolated with 12% yield and an enantiomeric excess of 27%.

III.2.2.3. Towards the asymmetric Michael addition of aziridine 102 to cyclohexenone 93

An asymmetric version of the reported[184] aza-Michael addition of commercially available aziridine **102** to cyclohexenone **93** has also been investigated.

93 **102** **117**

Figure 146: Michael addition of aziridine **102** to cyclohexenone **93**

The conditions we tested, allow only the formation of the Michael adduct **117** as a racemic mixture. Performing the reaction in the ionic liquid BmimOH[188c] (Table 18, entry 2) enhanced, as described by Xhia *et al*[188c], the reaction, but addition of L-proline **I** to the reaction mixture did not provide any enantioselectivity (Table 18, entry 3).

Entry	Catalyst	Tempera-ture	Base	Solvent	Reaction time	Conversion (%area)	ee (%)
1	-	rt	-	water	35 min	2	-
2	-	rt	-	BmimOH	24 hours	16	-
3	**I**	rt	-	BmimOH	18 hours	80	8
4	**I**	rt	triethylamine	$CHCl_3$	3 days	13	2
5	**I**	rt	triethylamine	$CHCl_3$	18 hours	1	2
6	**I**	0°C	triethylamine	$CHCl_3$	18 hours	1	6
7	**I**	-50°C	triethylamine	$CHCl_3$	4 days	-	-
8	**V**	rt	triethylamine	$CHCl_3$	2 days	2	10
9	**VI**	rt	triethylamine	$CHCl_3$	18 hours	1	10
10	**VI**	rt	*trans*-2,5-dimethylpiperazine	$CHCl_3$	18 hours	1	10
11	**VIII**	rt	triethylamine	$CHCl_3$	18 hours	-	-

Table 18: Iminium catalysis, aziridine as nucleophile Reactions were performed on 2 mmol scale at a concentration of 4 mL/mmol with 15% of catalyst in the presence of 1 equivalent of base, 3 equivalent of cyclohexenone and 1 equivalent of nucleophile. Conversion rate and enantiomeric excess were determined by chiral phase HPLC (CHIRALPAK AD-H).

III.2.2.4. Towards the asymmetric aza-Michael addition of 107 to cyclohexenone 93

Conducting the Michael addition of the nucleophile **107** on cyclohexenone **93**, in the presence of L-proline **I**, morpholine at room temperature, provided after 7 days the desired product in a mixture of unknown side products. No enantioselectivity was observed. No more experiments have been done with this nucleophile.

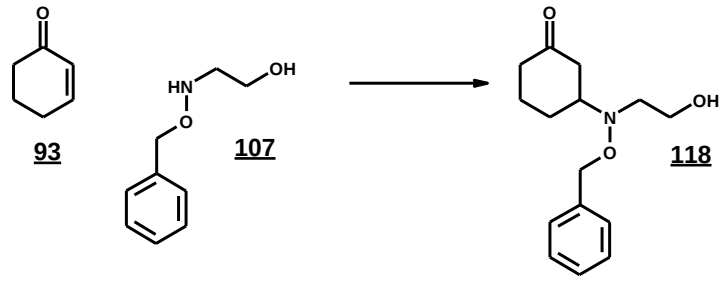


Figure 147: Aza-Michael addition of **107** to cyclohexenone **93**

III.2.2.5. Aza-Michael addition of the hydrazone derivative 110

One last study was undertaken based on the work of Jorgensen *et al* [186] concerning the first organocatalysed asymmetric aza-Michael addition of hydrazones to cyclic enones, mediated by cinchona alkaloids. He reported the possibility to prepare the Michael adducts with good enantioselectivities *via* the formation of a chiral intermediates resulting from the interaction of all reactants.

Using the reaction conditions described by Jorgensen *et al*, we hoped to be able to prepare the following Michael adducts with good enantioselectivities (Figure 148). Further steps could allow us to prepare the chloride, bromide or mesylate derivatives, which could afford the desired AFQ056 intermediate **121** *via* intermolecular alkylation via enamine catalysis.

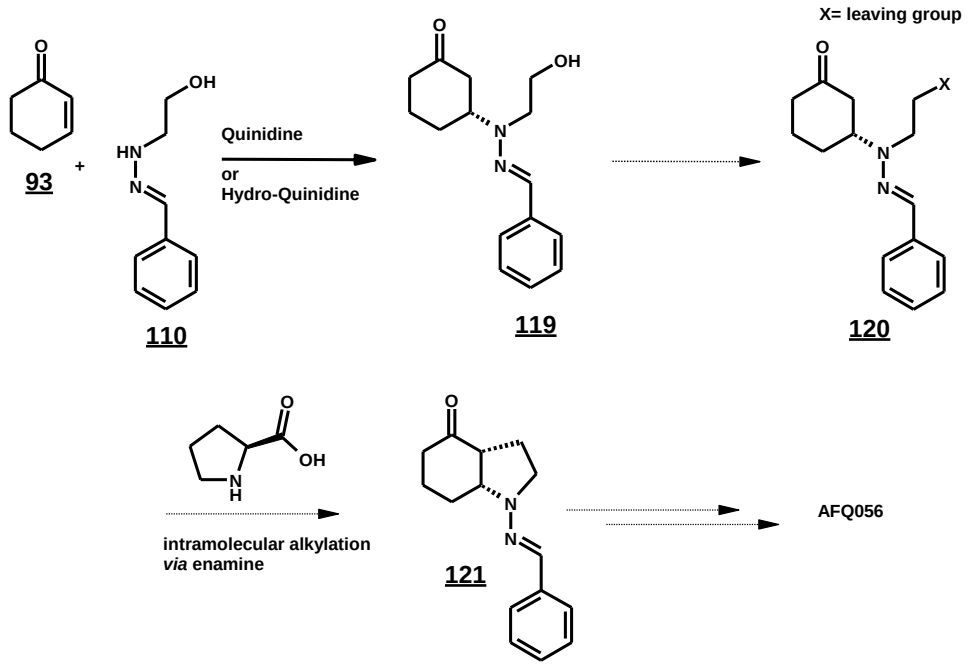


Figure 148: Hydrazone strategy for the enantioselective preparation of AFQ056 **90**

Applying the procedures of Jorgensen, by mixing three equivalents of cyclohexenone **93** with one equivalent of the hydrazone derivative **110** in the presence of 20% of hydro quinidine in toluene at room temperature afforded complex mixture. The major component was the desired Michael adduct **120** (Figure 23).

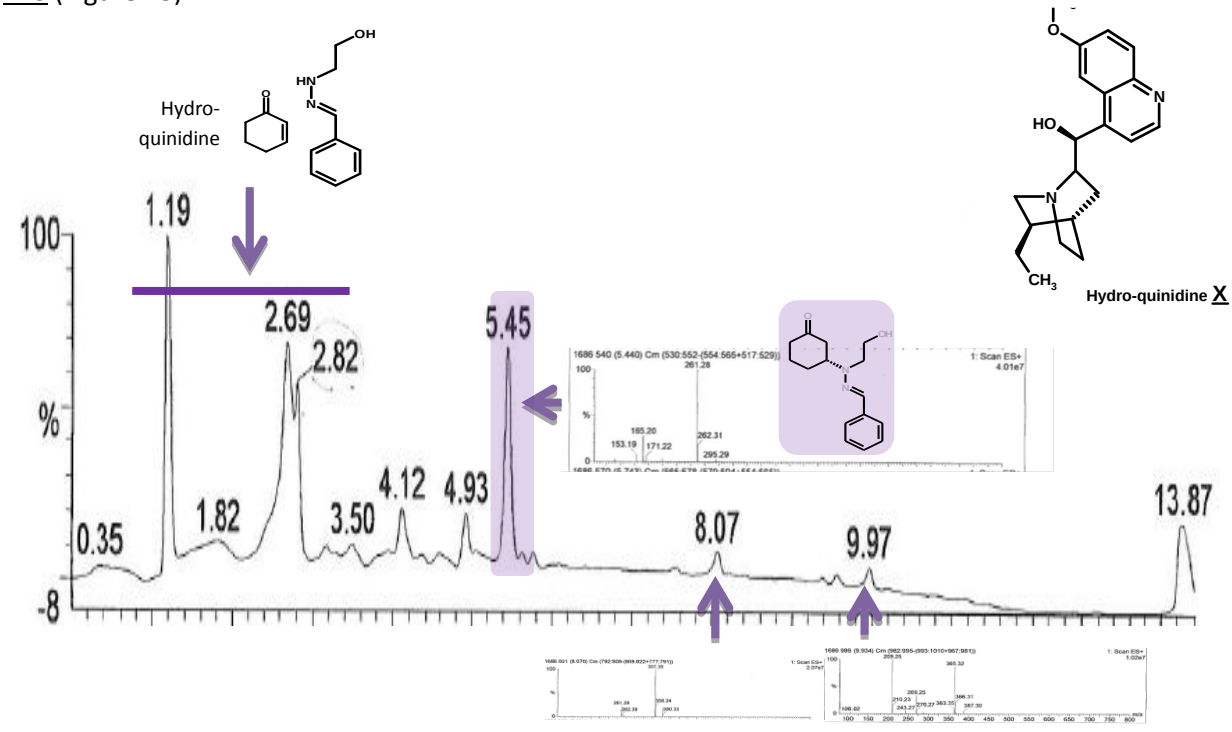


Figure 149: LCMS chromatogram of the reaction residue

Purification on preparative TLC using a mixture of heptan fraction/ethyl acetate yielded in the purest fraction the desired compound in mixture with the starting material and unknown compounds (Figure 150). Further investigations will be conducted in the next future to find out all of the side

products presents in the reaction mixture, LCMS analysis revealing that one of them could be the iminium specie **122** generated from cyclohexenone **93** and the nucleophile **110**.

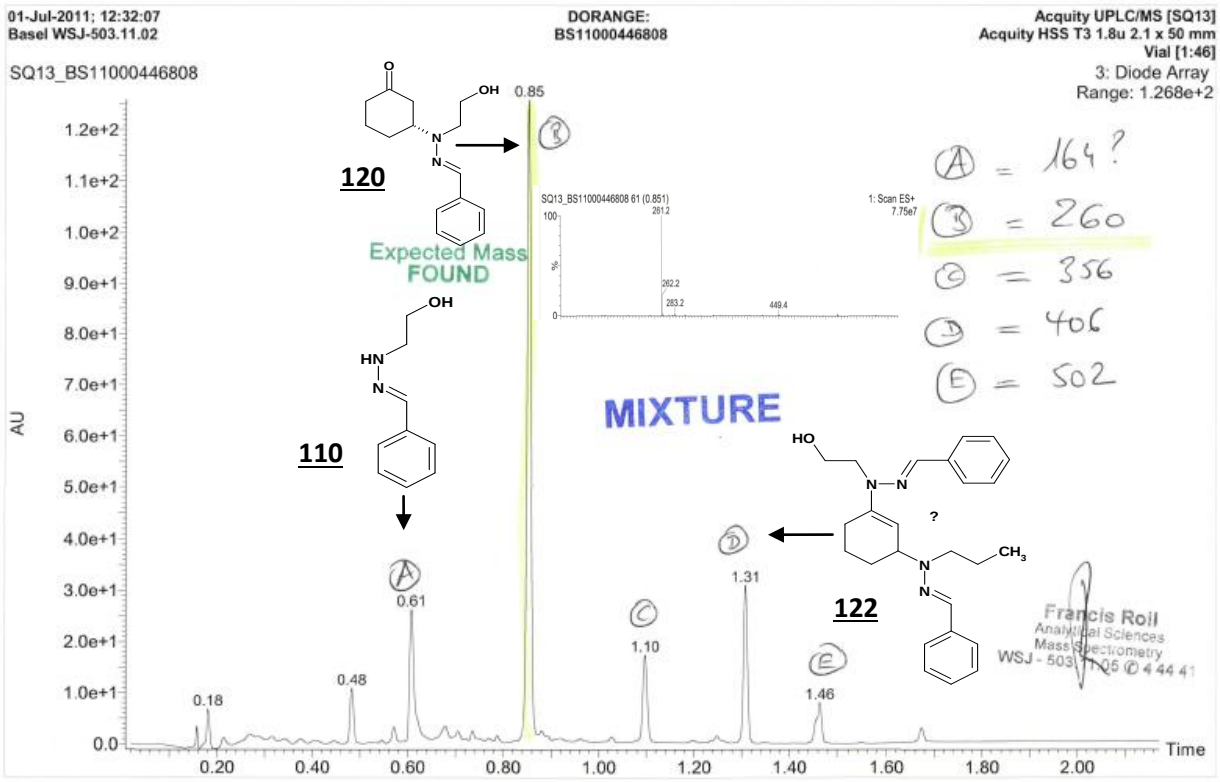


Figure 150: LCMS chromatogram of the purest fraction

III.2.3. Towards the preparation of the chloride derivative 92 and iminium ion formation

The next step of the synthesis of AFQ056 **90** involved the removal of the protective group of the Michael adduct **115**. We performed the reaction using trifluoroacetic acid in dichloromethane (Figure 151).

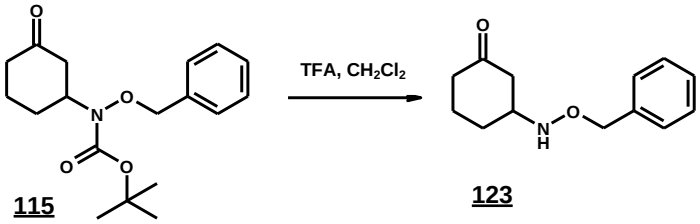


Figure 151: Deprotection of **115**

Under these conditions, the cleavage of the C-N bond occurred (retro-Michael addition), affording the nitrogen species **124**. It subsequently condensed with the generated cyclohexenone yielding stable iminium species **126**[202] as trifluoroacetic salt with 55% yield and an isomeric ratio of 44:56 (E and Z isomers). The formation of **126** resulted from the condensation of the *in situ* generated amine **124** and cyclohexenone **93**. **124** and **93** were formed through the retro-Michael addition on the deprotected analogue of **115**.

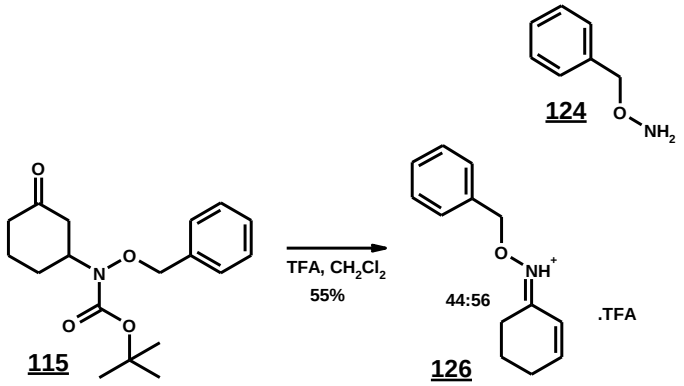


Figure 152: Formation of the iminium species **126**

III.2.4. Cyclisation step *via* enamine catalysis

The next step in the synthesis of AFQ056 involves a ring closure step to yield **91**.
As reported in 2004 by List *et al*[193], chiral cyclopentane, propane and pyrrolidine derivatives can be prepared in high yields and ee's, via a highly enantioselective intramolecular direct aldehyde α-alkylation, through the formation of enamine intermediates with L-proline **I** and α-methyl proline **II**. According to his procedures we prepared the bicyclic species **96**, from a racemic mixture of **95** (Figure 153). **95** was prepared in the laboratory by M. Blatter according to the literature reported by Küsters *et al*[184].

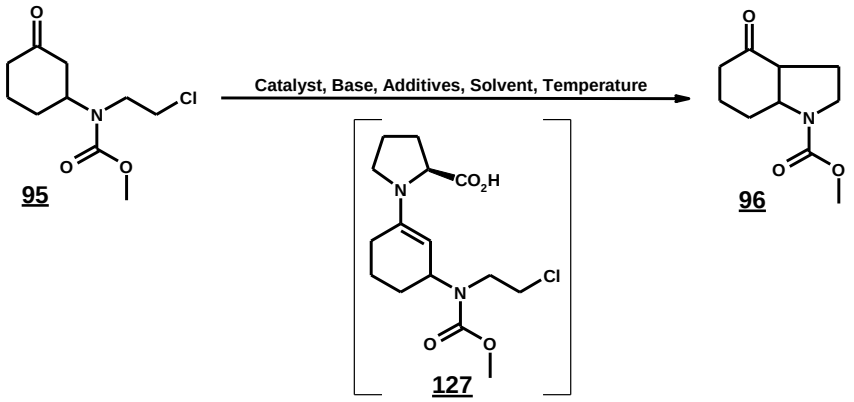


Figure 153: Cyclisation step *via* the formation of an enamine intermediate **127**

III.2.4.1. Batch results

A selection of solvents has been screened using L-proline **I** (known to be able to form enamine intermediates) as catalyst in the presence of an organic base and 10% of potassium iodide. The investigations presented on Table 19 demonstrated the influence of the temperature and the solvent used and afford us the best solvent, base and temperature conditions for the intramolecular α-alkylation (Table 19, Entry 6): triethylamine in DMSO at 150°C (Table 19). Conducting the reaction on an isomeric mixture of the starting material yielded only two diastereoisomers (R,R) and (S,S), in an equimolar ratio.

Entry	Solvent	Base	Temperature (°C)	Time(hours)	Conversion (%area)
1	dichloromethane	triethylamine	40	3h20	30
2	chloroform	triethylamine	60	3h20	88
3	dichloroethane	triethylamine	80	3h00	90
4	chlorobenzene	triethylamine	130	2h20	94
5	trifluorotoluene	triethylamine	140	2h30	33
6	DMSO	triethylamine	150	25 min	100
7	xylene	Hünig base	140	50 min	60

Table 19: Enamine catalysis. Reactions were performed on 1 mmol scale at a concentration of 4 mL/mmol with 10% of L-proline **I** in the presence of 10% of KI and 1 equivalent of base. Conversion rate was determined by chiral phase HPLC.

A selection of additives has also been tested. Using TBAI as additive did not improve the reaction, in comparison to KI. But using 1% of TBAI still provides complete conversion within 15 min at 150°C (Table 20, Entry 5). Moreover, conducting the reaction in NMP or DMA at higher temperature didn't enhance the conversion rate (Table 20, Entries 6-7).
In conclusion, utilizing KI in DMSO at 150°C seemed to be the most appropriate conditions.

Entry	Solvent	Base	Additives	Temperature (°C)	Time(min)	Conversion (%area)
1	DMSO	triethylamine	5% KI	150	7 min	100
2	DMSO	Hünig base	5% KI	130	>25 min	100
3	DMSO	Hünig base	5% KI	150	15 min	100
4	DMSO	Hünig base	5% TBAI	150	15 min	100
5	DMSO	Hünig base	1% TBAI	150	15 min	100
6	DMSO	Hünig base	-	150	25 min	100
7	NMP	Hünig base	10% KI	180	15 min	100
8	DMA	Hünig base	10% KI	166	15 min	100

Table 20: Enamine catalysis Reactions were performed on 1 mmol scale at a concentration of 4 mL/mmol with 10% of L-proline **I** in the presence of the additive and 1 equivalent of base. Conversion rate was determined by chiral phase HPLC.

A selection of proline related catalysts has been tested. And as presented in Table 21, the nature of the substituent on the proline related catalyst doesn't a have a huge influence on the kinetic of the reaction. Even if the organocatalyst **VI** seems to be more efficient (Table 21, Entry 2), L-proline **I** being a cheap commercially available compound, it will be used as organocatalyst in the next studies.

Entry	$R_{catalysts}$	Base	Additives	Temperature (°C)	Time(min)
1	**I**	Hünig base	10% KI	180	15 min
2	**VI**	Hünig base	10% KI	180	7 min
3	**VIII**	Hünig base	10% KI	180	15 min

Table 21: Enamine catalysis. Reactions were performed on 1 mmol scale at a concentration of 4 mL/mmol with 10% of catalyst in the presence of 10% of KI and 1 equivalent of Hünig base in NMP. Conversion rate was determined by chiral phase HPLC.

Having good conditions for the rapid formation of the 1,5,6,7-tetrahydroindol-4-one derivative **96**, we investigated the possibility of developing a continuous flow process.

III.2.4.2. Continuous flow results

The rapidity of the reaction and the low concentration of inorganic salts required let us to study an alternative continuous flow process. It was performed by injecting at a flow rate of 1 mL/min a pre-mixed DMSO solution containing all the reactants into a heated tube. The collected fractions were analyzed by chiral HPLC using CHIRALPAK AD-H.

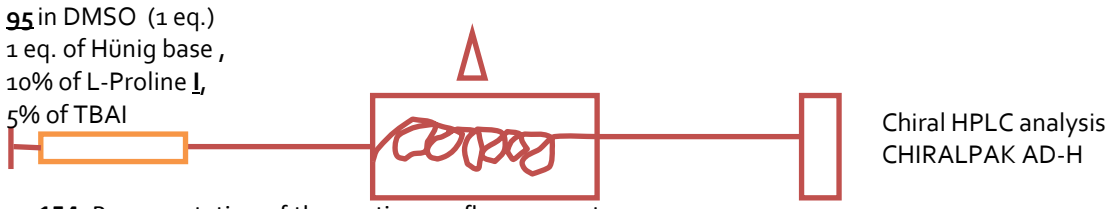


Figure 154: Representation of the continuous flow apparatus

We tested for practical and economic reasons the cyclisation step under the following conditions: 1 equivalent of Hünig base in presence of 10% of L-proline **I** and 5% of TBAI at various temperatures.

Entry	Solvent	Temperature (°C)	Contact time(min)	Conversion (%area)
1	DMSO	160	2 min	84
2	DMSO	160	5 min	94
3	DMSO	160	8 min	100
4	DMSO	160	15 min	100
5	DMSO	150	5 min	96
6	DMSO	150	10 min	100
7	DMSO	150	15 min	100
8	DMSO	140	5 min	99
9	DMSO	140	10 min	100

Table 22: Enamine catalysis Reactions were performed on 1 mmol scale at a concentration of 4 mL/mmol with 10% of catalyst **I** in the presence of 10% of TBAI and 1 equivalent of Hünig base. Conversion rate was determined by chiral phase HPLC.

This rapid screening proved the feasibility of a continuous flow process. With contact times less than 10 min, we were able to convert 100% of the starting material (Table 22, Entries 3,5,9).

IV. Conclusion

The aza-Michael addition of N-nucleophiles to cyclohexenone **93** still remains a challenge. Some interesting procedures were nevertheless reported in the literature for the Michael addition of nitroalkane (Ley *et al*) or hydrazine derivatives (Jorgensen *et al*) to cyclohexenone. Using similar procedures, we reported here a new strategy for the enantioselective preparation of AFQ056 precursors, involving in the first step, the organocatalyzed aza-Michael addition of a selection of *N*-nucleophiles to cyclohexenone. In the best case, we were able to isolate the two aza-Michael products **115** and **116** with moderate enantiomeric excess up to 30% and poor isolated yields (12% and 19%).

Furthermore, we described a successful approach for the intramolecular alkylation step yielding the the 1,5,6,7-tetrahydroindol-4-one building block **96** of AFQ056 **90** within short reaction time and high conversion rate. That proved the possibility of a continuous manufacturing of AFQ056. The next study should include the preparation of the the 1,5,6,7-tetrahydroindol-4-one building block pattern from an enantiomeric pure starting material.

CHAPTER 4: TOWARDS THE ASYMMETRIC PREPARATION OF THE ANTI-MALARIA DRUG CANDIDATE KAE609

I. Pharmacological activity

KAE609 **129** (NITD609) (Figure 155) is a phase I candidate belonging to a new class of potent anti-malaria compounds: the tetrahydrospiroindole-β-carbolines[203] and, which was awarded in 2009 MMW[204] Project of the Year 2009.

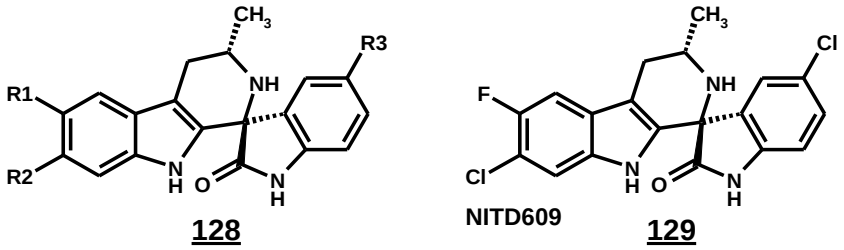


Figure 155: New anti-malaria drug candidates

Its identification is linked to the effort to discover new anti-malarial chemotypes with novel mode of actions to fight current drug resistances. Malaria is recognized as one of the major health problems especially in developping countries.

Malaria is transmitted by an infected mosquito that transfers a parasite (*Plasmodium*) in the human blood (Figure 156). The parasites enter the human liver, where they multiply. They invade then the blood cells, where they multiply again, causing the rupture of the membrane of erythrocytes, producing the symptoms of the disease (generally fever, headaches).

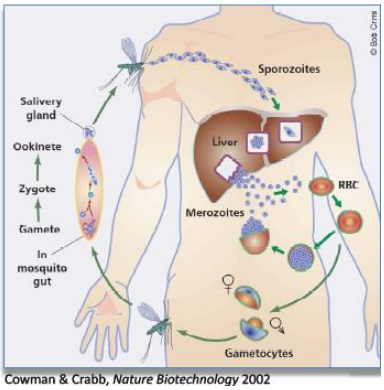


Figure 156: Transmission of malaria and *Plasmodium* development

There are four species of parasites (*vivax*, *ovale*, *malariae, falciparum*) but only *P. falciparum* is known to cause the patient's death.

In vitro and *ex vivo* data studies[205] of the inhibitory activity of spiroindoles proved the new mechanism of action of these compounds. In contrast to the current medicines (mefloquine,

artemisinine), the spiroindoles suppress the protein synthesis at the erythrocytic stage of development of the parasites *P. falciparum* and *P. vivax* and so retain activity against drug-resistant strains.

II. Preparation

The KAE609 analogues are synthesized[1] in eight chemical transformations from the corresponding indoles[203]. The strategy of the synthesis is based on the preparation of a racemic mixture of the amines **133**, which afford the active compounds **128** and **134** via a Pictet-Spengler[206] cyclisation with 5-chloroisatin, with a 9:1 diastereoisomeric excess of the favored (*1R, 3S*) and (*1S, 3R*) enantiomers[203]. The (*1R, 3S*) and (*1S, 3R*) enantiomers are in the end of the synthesis resolved by chiral chromatography.

The racemic aminopropenylindoles intermediates **133** were prepared by Vilsmeyer-Haack formylation of the indoles, followed by Knoevenagel condensation with nitroethane in presence of ammonium acetate and reduction of the resulting nitro alkene derivatives in presence of LAH (Figure 157).

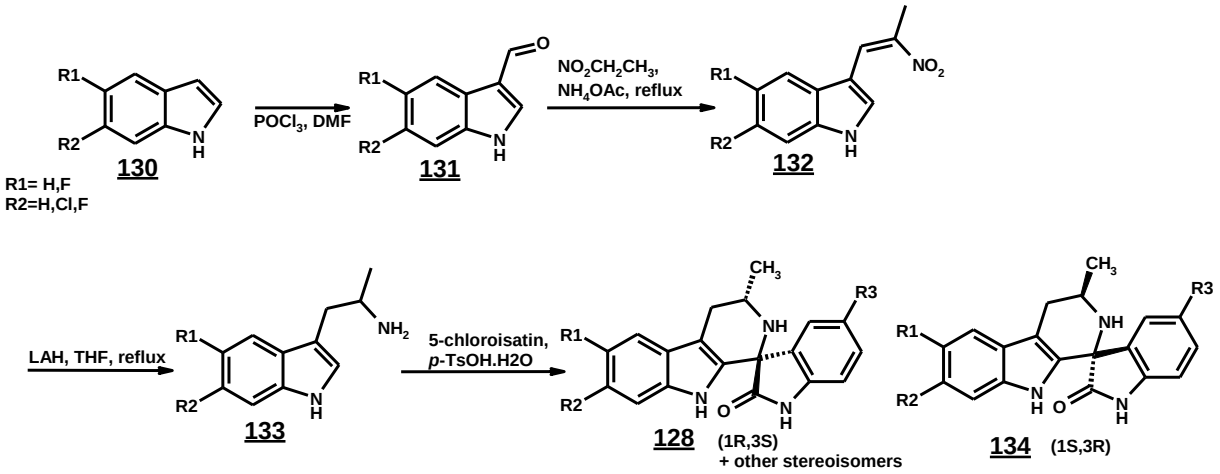


Figure 157: Racemic synthesis of KAE609 spiroindoles[203] **128** and **134**

Nevertheless *in vitro (P. falciparum)* and *in vivo (P. berghei)* studies have proved the influence of the chirality on the parasitic activity of some tested compounds. As shown in Table 23 (entry 1-4), only the (1R,3S) stereoisomer presents a satisfactory IC_{50} (<10 nM) similar to the one of artesunate[205,14].

[14] For a review about the bio-activity of artesunate see Q. Li , P. Weina, *Pharmaceuticals* **2010**, 3, 2322-2332; For the structure of artesunate, see J. N. Lisgarten, B. Potter, R. A. Palmer, B. Chimanuka, J. Aymami, *Journal of Chemical Crystallography* **2002**, 32(1-2), 43-48.

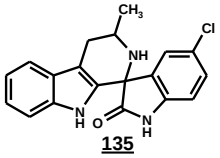
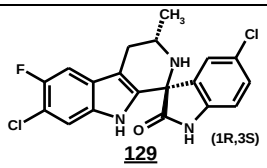
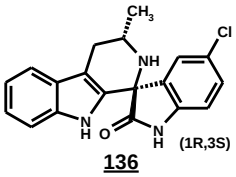
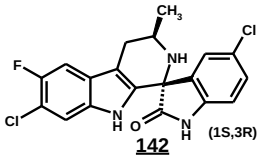
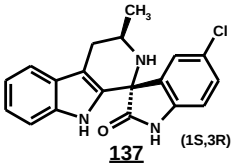
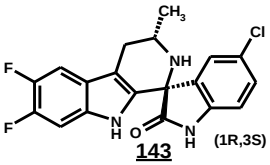
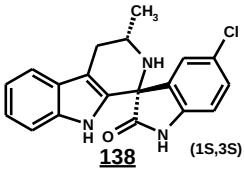
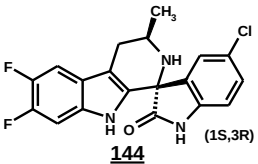
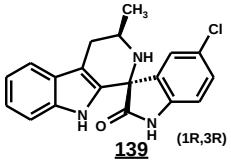
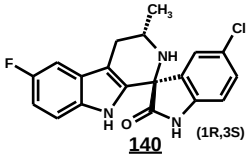
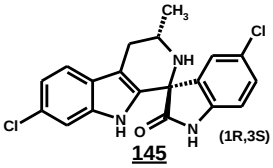
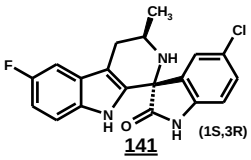
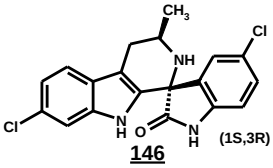
Entry	Structure	NF54 IC_{50} (nM)	KI IC_{50} (nM)	Entry	Structure	NF54 IC_{50} (nM)	KI IC_{50} (nM)
1	 **135**	27	21	8	 **129**	0.9	
2	 **136**	9	9	9	 **142**	77	
3	 **137**	> 5000	> 5000	10	 **143**	0.2	
4	 **138**	1808		11	 **144**	83	
5	 **139**	444					
6	 **140**	3		12	 **145**	4	
7	 **141**	182		13	 **146**	116	

Table 23: *In vitro* activity against two cell strains of *P. falciparum*: NF54 and Chloroquine resistant K1 strains[203]

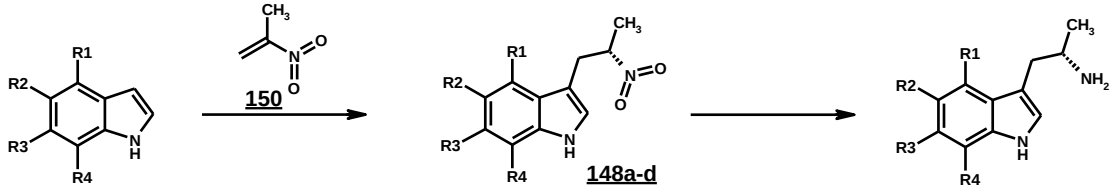
The promising anti-malaria activities of the enantiopure spirolindole derivatives **129** and **143** (Table 23, Entries 8 and 10) resulted in an effort to provide alternative routes for their large scale preparation.

III. New alternative route

III.1. Introduction

III.1.1 Asymmetric route

We based our strategy on the preparation of chiral α-substituted nitro indole derivatives **148a-d** (Figure 158), from the corresponding indoles, *via* enantioselective Friedel-Crafts addition of the adequate α-substituted nitro alkenes (Figure 158).



147a R1 = R2 = R3 = R4 = H
147b R1 = R4 = H, R2 = R3 = F
147c R1 = R4 = H, R2 = F, R3 = Cl
147d R1 = R2 = R3 = R4 = F

149a R1 = R2 = R3 = R4 = H
149b R1 = R4 = H, R2 = R3 = F
149c R1 = R4 = H, R2 = F, R3 = Cl
149d R1 = R2 = R3 = R4 = F

Figure 158: New asymmetric strategy for the preparation of indole intermediates **148a-d** and**149a-d** of NIDT609

Although the Friedel-Crafts alkylation (first reported by Friedel and Crafts in 1887[207]) type addition of electron rich heterocyclic compounds with nitroalkenes has been described for a long time[208], the development of enantioselective catalytic processes had to wait until 2005. Many type of metal based Lewis acids and organocatalysts have been described in the literature[209,102a-b] for the Friedel-Crafts addition of indoles to substituted nitro alkenes: salen(Al)catalysts[210], thioureas[211], phosphoric acids[212], bissulfonamides[213], zinc[214] and copper[215] catalysts, cinchona alkaloids[216], yielding to the formation of various β- substituted indoyl nitroalkanes (Figure 159).

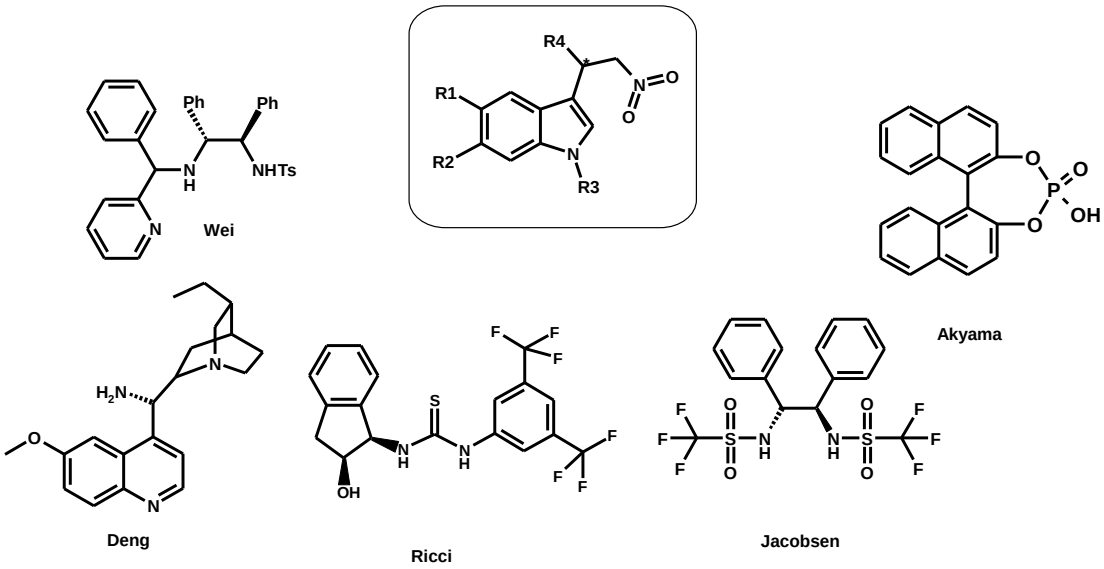


Figure 159: β-substituted amino indoles pattern and chiral organocatalysts

However the catalytic enantioselective preparation of chiral α- substituted indolyl nitroalkanes *via* Friedel-Crafts alkylation still remains a challenge. Only some examples[217] are available in the literature for their racemic preparation, by condensation of (substituted or non-substituted) indole derivatives with nitroolefins; the former procedure being published by Ranganathan[218] in the course of his study on the use of nitroethylene in organic chemistry.
Nevertheless, using the available procedures for the conjugate addition of indoles to nitroalkenes and catalysts cited (Figure 159), we tried to develop a methodology to prepare the key α- substituted indolyl nitroalkane intermediates **148a-d** in an asymmetric manner.

III.1.2. New racemic route

A shorter version of the current two-step Vilsmeier–Henry procedure[203] process is possible in one step *via* the preparation of the α- substituted indoyl nitroalkenes intermediates using an adapted version of the procedure of Mak and Büchi[219] (Figure 160) relative to nitro olefination of indoles with commercially available dimethylamino-2-nitroethylene **151**. According to the literature[203], subsequent reduction of the nitroalkene derivatives in presence of LAH or $NaBH_4$ should deliver the desired tryptamine derivatives **149a-d**.

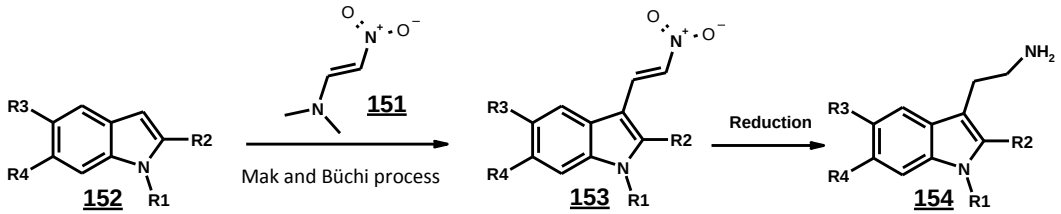


Figure 160: "Mak and Büchi strategy" for the preparation of substituted nitro alkenes

It is worth to mention that such procedures have been often employed for the preparation of natural products or pharmaceutical active compounds[220], such as melatonin derivatives or Haplophytine during the last years.

Thus, the α-methyl tryptamine intermediates **149a-d** could be obtained by reaction of the corresponding indoles **147a-d** with 4-((E)-2-nitro-propenyl)-morpholine **155** (that are known to undergo stereoselective nitroolefination of active methane of various carbonyl compounds[221]) in presence of TFA, followed by *in situ* reduction of the generated indolyl nitro alkene intermediates **156a-d** with LAH or $NaBH_4$.

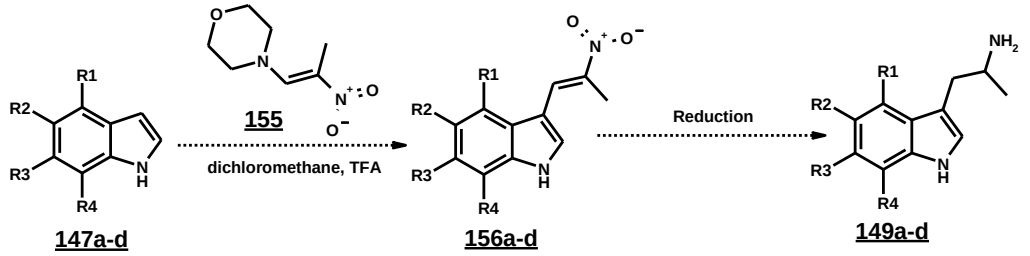


Figure 161: One-step procedure for the preparation of the indolylnitroalkene **156a-d**

The advantage of this procedure is its potential application to the synthesis of various α-substituted indolyl nitro alkane derivatives by variation on the α-substituent of the morpholino nitro alkene reactant.

Using an asymmetric reduction procedure (Baker yeast[222], Josiphos Ligand[223], chiral TarB-NO_2-BH_4 complex[224]) of the nitro alkene derivatives **156a-d**, it could be possible to access enantiopure or enriched nitro alkane compounds **149a-d**.

III.2. Results and discussion

III.2.1 Asymmetric Friedel-Crafts alkylation

In an effort to develop a methodology to access the enantiopure α- substituted indolyl nitroalkane precursor of KAE609 (**156a-d**), a selection of catalysts has been tested in the Michael addition of a range of substituted indoles to nitropropene. The racemic version of the Friedel-Crafts alkylation was also investigated.

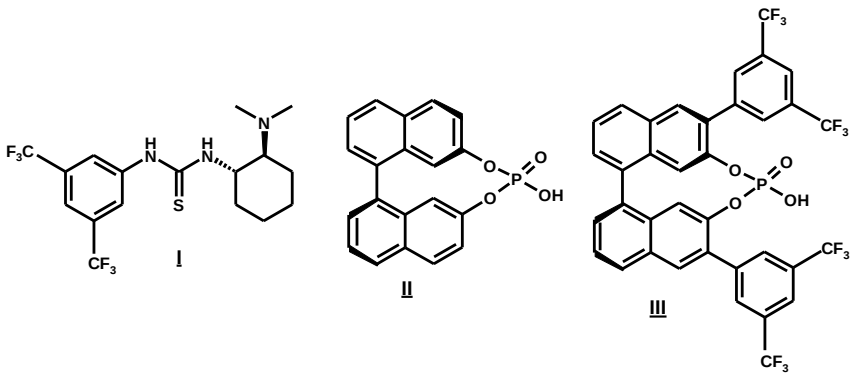


Figure 162: Selection of catalysts investigated in the NIDT609 Friedel- Crafts alkylation

We selected the test thiourea catalyst **I** designed by Takemoto. Chiral ureas and thioureas have been successfully be used[225] for diverse catalytic asymmetric reactions. The possibility of a double Hydrogen-bond interaction between the two basic oxygen atoms of the nitroalkene partner and the acidic protons of the urea moiety (Figure 163) led to the exploitation of these molecules for the asymmetric Friedel-Crafts alkylation of nitroalkenes.

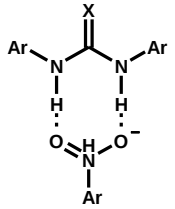


Figure 163: Hydrogen-bond interaction between ureas and nitroarenes observed in solid state

We selected also two commercially available chiral Binol-phosphoric acids **II** and **III**. Such catalysts have been reported to perform Friedel-Crafts alkylation of indoles with nitroalkenes (Akiyama[226]), with excellent enantioselectivies and yields. The excellent enantioselectivities observed can be

explained by concomitant activation of the nitro group and of the indole partner *via* hydrogen bond formation with the phosphoryl oxygen as represented on Figure 164[227].

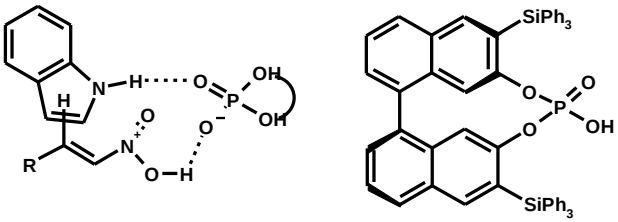


Figure 164: 3-3'-bistriphenylsilyl BINOL derived phosphoric acid and activation mode

The required nitropropene solution was prepared either from nitroethanol using acidic Alox (Brockman Activity I) as dehydrating agent or using phthalic anhydride at 150°C[228] (reaction performed in the laboratory by D. Grimler).

III.2.1.1. Preparation of 148a-d as racemic mixtures

As model reaction, we investigated first the Michael addition of indole **147a** to nitropropene (Figure 165). The racemic mixture of rac-**148a** was prepared in a procedure inspired by the publication of Nichols[229] by mixing one equivalent of **147a** in one equivalent of a diluted solution of nitropropene in toluene (C= 1.1 mmol/15 mL) at 40°C. We observed by HPLC analysis, that the reaction proceeded slowly. Only a very low conversion of the indole into its product rac-**148a** could be observed (6 area% product presents after 20 hours at 40°C). LCMS analysis of the reaction mixture confirmed the presence of the Michael product at a retention time of 6.4 min.

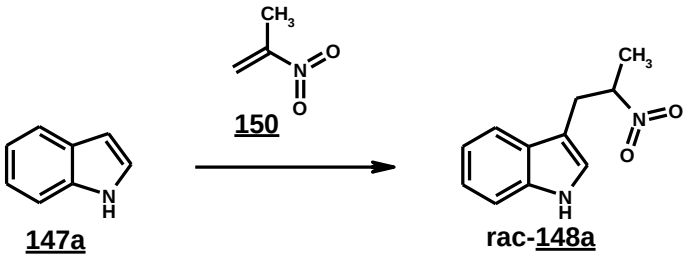


Figure 165: Michael addition of indole **147a** to nitropropene **150**

The racemic Friedel-Crafts alkylations of indoles **147b** and **147c** were also tested, but resulted in the low formation of complex mixtures. It seems that electron poor indoles with withdrawing substituents are no suitable partners in Friedel-Crafts reactions with nitroalkenes.

III.2.1.2. Towards the asymmetric preparation of the indolyl nitro alkanes 148a-d

Having developed an LC method for the detection of indolylnitroalkane **148a** in hand, we investigated its asymmetric preparation screening the selection of catalysts of Figure 162. For the screening, we used 1.5 equivalents of a diluted solution of nitropropene in toluene (1.1 mmol/15 mL) were added to 1 equivalent of indole, and 0.1 equivalent of the selected catalyst (**I**, **II** and **III**) at room temperature. HPLC analysis of the reaction mixture on Inertsil ODS 3 C18 (using acetonitrile and

demineralized water buffered with 0.01% of $NH_4H_2PO_4$ and a gradient of 55% to 97% acetonitrile in 15 min at 40°C) revealed the presence of the desired product in mixture with side-products. The results were confirmed by LCMS analysis. It is noteworthy that, using **147a** and **150** in solution, complete conversion could not be obtained; yielding only complex mixtures. Performing the reaction using pure nitropropene accelerated the conversion. Nevertheless for safety considerations, the use and handling of nitropropene as a solution in toluene is prefered.

Optimization of the reaction conditions is still required to perform the asymmetric synthesis of the KAE609 precursor **148a**. Also further investigations to identify the generated side products are necessary.

III.2.2. New one-pot approach for the preparation of the nitropropenyl indoles 156b-d

According to a modified version of the procedures of Mak and Büchi[219], the reaction of the indoles **147b-d** with 4-((E)-2-nitro-propenyl)-morpholine **155**[15] in dichloromethane in the presence of trifluoroacetic acid afforded the α-substituted indoyl nitro alkanes **156b-d** with very good yields (up to 86%).

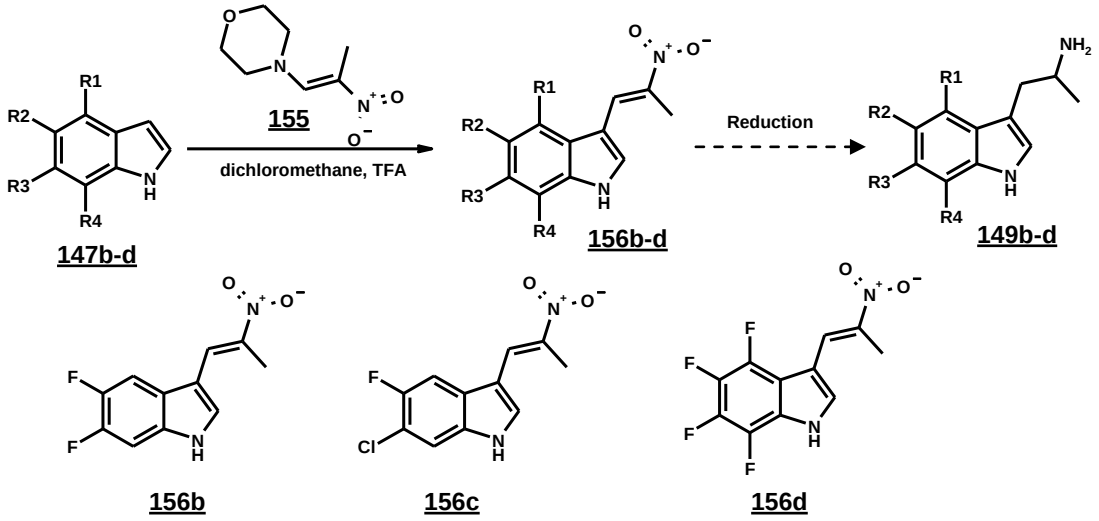


Figure 166: Novel one-pot approach for the preparation of **156b-d**.

The X-Ray analysis (Figure 167) of **156b** revealed, that in the crystal state, the molecules of **156b** form planar layers with an approximate spacing of 3.28 Å. Hydrogen bonding between two independent molecules in the crystal structure explain the infinite chains parallel formed to the crystallographic 1 0 1 direction.

[15] **155** was prepared in the laboratory, on a multigram-scale, by D. Grimler with 78% yield according to a procedure[221] of Fuji *et al* by refluxing 5 equivalents of nitroethane, 2 equivalents of triethyl orthoformate and one equivalent of morpholine in the presence of *p*- toluenesulfonic acid.

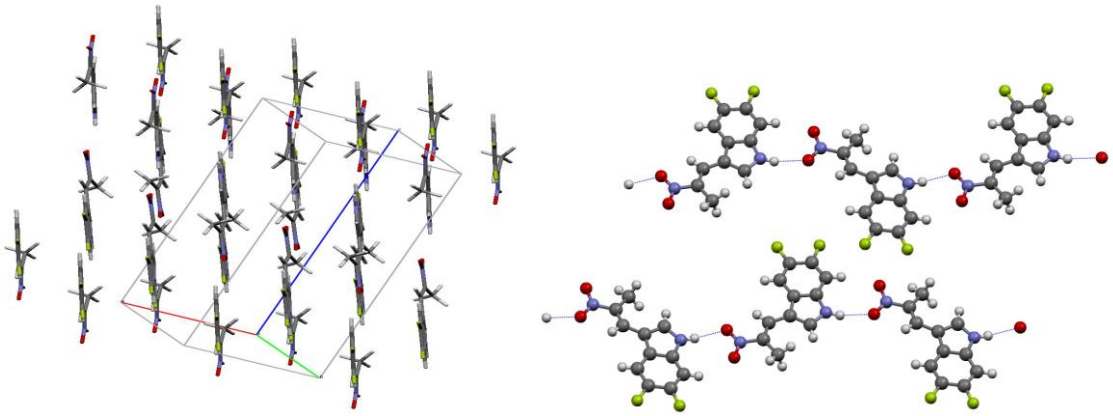


Figure 167: Packing of **156b** in the crystal and Hydrogen bonding in the crystal structure

As despicted in Figure 168, we observed also the distortion of the side chain out of the plane of the indole moiety. The angle between the best plane through C2, C3, C4, C5, C6, N7, C8, C9, C10 and the best plane through C12, C13, C14, N15, O16, O17 is indeed 6.6(1)°, when in the molecule 2 the corresponding dihedral angle is 7.2(1)°. Moreover the distance of C14 (methyl group) to the indole plane is 0.455(4) Å, but C34 is 0.298(4) Å away from the indole plane. We can thus note a slight vertical displacement of the nitropropenyl moiety in molecule 1.

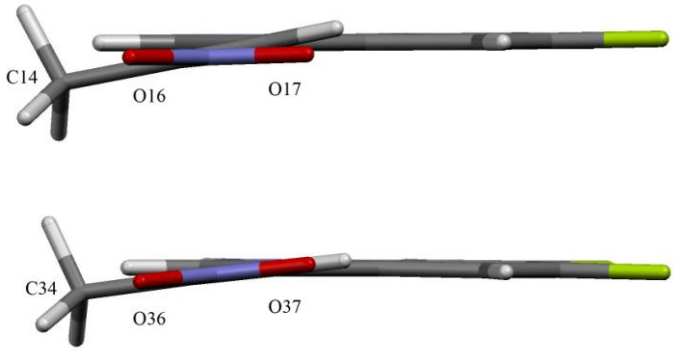


Figure 168: Intramolecular twist in **(E)-156b**

The X-Ray analysis of **156d** (Figure 169) reveals the herringbone type pattern formed by the molecules of **156d**, with an angle of 92.4(2)° between the bones, the distance between parallel planes being 3.19(2) Å. Hydrogen bonding in the crystal structure of **156d** explains the formation of infinite chains. In contrast to the in-plane arrangement in **156b,** the chains are parallel to the crystallographic 3 0 1 direction. However, the neighboring molecules in **156d** are almost perpendicular to each other.

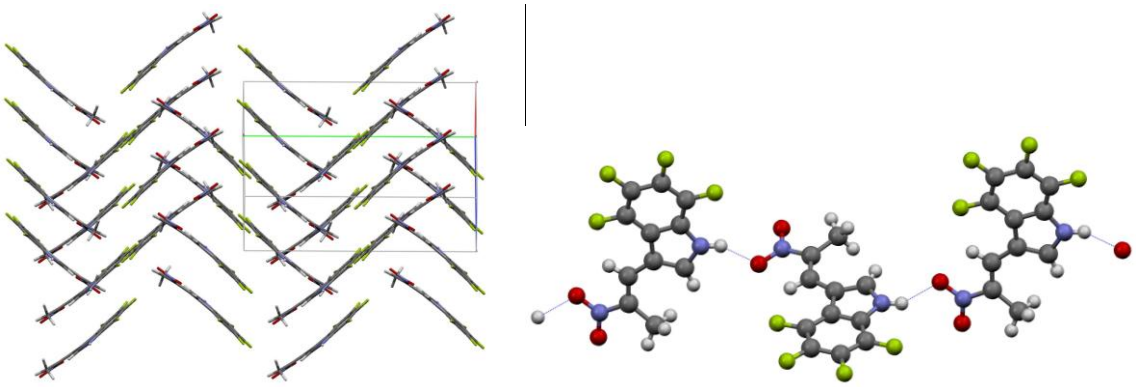


Figure 169: Packing of **156d** in the crystal and Hydrogen bonding in the crystal structure

An intramolecular twist in **156d** is also observed (Figure 170). The angle between the best plane through C1, N2, C3, C4, C5, C6, C7, C8, C9 and the best plane through C10, C11, C12, N13, O14, O15 is 11.4(1)°. The distance of C12 (methyl group) to the indole plane is 0.445(2) Å.

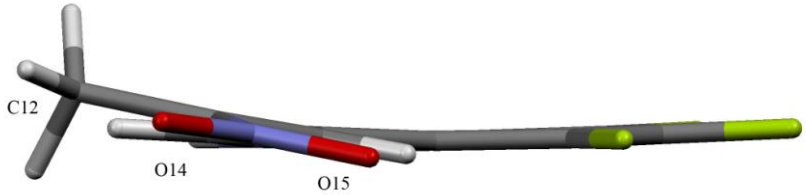


Figure 170: Intramolecular twist in **(E)**-**156d**

IV. Conclusion

Preliminary experiments have been executed evaluating the viability of an asymmetric preparation of the Novartis promising drug candidate KAE609 from Novartis using an organocatalytic approach. We were able to prepare the indolylnitroalkene analogues **156b-c** with high yields. Based on these results we proposed a general one-step procedure to synthesize a range of precursors for potential bioactive analogues of KAE609. So far our trials to prepare the desired chiral indolylnitroalkane **148a-d** in enantiomerically enriched form failed. We had to separate the synthesized racemic precursors by chiral chromatography.

Applying asymmetric reduction procedures (Figure 171) (Baker yeast[230], Josiphos ligand[223], chiral TarB-NO_2-$NaBH_4$ complex[231]) of the nitro alkene derivatives or chiral protonation processes have to be investigated allowing the preparation of the drugs KAE609 in large scale.

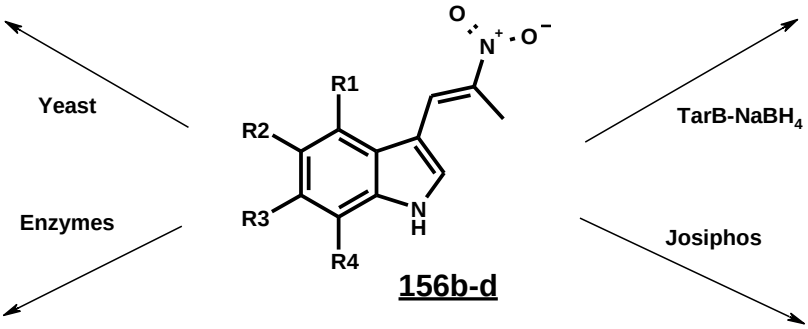


Figure 171: Strategies available for the asymmetric preparation of **149b-d** reducing the prochiral precursors **156b-d**

CHAPTER 5: MULTI COMPONENT DOMINO REACTIONS

I. Introduction

In the recent years, the new trends in the chemical community to produce drugs or natural products in a cheaper, safer, more efficient manner, led to the emergence of a new powerful tool in organic chemistry: domino multi component reactions received considerable attention (as proof: the increasing number of publications on the topic, see Figure 172).

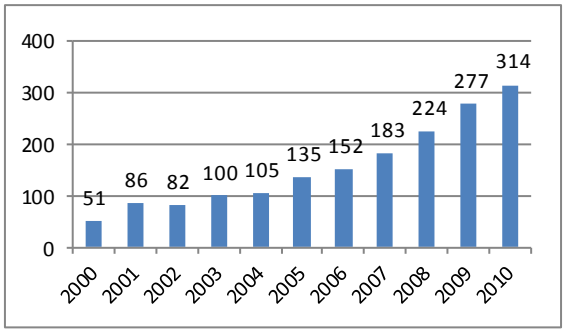


Figure 172: Number of publications edited from 2000 to 2010, on the topic "domino reactions"(SciFinder search)

In a domino multicomponent reaction several C-C bonds and stereocenters are formed from simple precursors. They therefore allow the rapid construction of structurally complex molecules[232,12h,12e].

In 2011, Hayashi *et al* [233] reported his asymmetric one-pot-four-component coupling reaction affording substituted tetrahydropyran derivatives *via* catalyzed Michael-Henry reactions. We discovered in 2009 in the course of our studies on alternative asymmetric preparation of the (S)-Aliskiren precursor **8** (Figure 173) (see also chapter 2) from isovaleraldehyde, the formation of chiral substituted tetrahydropyran derivatives under our reaction conditions.

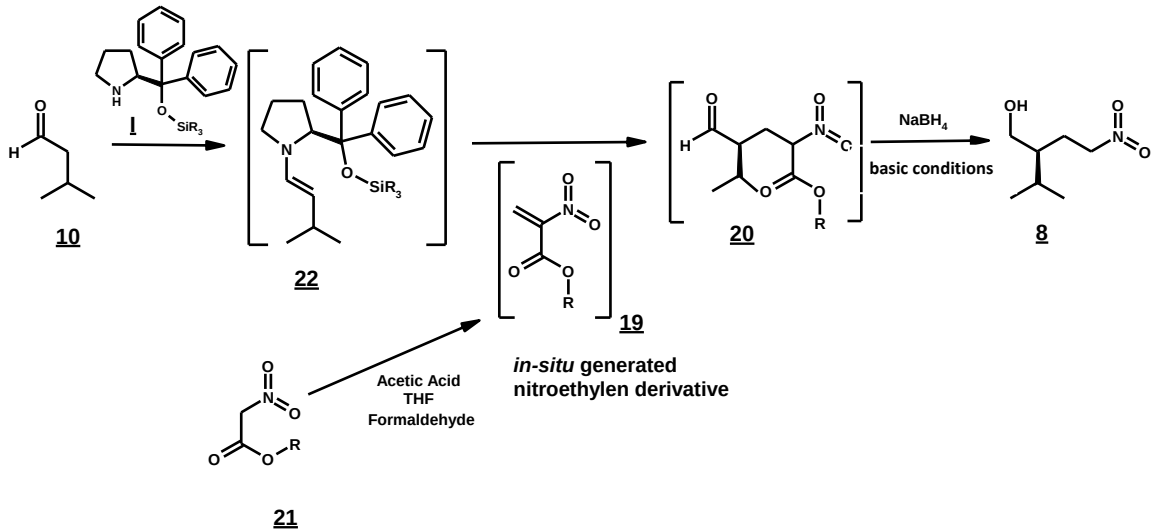


Figure 173: Preparation of nitroalkohol **8** *via* organocatalyzed Michael addition of isovaleraldehyde to nitroethylene ester **19**

As depicted in Figure 173, the multi component preparation of **8** was performed *via* the *in situ* Knoevenagel condensation of the commercially available nitro acetate **21** and formalin to the α-nitroacrylic ester **19**. Using an excess of formalin **24** led to the formation of the chiral tetra substituted tetrahydropyran derivatives **157** as represented in Figure 174.

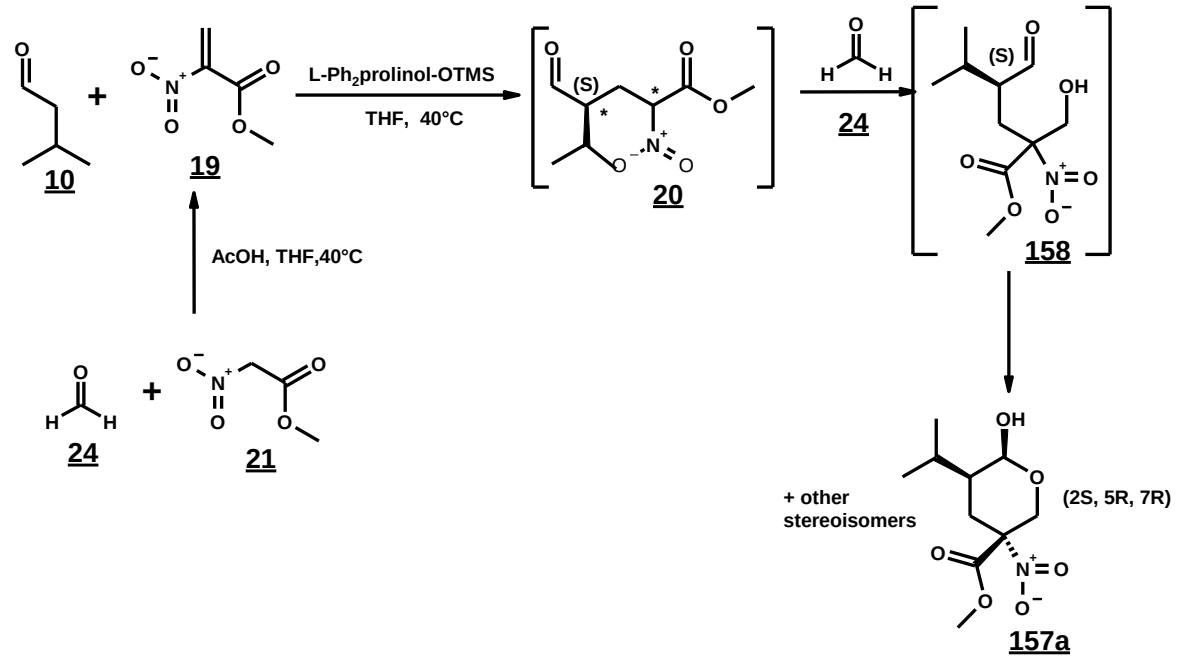


Figure 174: Asymmetric Knoevenagel/Michael/Henry/acetalization reaction sequence for the preparation of **157a**

Assuming that the chiral center carrying the isopropyl group has the (S)-configuration, four diastereoisomers of the constitution **157** can be formed. Applying an oxidation, saponification, decarboxylation, epimerization sequence the single isomer **89** (precursor of Aliskliren base **1**) could be prepared from **157a-d**. The formation of **89** should be favored due to the equatorial conformation of the nitro and isopropyl substituents.

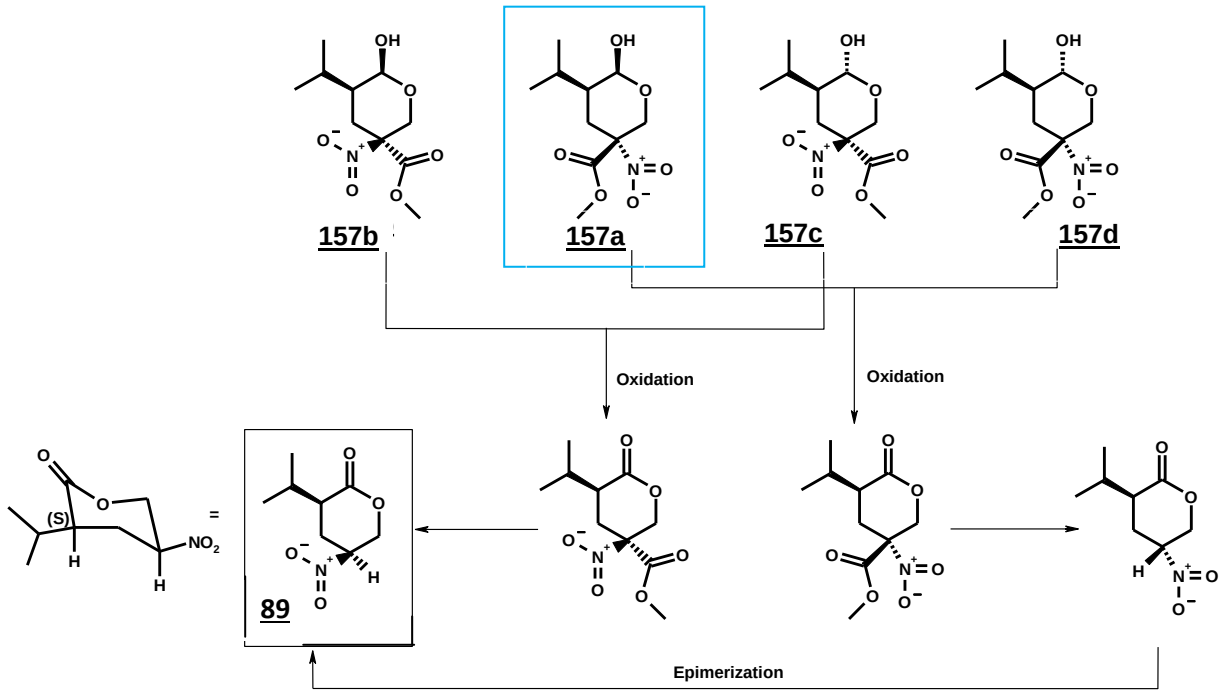


Figure 175: Substituted tetrahydropyran derivatives **157** and formation of the Aliskiren precursor **89**

We rationalized our results by the sequence of reactions shown in Figure 174. According to our postulated mechanism the excess of formaldehyde reacts with the *in situ* generated β-substituted γ-nitroaldehyde *via* a Henry reaction, producing the corresponding nitroaldol product. A subsequent intramolecular cyclisation of the hydroxyl group formed by the $NaBH_4$ reduction leads to the formation of the observed acetal product of Figure 176.

Based on our mechanistic proposal, we proposed a novel four-component organocatalyzed Knoevenagel/Michael/Henry/acetalization reaction sequence, varying the Michael partners and two different aldehydes to deliver pentasubstitued tetrahydropyran derivatives **172** (Figure 176).

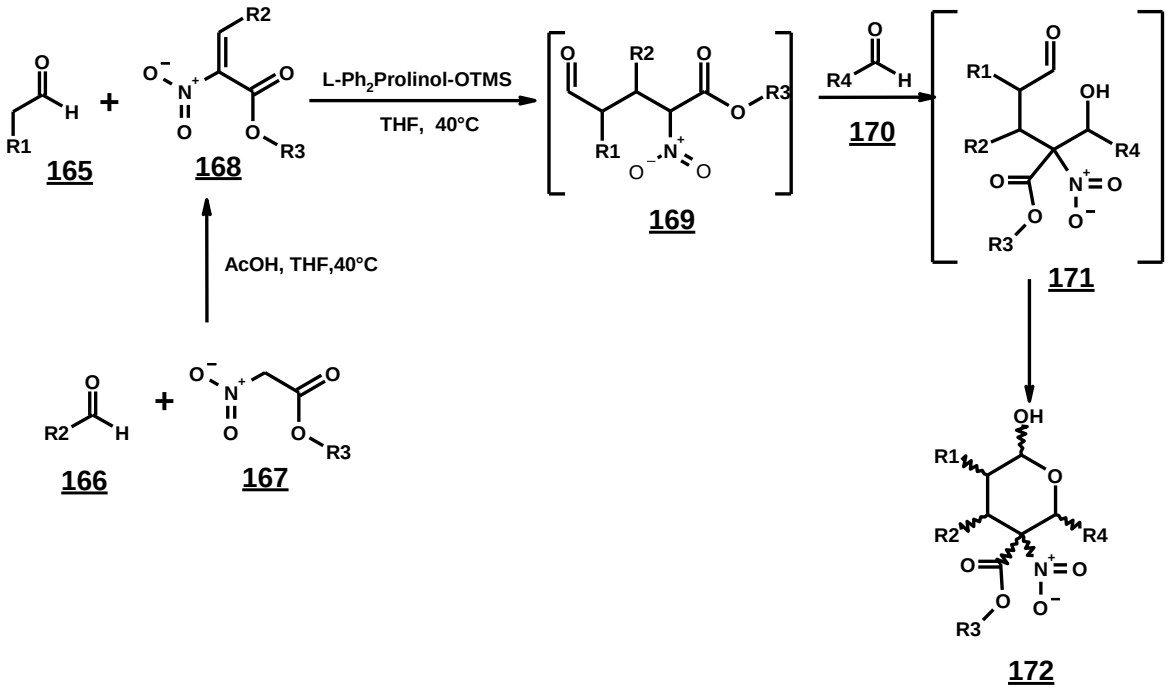


Figure 176: Postulated four-component domino synthesis of substituted tetrahydropyran derivatives **172**

The same year, similar reaction sequences were reported[234] in the literature for an asymmetric three-component reaction, in which the conjugate addition of an aldehyde to a Michael acceptor was catalyzed by diphenylprolinol silyl ether, with a subsequent base-catalyzed addition/cyclization step.
We report here the results of the experiments performed to validate the feasibility of our postulated process and the four-component domino synthesis of tetrahydropyran derivatives, in where all of the positions of the pyranol ring could be substituted with different groups.

II. Results and Discussion

II. 1. Experimental results

We first reinvestigated the preparation of the compound **8** of Figure 173. Using our established method for the Michael addition of isovaleraldehyde **10** to the *in situ* generated β-substituted nitroalkene derivative[16], we prepared the γ-nitroaldehyde derivative. Subsequent treatment of the intermediate **20** with 3 equivalents of an aqueous solution of formaldehyde and 5 equivalents of sodium hydroxide produced the desired tetrahydrofuran products **157** as a mixture of four diastereoisomers with a ratio of 61:26:13, **157a** being the major one (Figure 177).

[16] See chapter 2, III.2.3

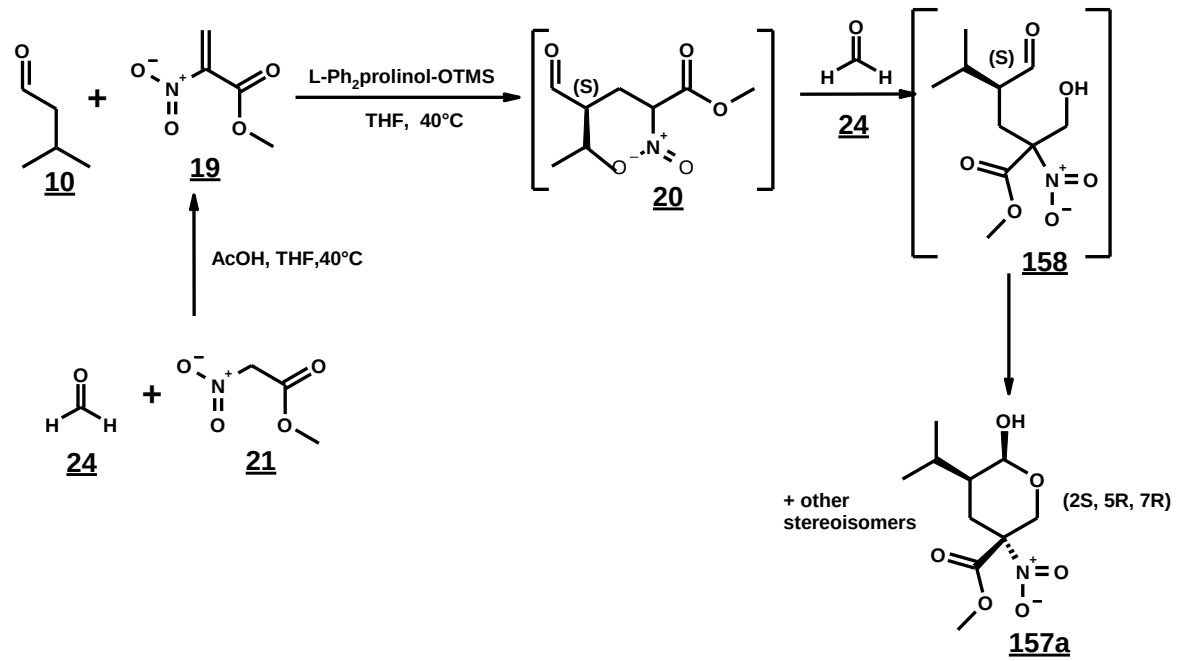


Figure 177: Asymmetric Knoevenagel/Michael/Henry/acetalization reaction sequence for the preparation of **157a**

The asymmetric Michael addition and the concomitant Knoevenagel reaction proceeded over 30 min in THF at 35°C in the presence of 10% of (S)-diphenylprolinol silyl ether and acetic acid (4.5 equivalents). As reported, the Michael product could be isolated. The determination of the diastereoisomeric ratio of **20** by ^{1}H NMR ($CDCl_3$, 400 MHz) showed the presence of two diastereoisomers in a ratio of 71:29.

Three equivalents of formaldehyde were added dropwise to the reaction mixture at 35°C. The Henry reaction proceeded over 7 hours, and 5 equivalents of an aqueous solution of sodium hydroxide (2M) were added to the reaction mixture, affording the desired lactols as a mixture of diastereoisomers with moderate yield (41% isolated yield). The crude mixture of four diastereoisomers was purified by column chromatography on silicagel. The (*2S, 5R, 7R*) lactol **157a** could be obtained as white crystals (Figure 177).

X-Ray analysis revealed the chair conformation of **157a**. The anomeric hydroxyl group and the nitro groups are in axial position. The isopropyl group and the ester group are in the preferred equatorial position ensuring the thermodynamically favorable conformation of these bulky substituents (Figure 178)[235].

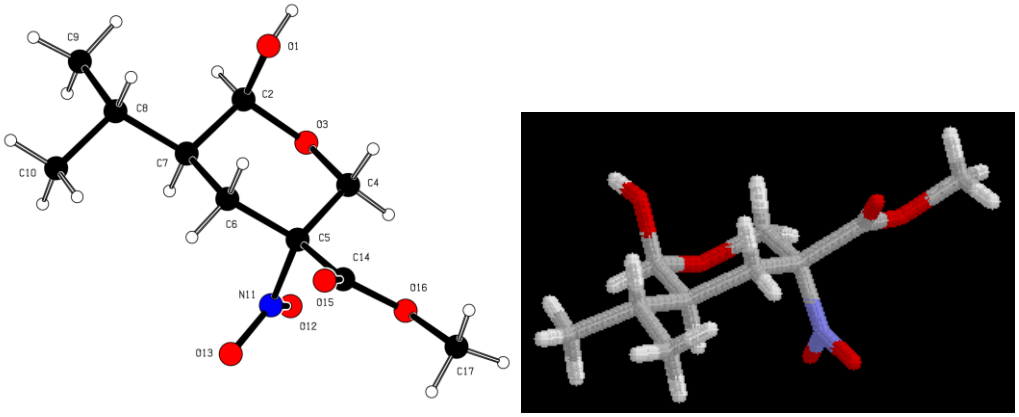
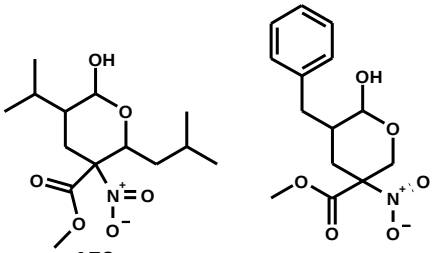


Figure 178: X-Ray structure of **157a**

The other stereoisomers could not be separated by column chromatography on silicagel.

We investigated also the four-component Knoevenagel/Michael/Henry/acetalization reaction sequence, by modification of the nature of the aldehyde partners (Figure 179).



159 **160**

Figure 179: Chiral lactol derivatives **159** and **160** resulting from the variation of the nature of aldehyde partners

For these studies, we condensed the *in situ* generated aldehyde **20** with isovaleraldehyde by performing the reaction in an excess of isovaleraldehyde (five equivalents) in acetic acid / THF media. After eight days an aqueous work-up and the purification of the crude material (isomeric mixture of five diastereoisomers with a ratio of 29:9:42:10:10) by column chromatography on silicagel afforded the desired lactol as isomeric mixture of four diastereoisomers with a ratio of 17:26:45:12 (38% yields). A white material could be obtained adding an 8:1 solution (v/v) of hexan-ethyl acetate and then by triturating in a 1:1 solution (v/v) of hexan-diethyl ether. Crystallization experiments and a second purification of the crude material by column chromatography on silicagel provided in the best case **159** as an isomeric mixture of two diastereoisomers with a ratio of 88:12. Unfortunately we could not get crystals of **159**, which were suitable for X-Ray measurements.

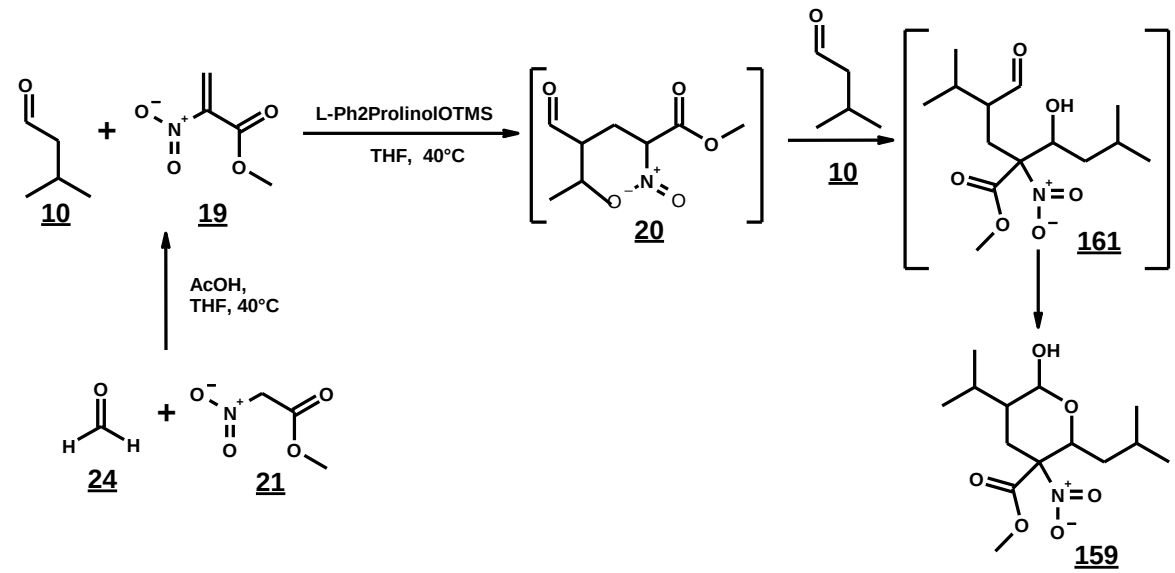


Figure 180: Asymmetric Knoevenagel/Michael/Henry/acetalization reaction sequence for the preparation of **159**

We prepared also, under the same conditions the γ-nitroaldehyde **163** by the concomitant addition at 35°C over 20 min of one equivalent of formalin (37%) in water and nitro acetate to a solution in THF of one equivalent of hydrocinnamaldehyde **162**, 10% of diphenylprolinol silyl ether and acetic acid (4.5 equivalents) . After subsequent addition of two equivalents of formaldehyde, the reaction mixture was allowed to stir at 35°C over 24h. A basic work up afforded the desired lactol derivative **160a** (30% isolated yield) as an isomeric mixture of three diastereoisomers (diastereoisomeric ratio 62:38).

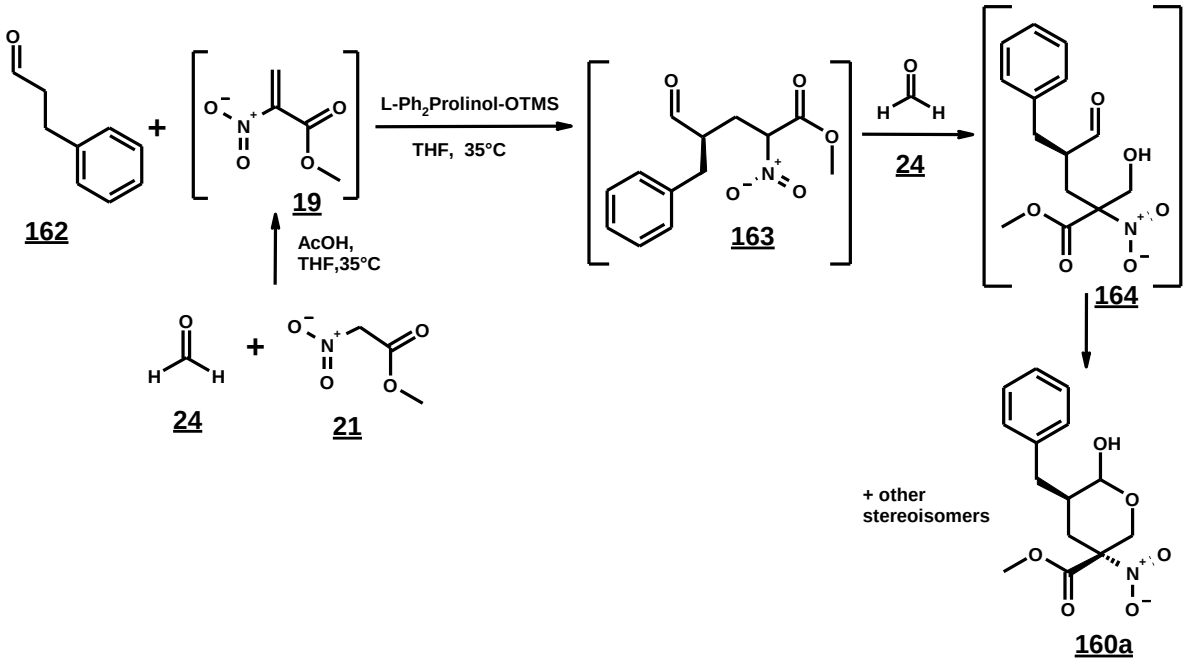


Figure 181: Asymmetric Knoevenagel/Michael/Henry/acetalization reaction sequence for the preparation of **160a**

Purification of the crude material by column chromatography on silicagel with hexane/ ethyl acetate (5:1) provided the (2S, 5R, 7R) lactol **160a** in pure form (Figure 182). The other diastereoisomers could not be obtained in pure form. X-Ray analysis revealed the chair conformation in the crystalline state of **160a**. The anomeric hydroxyl group and the nitro groups are in axial position. The isopropyl group and the ester group are in the preferred equatorial position ensuring the thermodynamically favorable conformation of these bulky substituents (Figure 182).

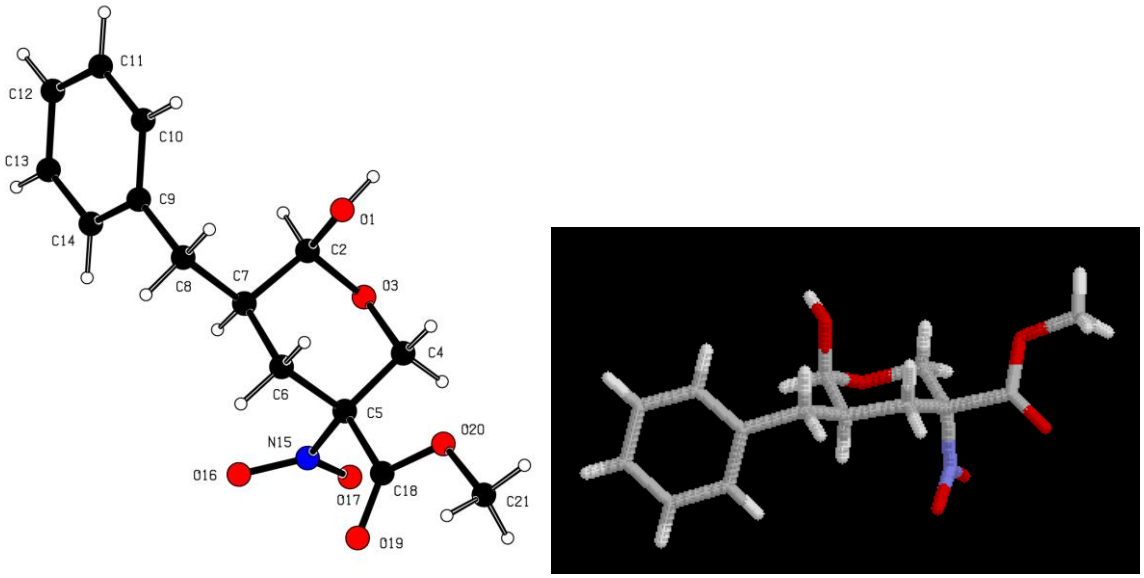


Figure 182: X-Ray structure of **160a**

II.2. Preliminary remarks on the reaction sequence

Hayashi *et al* recently published[233] a paper for a similar organocatalytic sequence.
The following comments are based on our experimental observations.
While Hayashi *et al* [233] performed the condensation step in the presence of a base (DBU), the Henry reaction between **174** and the aldehyde **170** could be performed under base-free conditions, resulting from the higher reactivity of our α-ester substituted nitro intermediate **174**. Additionally, in contrast to the Hayashi sequence, in our system the nitro olefinic intermediate **168** is generated *in situ* from **166** and **167** (Figure 183).
The formation of **172** can be explained by an intermolecular Henry reaction[236] where the zwitterionic intermediate **174** (Figure 183) would react with the aldehyde **170** to deliver the intermediate **175**. After hydrolysis, **175** will afford the δ-hydroxy aldehyde **171**, which is spontaneously cyclized to the final pentasubstituted intermediate **172**.

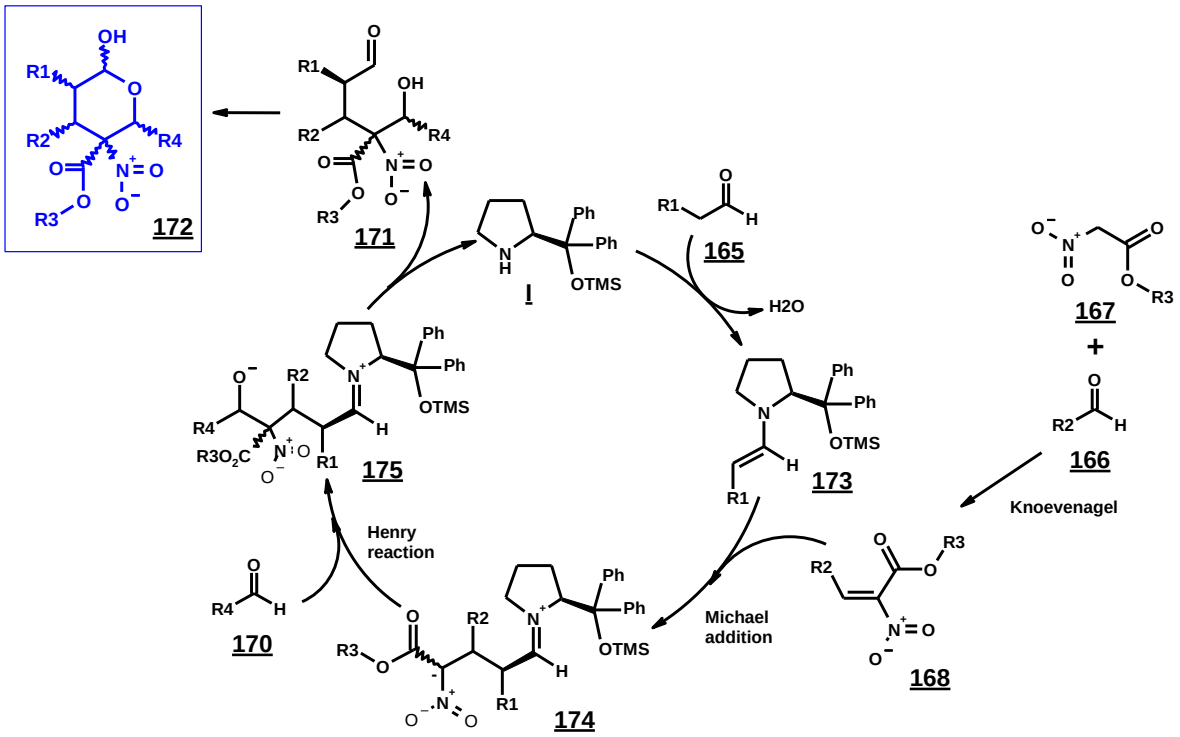


Figure 183: Postulated mechanism for the Michael/Henry sequence

III. Conclusion

We reported here the preparation of stable tetrasubstituted tetrahydropyranol derivatives, from *in situ* generated nitroalkene derivatives and two different aldehydes, by a one-pot-four-component-domino sequence involving the asymmetric Knoevenagel/Michael/Henry/acetalization reactions.

Thanks to possibilities of variation of the nature of the reactants that offers the presented reaction sequence, we could rapidly access a wide range of derivatives presented in Figure 183. Optimization of the reaction conditions is still needed. Investigations of the scope and limitation of this interesting field will continue in the future in Novartis.

CHAPTER 6: EXPERIMENTAL PART

All chemicals were purchased either from commercial suppliers or internal sources. They were used without further purification unless otherwise stated. All the products were satisfactorily characterized by IR, ^{1}H and ^{13}C-NMR, MS, HR-MS. When possible, comparison of their analytical data was made with available literature data.

Flash Chromatography

Compounds were purified on Merck silica gel 60, particle size 0.040-0.063 mm, at room temperature and eluted with the solvent system indicated. Thin-layer chromatographys were performed on Merck pre-coated glass silica gel plates of type 60 F_{254}.

High Performance Liquid Chromatography

HPLC analysis were performed with an Agilent Series 1100. Column: inertsil ODS3 C18 4.6 mu 22 cm ,
The mobile phase was AcN / H_2O + 0.01% $NH_4H_2PO_4$
Gradient: from 55% to 97% AcN, 40°C, λ=220nm,

High Performance Chiral Liquid Chromatography

HPLC analysis were performed with an Agilent Series 1100.
Column: CHIRALPAK AD-h or CHIRALCEL OD-H.

Nuclear magnetic resonance spectrometry (NMR)

NMR spectra were done on a Bruker dpX400 (operating at 400.13 MHz for ^{1}H and 100 Mz for ^{13}C) or a Bruker dpX600 (operating at 600.00 MHz for ^{1}H and 150 Mz for ^{13}C) in the solvents indicated at 300 K and chemical shifts (in ppm) were referenced to residual solvent peaks ($CDCl_3$: 7.27 ppm for ^{1}H, 77.2 ppm for ^{13}C ; d_6-DMSO: 2.50 ppm for ^{1}H, 39.5 ppm for ^{13}C).

Mass spectral data (MS)

Mass spectral data were recorded on a Water ZQ2000 Quadruple, electrospray mass spectrometer operating in positive or negative ion mode as indicated, or with a
Varian 1200L Triple Quadrupole mass spectrometer.

High resolution (HR-MS) mass spectra

High resolution and high accuracy mass spectra were acquired on a 9.4 Tesla Bruker APEXIII Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (FT / ICR -MS) equipped with an electrospray ion source operated in both positive and negative ion mode; 32 spectra were accumulated and internally calibrated using the signals from the Agilent ES tune mix solution.

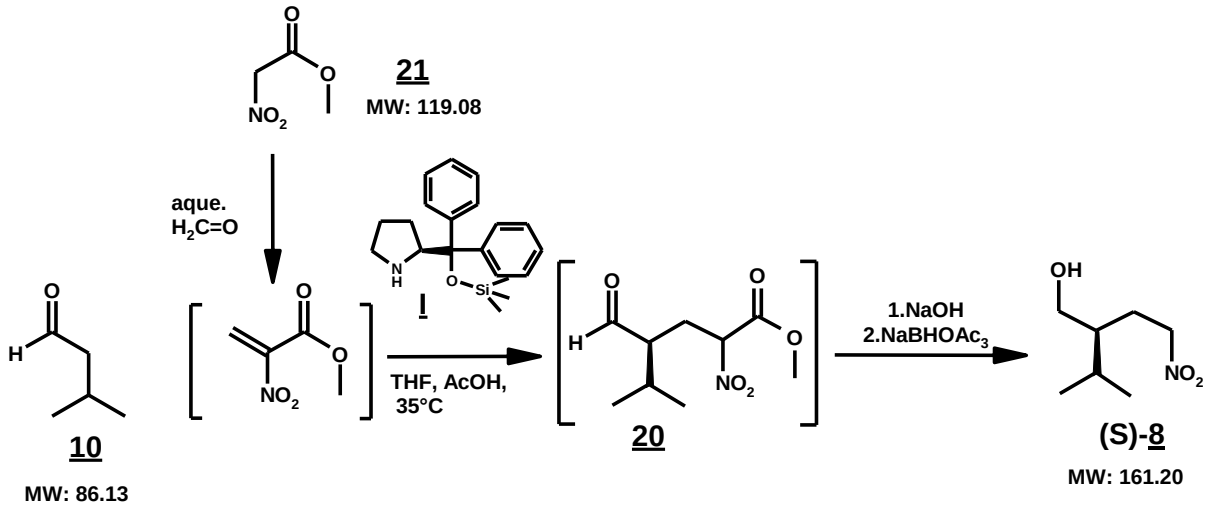
X-Ray analyses

Diffraction data for all compounds were collected at 100 K with a Bruker AXS SMART 6000 CCD detector on a three-circle platform goniometer with Cu(K_{α}) radiation from a fine-focus sealed tube generator equipped with a graphite monochromator or a microfocus rotating anode equipped with multilayer optics.

I. EXPERIMENTAL PART OF CHAPTER 2

I.1. Enamine catalysis

(S)-3-methyl-2-(2-nitro-ethyl)-butan-1-ol 8
CAS Number: 1067910-79-5
G. Sedelmeier, WO-**2008**-119804
Method 1



63.4 mg of (S)-diphenyl-prolinol-O-TMS-ether **I** (0.18 mmol, 0.11 eq.) are dissolved in 4 mL THF. 282 µL of acetic acid (4.8 mmol, 4.0 eq.) and 165 µL of isovaleraldehyde **10** (1.8 mmol, 1.0 eq.) are added to the mixture at room temperature. The mixture is then warmed to 35°C. A solution of 148.1 mg of methyl nitroacetate **21** (1.8 mmol, 1.0 eq.) in 2 mL of THF and a solution of 194 µL of aqueous formaldehyde (~37%) (1.8 mmol, 1.0 eq.) in 2 mL of THF are added simultaneously at 35°C over 30 min (flow: 0.06 mL/min). This solution is then stirred at 35°C during 40 minutes. The mixture is cooled to 0°C and 280 mg of a solution of aqueous NaOH (50%) is added dropwise until pH 7. A solution of 600 mg of $NaBH_3OAc$ (2.8 mmol, 15 eq.) and 2 mL of ethanol (95%) is added portionwise. The reaction mixture is then allowed to warm to room temperature and is stirred over night (over 17 hours). HLPC and NMR controls show the presence of the desired nitroalcohol **8** as major compound. The reaction mixture is quenched with 5 mL of water, and extracted with 10 mL of ethyl acetate. The organic phase was dried over $MgSO_4$, and concentrated in vacuum to yield 202 mg of crude product **8**.

The crude is purified by column chromatography on silicagel (0.040-0.063 nm) (40 g) with heptane:ethyl acetate (4:1) to give in the pure fractions 163 mg of the title nitro compound **8** as colorless oil (56%).

Determination of the enantiomeric ratio by HPLC with a CHIRALPAK AD-H columm at λ = 205 nm (Hex/MeOH/EtOH/ iPrOH = 973:9:9:9, 2mL/min, 40°C) reveals the presence of 95% of the (S)-enantiomer of **8** at 14.1min and 5% of the (R)-enantiomer of **8** at 14.8min.

Spectroscopic data of nitroalcohol **8** are confirmed by the literature data.

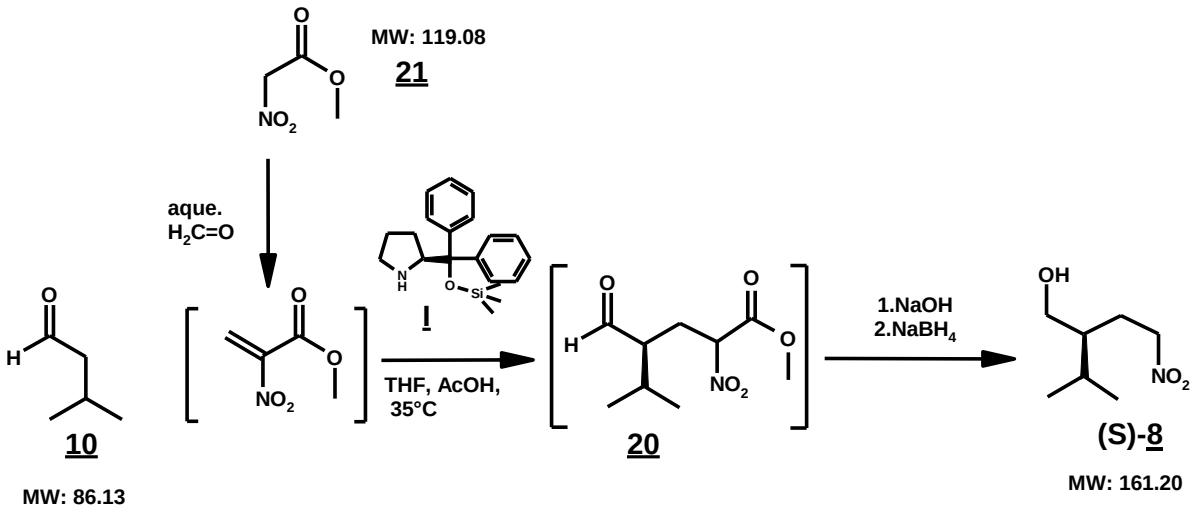
^{1}H-NMR (400 MHz, $CDCl_3$) δ_H (ppm)
0.92 (d, 6H, CH_{3iPr}). 1.43 (ddd, J_1=8 Hz, J_2=7.09 Hz, J_3=4 Hz, 1H, CHiPr), 1.71 - 1.81 (m, 1H, $CH_{iPr,}$) 1.96 - 2.06 (m, 1H, CH_2CH_2NO2), 2.08 - 2.22 (m, 1H, CH_2CH_2NO2), 3.58 (dd, J_1=11 Hz, J_2=7 Hz, 1H, CH_2OH), 3.72 (dd, J_1=11 Hz, J_2=4 Hz, 1H, CH_2OH), 4.42 - 4.65 (m, 2H, CH_2NO_2)

IR: (FTIR-microscopy in transmission)
3387 (OH), 2961, 2887 (C-Haliphatic), 1552 (NO_2 ν_{as}), 1389 (NO_2 ν_s), 1031 (C-O)

MS: $[M+NH_4]^+$ = 179

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm. t_r=2.7 min

(S)-3-methyl-2-(2-nitro-ethyl)-butan-1-ol 8
CAS Number: 1067910-79-5
G. Sedelmeier, WO-**2008**-119804
Method 2



624.0 mg of (S)-diphenyl-prolinol-O-TMS-ether **I** (1.9 mmol, 0.15 eq.) are dissolved in 40 mL THF. 2.5 mL of acetic acid (43 mmol, 3.6 eq.) and 1.3 mL of isovaleraldehyde **10** (12 mmol, 1.0 eq.) are added to the mixture at room temperature. The mixture is then warmed to 35°C. A solution of 1.424 g of methyl nitroacetate **21** (12 mmol, 1.0 eq.) in 21 mL of THF and a solution of 1.071 g of aqueous formaldehyde (~37%) (13 mmol, 1.0 eq.) in 21 mL of THF are added simultaneously over 30 min (flow: 0.6 mL/min). This solution is then stirred at 35°C over an additional period of 15 min (although nitroacetate **21** is already consumed at the end of the addition (HPLC control)). The mixture is cooled to room temperature and an aqueous solution NaOH (2M) is added dropwise over 15 min until pH 7.6. The reaction mixture is diluted at 0°C in 15 mL of ethanol (95%) . 500.3 mg of solid $NaBH_4$ (13.2 mmol, 1.1 eq.) are added portionwise at 0°C over 10 minutes. At the end of the addition all the *in situ* generated aldehyde is consumed (HPLC control), the reaction mixture is quenched with 200 mL of water, and extracted two times with 100 mL of dichloromethane, and once with 100 mL of *tert*-butyl

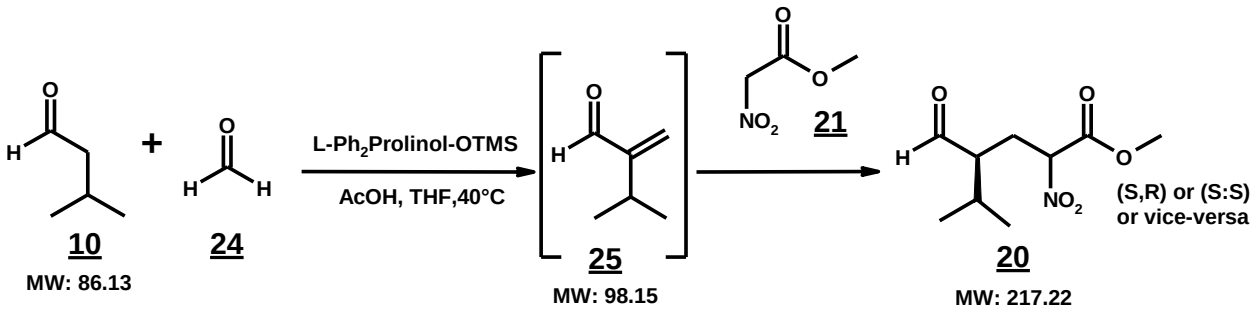
methyl ether. The organic phase is dried over $MgSO_4$, and concentrated in vacuum to yield 1.13 g of crude product **8**.
Determination of the enantiomeric ratio of this crude material by HPLC with a CHIRALPAK AD-H column at λ=205.5 nm (Hex:MeOH:EtOH: *i*PrOH = 973:9:9:9, 2mL/min, 40°C) showed 93% of the enantiomer S and 7% of the enantiomer R.
The aqueous phase is extracted again four times with 100 mL of ethyl acetate. The ethyl acetate phase is dried over $MgSO_4$, and concentrated in vacuum to yield 170 mg of crude product **8**.
Yield: 67%
Determination of the enantiomeric ratio by HPLC with a CHIRALPAK AD-H column at λ=205.5 nm (Hex:MeOH:EtOH: iPrOH = 973:9:9:9, 2mL/min, 40°C) shows the formation of 92% of (S)-**8** and 8% of the enantiomer (R)-**8**.

Spectroscopic data of nitroalcohol **8** are confirmed by the literature data.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ_H (ppm)
4.64-4.41 (m, 2H, CH_2NO_2), 3.72 (dd, 1H, J=10.8 Hz, 7.0 Hz, CH_2OH), 3.58 (dd, 1H, J=10. 8 Hz, 7.0 Hz, CH_2OH), 2.18-2.17 (m, 1H, CH_2), 2.06-1.97 (m, 1H, CH_2), 1.81-1.72 (m, 1H, $CH(CH_3)_2$), 1.47-1.39 (m, 1H, CH), 0.92 (dd, 6H, J=7.0 Hz, -CH_3)

I.2. Iminium catalysis

(S, R) and (S, S)-4-hydroxymethyl-5-methyl-2-nitro-hexanoic acid methyl ester 20

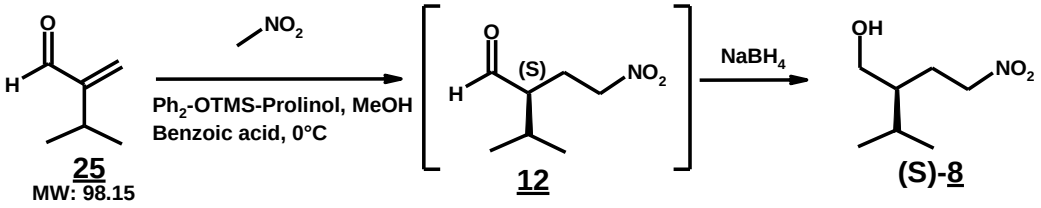


10 MW: 86.13 + **24** → **25** MW: 98.15 → **20** MW: 217.22

1.235 g of the catalyst (3.4 mmol, 0.15 eq.) is dissolved in 70 mL of THF. 7 mL of acetic acid (115 mmol, 4.9 eq.) and 1.60 mL of isovaleraldehyde **10** (23mmol, 1.0 eq.) is added to the reaction mixture at room temperature. The mixture is then warmed to 35°C and a solution of 1.855 g of formaldehyde **24** (~37% in water) (23 mmol, 1.0 eq.) in 10 mL of THF is added. The reaction mixture is stirred at 35°C over a period of 2 hours 45 min. ^{1}H NMR (400 MHz, $CDCl_3$) control shows the formation of the 2-isopropyl acrolein **25**, and complete conversion of the reactants.
To 40 mL of the reaction mixture, is added dropwise at 35°C a solution of 686.1 mg of methyl nitroacetate **21** (5.7 mmol, 0.5 eq.) in 6 mL THF. The reaction mixture is stirred over 48 hours. NMR-controls (^{1}H, 400 MHz, $CDCl_3$) show the formation of the desired α-methyl ester aldehyde **20**, with a conversion ratio of 25% after 2 hours, 74% over night and 82% over two nights and a diastereoisomeric ratio of 70:30.
No further purification is done.

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ_H (ppm) *mixture of two diastereoisomers, d.r. 70% diastereoisomer* ***1*** *and 30% of diastereoisomer* ***2***
0.94 - 1.07 (m, 6H, CH_{3iPr}), 2.19 - 2.34 (m, 3H, CH_2CHNO2, CHiPr, CH_{iPr}) 2.40 - 2.62 (m, 1H, CH_2CHNO2), [3.84 (s, $CH_{3ester\ dia1}$), 3.86 (s, $CH_{3ester\ dia2}$), 3H], [5.22 (dd, J_1=9Hz, J_2=5Hz, $CHNO_{2\ dia1}$), 5.25 - 5.32 (m, , $CHNO_{2\ dia2}$), 1H], 9.70 (d, *J*=6Hz, 1H, HC=O)

(S)-3-methyl-2-(2-nitro-ethyl)-butan-1-ol 8
CAS Number: 1067910-79-5



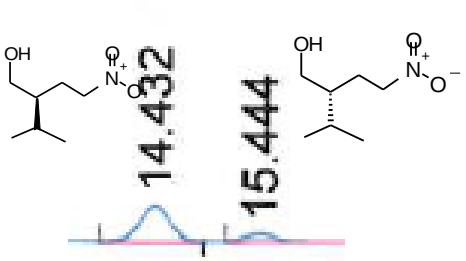
25
MW: 98.15

12

(S)-8
MW: 161.20

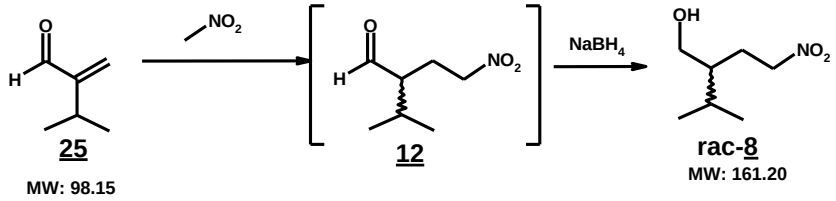
98.8 mg of 2-isopropyl acrolein **25** (1.0 mmol, 1.0 eq.) are dissolved at room temperature in 2 mL of methanol. The solution is then cooled down to 0°C and 36.7 mg of (S)-diphenyl-prolinol-O-TMS-ether (0.10 mmol, 0.1 eq.) and 12.3 mg of benzoic acid (0.1 mmol, 0.1 eq.) and 209.2 mg of nitromethane (3.4 mmol, 3.4 eq.) are added to the reaction mixture. The reaction mixture is stirred at 0°C over 5 days. HPLC controls (reverse and chiral AD-H phase) reveal the low formation of the desired aldehyde **12**, with an enantiomeric ratio of 24 % (R-enantiomer) and 76% (S-enantiomer).
80.7 mg of $NaBH_4$ (2.1 mmol, 2.1 eq.) are added to the reaction mixture at 0°C in three portions, followed by addition 0.5 mL of acetic acid to maintain the pH=4. The reaction mixture is quenched by addition of 0.5 mL of water and is diluted in 1 mL of toluene. The organic phase is dried over $MgSO_4$, and concentrated in vacuum.

The enantiomeric ratio measured on CHIRALPAK AD-H (Hex:MeOH:EtOH:iPrOH = 973:9:9:9, 2mL/min, 40°C) is 82 % of S-**8** and 18% of R-**8**.



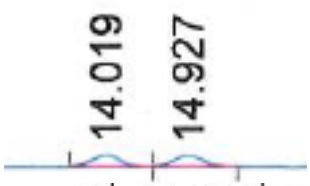
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.430	BB	0.3089	408.59198	20.64891	81.9139
2	15.437	BB	0.3214	90.21486	4.35953	18.0861

(S)-3-methyl-2-(2-nitro-ethyl)-butan-1-ol 8, as a racemic mixture
CAS Number: 1067910-79-5



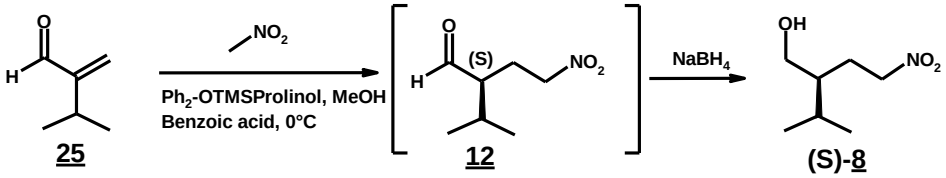
25 **12** **rac-8**
MW: 98.15 **MW: 161.20**

47.5 mg of 2-isopropylacrolein **25** (0.48 mmol, 1.0 eq.) are dissolved at room temperature in 2 mL of dichloromethane. 19.9 mg of DBU (0.12 mmol, 0.25 eq.) and 223.4 mg of nitromethane (3.6 mmol, 7.6 eq.) are added at room temperature. The reaction mixture is stirred at room temperature over 2 hours. HPLC controls (reverse and chiral AD-H phase) reveal the complete formation after two hours of the desired aldehyde **12**, with an enantiomeric ratio of 50 % (R-enantiomer) and 50% (S-enantiomer).
Th reaction mixture is cooled down to 0°C and 40.2 mg of $NaBH_4$ (1.1 mmol, 2.2 eq.) are added to the reaction mixture. The reaction mixture is quenched by addition of 0.5 mL of water and is diluted in 1 mL of toluene. The organic phase is dried over $MgSO_4$, and concentrated in vacuum.
The enantiomeric ratio measured on CHIRALPAK AD-H (Hex:MeOH:EtOH:iPrOH = 973:9:9:9, 2mL/min, 40°C) is 50 % of the S-enantiomer at 14.0 min and 50% of the R-enantiomer at 14.9 min.



1	14.019	BB	0.3030	91.59443	4.62537	49.9837
2	14.927	BB	0.3247	91.65431	4.33528	50.0163

(S)-3-methyl-2-(2-nitro-ethyl)-butan-1-ol 8 (representative scale)
CAS Number: 1067910-79-5



25 **12** **(S)-8**
MW: 98.15 **MW: 161.20**

338.2 mg of (S)-diphenyl-prolinol-O-TMS-ether (1.0 mmol, 0.09 eq.) are dissolved at 0°C in 10 mL of methanol. 1.071 g of 2-isopropylacrolein **25** (10.9 mmol, 1.00 eq.) and 234.2 mg of benzoic acid (1.92 mmol, 0.17 eq.) are added to the reaction mixture at 0°C. After 5 min, 2 mL of nitromethane (36.9 mmol, 3.4 eq.) are added dropwise at 0°C. The reaction mixture is stirred at 0°C over 6 days. HPLC controls (reverse and chiral AD-H phase) show the low formation of the desired aldehyde **12**, with an enantiomeric ratio of 27 % (R-enantiomer) and 73% (S-enantiomer). NMR control (^{1}H NMR, 400 MHz, $CDCl_3$-*d*) reveals a conversion rate of 20%.

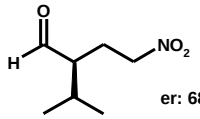
764.9 mg of $NaBH_4$ (20.9 mmol, 1.8 eq.) are added to the reaction mixture at 0°C in five portions. The reaction mixture is allowed to stir at 0°C over 1 hour until complete reduction of the aldehyde intermediate **12** to the desired compound **8** (HPLC control).
The reaction mixture is quenched by addition of 20 mL of water and is diluted in 20 mL of ethyl acetate. The phases are separated ($pH_{aqueous\ phase}$ = 10) and the organic phase is washed three times with 20 mL of water ($pH_{aqueous\ phase}$ = 8 to 6) until complete removal of nitromethane from the organic layer. The ethyl acetate phase is dried over $MgSO_4$, and concentrated in vacuum to yield 1.03 g of the desired nitroalcohol **8** as a crude product.

The enantiomeric ratio of the crude material measured on CHIRALPAK AD-H (Hex:MeOH:EtOH:iPrOH = 973:9:9:9) 2mL/min, 40°C, ג = 205 nm and 215 nm) is 66 % of the S-enantiomer and 34% of the R-enantiomer .

The crude material is purified by column chromatography on silicagel (0.040-0.063 nm) (50 g) with heptane:ethyl acetate (4:1) to give in the pure fractions 311.5 mg of desired nitro compound **8** as a colorless oil.

The enantiomeric ratio measured on CHIRALPAK AD-H (Hex:MeOH:EtOH:iPrOH = 973:9:9:9, 2mL/min, 40°C, ג = 205 nm, 215 nm and 280 nm) is 68 % of the S-enantiomer and 32% of the R-enantiomer .

Spectroscopic data of nitro-aldehyde 12:



er: 68:32

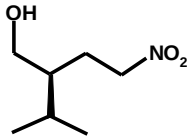
(S)-12

MW: 159.19

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ_H (ppm)
0.95 - 1.12 (m, 6H, CH_{3iPr}), 2.07 - 2.43 (m, 4H, $CHCH_{iPr,}$ $CH_{iPr,}$ $CH_2CH_2NO_2$), 4.35 (ddd, J_1= 13 Hz, J_2= 8 Hz, J_3= 6 Hz, 1H, CH_2OH), 4.42 - 4.59 (m, 1H, CH_2OH), 9.73 (s, 1H, HC=O)

Spectroscopic data of nitro-alcohol 8:

Spectroscopic data of nitroalcohol are confirmed by the literature data.



(S)-8

MW: 161.20

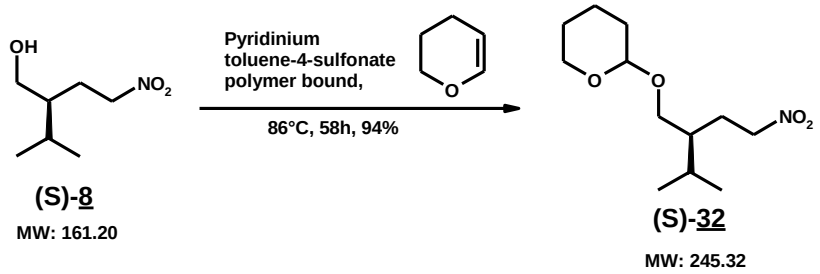
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ_H (ppm)
0.94 (d, 6H, CH_{3iPr}), 1.40 - 1.52 (m, 1H, $CHCH_{iPr}$), 1.70 - 1.85 (m, 1H, CH_{iPr}), 1.98 - 2.11 (m, 1H, , $CH_2CH_2NO_2$), 2.12 - 2.26 (m, 1H, $CH_2CH_2NO_2$), 3.61 (dd, J_1=11 Hz, J_2=7 Hz, 1 H, CH_2OH), 3.74 (dd, J_1=11, J2= 5 Hz, 1H, CH_2OH) 4.34 - 4.68 (m, 2H, CH_2NO_2)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C (ppm)
19.36 (-CH_{3iPr}), 19.67 (-CH_{3iPr}), 27.24 (CH_2CH_2NO2), 28.74 (CH_{iPr}), 43.77 ($CHCH_{iPr}$), 63.95 (CH_2OH) 74.85 (CH_2NO_2)

I.3. From nitro compound 8 to its aldehyde analogues

I.3.1. (S)-3-methyl-2-(2-nitro-ethyl)-butoxy derivatives

2-[(S)-3-methyl-2-(2-nitro-ethyl)-butoxy]-tetrahydro-pyran 32



(S)-8
MW: 161.20

(S)-32
MW: 245.32

To a mechanically stirred solution of 20.0 g of nitroalcohol **8** (124 mmol, 1.0 eq.) in 3,4-dihydro-2H-pyran (180 mL) are added at room temperature 7.14 g of polymer bound pyridinium toluene-4-sulfonate (3.5 mmol/ g, 25 mmol, 0.2 eq.). The yellow suspension is warmed up to 86°C and stirred over 58 hours in refluxing 3,4-dihydro-2H-pyran. The suspension is then cooled down to room temperature. The polymer is filtered off and washed with dichloromethane. The yellow organic phase is concentrated in vacuum to yield 42.4 g of a brown liquid.
The crude product is purified by column cromatography on silica gel with heptane:ethyl acetate (10:1) to give in the pure fractions 28.77 g of 2-((*S*)-3-methyl-2-(2-nitroethyl)butoxy)-tetrahydro-2H-pyran **32** as a slight yellow liquid (94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm) (mixture of diastereoisomers 1:1)
0.94 (dd, *J* =7Hz, 6H CH_{3iPr}) , 1.61-1.51 (m, 5H, CH_2-CH_2-NO_2, CH-CH_{iPr}, 2*HCH_{THP}), 1.82-1.67 (m, 3H, CH_{iPr}, 2*HCH_{THP}), 2.06-1.93 (m, 1H, HCH_{THP}), 2.33-2.13 (m, 1H, HCH_{THP}), [3.86-3.80 (m, 1.5H,), 3.72-3.67 (m, 0.5H), 3.49-3.56 (m, 1H), 3.40 (dd, *J*=9Hz, 0.5H), 3.25 (dd, *J* 9Hz, 0.5H) (CH_{2THP}-O, CH_2-O)], 4.62-4.46 (m, 3H, CH_2NO_2, CH_{THP})

^{13}C NMR (150 MHz, $CDCl_3$) δ_C (ppm)
19.15-19.23 (CH_{3iPr}) , 24.91 (CH_{2THP}), 27.34 (CH_{2THP}), 28.85 (CH_{iPr}), 30.09 (CH_{2THP}), 41.07 (CH-CH_{iPr}), 61.74 (CH_{2THP}-O), 68.59 (CH_2-O), 74.08 (CH_2NO_2), 98.62-98.75 (CH_{THP})

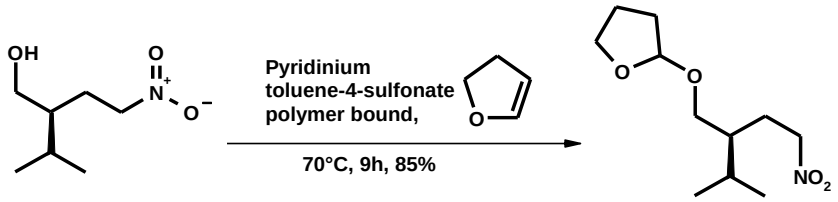
IR: (FTIR-microscopy in transmission)
2957 (C-H), 1554 & 1358 (NO_2), 1123 (C-O-C), 1033 (C-O)

MS: MH^+ = 246

HRMS ($C_{12}H_{24}O_4N$, 0.3 ppm/MH+): $[M+H]^+$= 246.16989, cal. 246.16999, $C_{11}H_{22}O_4N$

R_f (heptane/ethyl acetate, 8:1) = 0.39

2-[(S)-3-methyl-2-(2-nitro-ethyl)-butoxy]-tetrahydro-furan 33



(S)-8
MW: 161.20

(S)-33
MW: 231.2943

To a mechanically stirred solution of 20.08 g nitroalcohol **8** (124.0 mmol, 1 eq.) in 2,3-dihydrofuran (180 mL, 2.37 mol, 19 eq.) are added at room temperature 720 mg of polymer bound pyridinium toluene-4-sulfonate (3.5 mmol/ g, 2.5 mmol, 0.02 eq.). The yellow suspension is warmed up to 70°C and stirred over 6 hours in refluxing 2,3-dihydrofuran until complete conversion (GC measurement) of the starting material **8**. The suspension is cooled down to room temperature. The polymer is filtered off and washed with dichlomethane. The collected yellow organic phases are concentrated in vacuum to yield 32.10 g of protected alcohol.
The crude product is purified by column cromatography on silica gel with heptane:ethyl acetate (8:1) to give in the pure fractions 24.38 g of 2-((S)-3-methyl-2-(2-nitroethyl)butoxy)-tetrahydrofuran **33** as a yellow liquid (85 %).

^{1}H-NMR: (400 MHz, $CDCl_3$) δ_H (ppm) (mixture of diastereoisomers 1:1)
0.91 (m, 6H, CH_{3iPr}), 1.49-1.53 (m, 1H, C<u>H</u>-CH_{iPr}), 1.68-2.20 (m, 7H, CH_{iPr}, C<u>H$_2$</u>-CH_2-NO_2, 2*CH_{2THF}), [3.72 (dd, *J*= 9Hz, 0.5H), 3.68 (dd, *J*=9Hz, 0.5H), 3.39 (dd, *J*=9Hz, 0.5H), 3.26 (dd, *J*= 9Hz, 0.5H), CH_2-O], 3.85-3.90 (m, 2H, $CH_{2\ THF}$ -O), 4.40-4.55 (m, 2H, CH_2NO_2), 5.04-4.06 (m, 1H, CH_{THF})

^{13}C-NMR (150 MHz, DMSO-*d6*) δ_C (ppm)
18.9 (CH_{3iPr}), 19.3 (CH_{3iPr}), 23.0 (CH_{2THF}), 25.8 (<u>C</u>H_2-CH_2-NO_2), 28.3(CH_{iPr}), 31.7 (CH_{2THF}), 40.6 (<u>C</u>H-CH_{iPr}), 66.1 ($CH_{2\ THF}$ -O), 67.2 (CH_2-O), 74.3 (CH_2NO_2), 103.1 (CH_{THF})

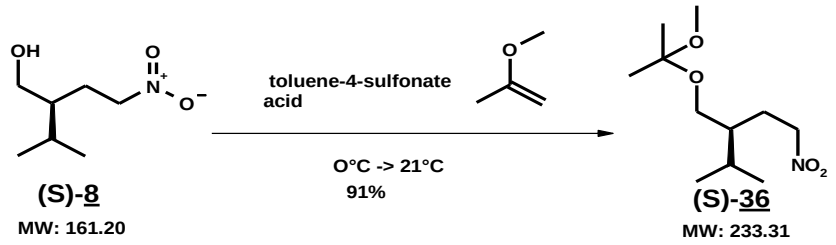
IR: (FTIR-microscopy in transmission)
2961 (C-H), 1554 & 1358 (NO_2), 1038 (C-O)

MS: MH^+ = 232

HRMS ($C_{11}H_{21}O_4N$, 0.5 ppm/MH+): $[M+H]^+$= 232.15422, cal. 232.15434, $C_{11}H_{22}O_4N$

R_f (heptane/ethyl acetate, 8:1) = 0.31

(S)-3-(1-methoxy-1-methyl-ethoxymethyl)-4-methyl-1-nitro-pentane 36



(S)-8
MW: 161.20

(S)-36
MW: 233.31

20 mL of 2-methoxypropene (212.4 mmol, 3.3 eq.) are added dropwise at 0°C to a mechanically stirred solution of 10.15 g nitroalcohol **8** (62.9 mmol, 1 eq.) and 35.2 mg *p*-toluene-sulfonate acid (0.19 mmol, 0.003 eq.). The yellow solution is allowed to warm up to room temperature and stirred over 63 hours until completion (GC mesurement) of the reaction. After evaporation of the excess of methoxypropene, the residue is diluted in 50 mL dichloromethane and washed with 50 mL of aqueous $NaHCO_3$ (20%). The collected yellow solution is dried over $MgSO_4$ and concentrated in vacuum to yield 13.38 g of compound **36** (91%).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm)
0.85 (d, *J*=6 Hz, 6H, CH_{3iPr}), 1.24 (s, 6H, CH_{2MIP}), 1.34 - 1.45 (m, 1H, CH_{iPr}), 1.67 - 1.88 (m, 2H, HCH-CH_2-NO_2, CH-CH_{iPr}), 1.92 - 2.05 (m, 1H, HCH-CH_2-NO_2), 3.07 (m, 3H, OCH_{3MIP}), 3.16 - 3.25 (m, 1H, HCH-O),3.28 - 3.34 (m, 1H, HCH-O), 4.47 - 4.70 (m, 2H, CH_2NO_2)

^{13}C NMR (101 MHz, DMSO-d_6) δ_C (ppm)
18.88 (CH_{3iPr}), 19.34 (CH_{3iPr}), 24.09 (CH_{3MIP}), 26.58 ($CH_2CH_2NO_2$), 28.10 (CH_{iPr}), 40.10 (CH CH_{iPr}), 47.83 (OCH_{3MIP}), 61.02 (CH_2-O), 74.57 (CH_2NO_2), 99.36 (C_{MIP})

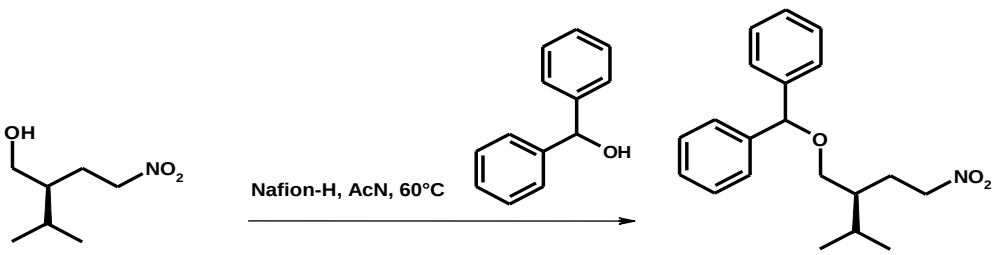
IR: (FTIR-microscopy in transmission)
2961 (C-$H_{aliphatic}$), 2830 (C-O). 1555 (NO_{2vas}), 1435 (C-H_δ), 1381 (C-$H_{3\delta}$), 1371(NO_{2vs}), 1213-1077-1043 (C-O)

MS: $[M+H]^+$ = no response

HRMS: no response

GC: column Optima-1MN, 25mx0.32mmx0.35µm, Hydrogen flow: 30.0 mL/min, Air flow: 400.0 mL/min, Helium flow: 20.0 mL/min, 75 to 200°C in 10 min, 3min at 200°C, 200 to 300°C in 10 min, 2min50 at 300°C, t_R = 13.18 min

4-methoxy-4-[(S)-3-methyl-2-(2-nitro-ethyl)-butoxy]-trityl 37



(S)-8
MW: 161.20

(S)-37
MW: 327.43

4.04 g of nitroalcohol **8** (25.0 mmol, 1.00 eq.) are diluted in 35 mL of acetonitrile at room temperature. 5.63 g of diphenylcarbinol (30.5 mmol, 1.2 eq.) and 1.57 g of Nafion-H NR50 are added to the yellow solution. The reaction mixture is then warmed to 60°C and allows to stir at 60°C over 3.5 days. The reaction mixture is then cooled down to room temperature and diluted in 15 mL of dichloromethane. Nafion H is filtered off and washed with 20 mL of dichloromethane. The organic phase is concentrated in vacuum to yield 9.99 g of crude material.
The crude product is purified by column chromatography on silicagel (250g) with heptane/ethyl acetate (8:1) to give in the purest fractions 6.49 g of the desired nitro compound **37** (yield 79%) as a colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm)
0.76 - 0.87 (m, 6H, CH_{3iPr}), 1.50 (ddd, J_1=9 Hz, J_2=5 Hz, J_3=5 Hz, 1H, C<u>H</u>-CH_{iPr}), 1.77 (dq, J_1=12 Hz, J_2=7 Hz, 1H, CH_{iPr}),1.82 - 1.96 (m, 1H, <u>H</u>CHCH_2NO_2), 1.96 - 2.12 (m, 1H, HC<u>H</u>CH_2NO_2), 3.17 - 3.50 (m, 2H, CH_2-0), 4.41 - 4.82 (m, 2H, CH_2NO_2) 5.41 (s, 1H, $CH_{Benzhydryl}$), 7.00 - 7.51 (m, 10H, CH_{arom})

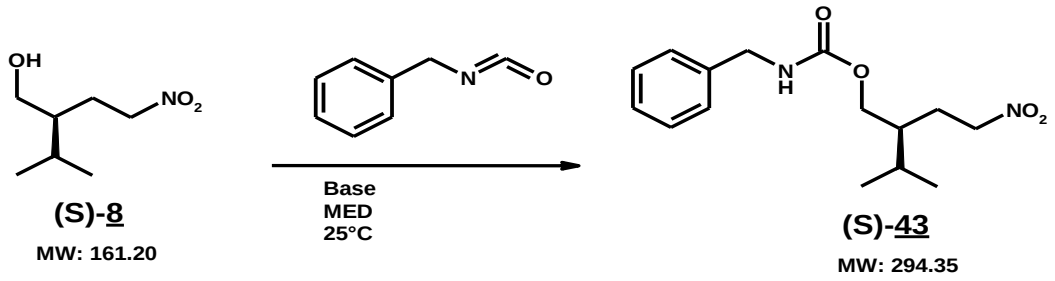
^{13}C NMR (101 MHz, DMSO-d_6) δ_C (ppm)
19.10 (CH_{3iPr}) 19.42 (CH_{3iPr}), 26.35 (<u>C</u>$H_2CH_2NO_2$), 28.25 (CH_{iPr}), 40.98 (CH CH_{iPr}), 69.02 (CH_2-O), 74.38 (CH_2NO_2), 82.73 ($CH_{Benzhydryl}$), 126.36 (CH_{arom}), 126.55 (CH_{arom}), 127.21 (CH_{arom}) 128.30 (CH_{arom}), 128.43 (CH_{arom}), 142.56 (C_{arom})

IR: (FTIR-microscopy in transmission)
3087-3029 ($CH_{aromatic}$), 2960-2874 (C-H_{aliph}), 1600 (Phenyl), 1551 (NO_{2vas}), 1493 (Phenyl), 1384 (NO_{2vs}), 1091-1072 (C-O), 1029 (C-$H_{\delta aromatic}$), 743 (C-$H_{\delta aromatic}$), 702 (Phenyl$_\delta$)

MS: $[M+NH_4]^+$ = 345.4
$[MH]^-$= 326.2

HRMS (0.5 ppm/MNH_4+): $[M+NH_4]^+$= =345.21710, cal. 345.21727, $C_{20}H_{29}O_3N_2$

benzyl-carbamic acid (S)-3-methyl-2-(2-nitro-ethyl)-butyl ester 43



(S)-8
MW: 161.20

(S)-43
MW: 294.35

162.4 mg of **8** (1.01 mmol, 1.00 eq.) are diluted in 1 mL of dry dichloromethane at room temperature (21°C). 123.5 µL of benzylisocyanate (1.00 mmol, 1.0 eq.) and 21.3 mg of DABCO (0.19 mmol, 0.19 eq.) are added at room temperature. The reaction mixture is then warmed to 25°C and stirred at 25°C over 2.5 hours, until complete conversion of benzylisocyanate. After 10 min, the precipitation of N,N-dibenzylurea **43b** is observed. **43b** is filtered off and washed with 10 mL of heptane resulting in the precipitation of **43b** in the organic phase. The solid is removed of the suspension and the combined white solids are washed with 10 mL of heptane (No precipitation occurs). The organic phase is concentrated in vacuum and the crude material is diluted into 0.5 mL of dry dichloromethane. 123.5 µL of benzylisocyanate (1.0 mmol, 1.0 eq.) and 6 mg of DABCO (0.04 mmol,

0.04 eq.) are added to the reaction mixture, which is stirred at 25°C over 20 min. 10 mL of heptane are added in the reaction mixture, resulting in the precipitation of **43b**. **43b** is filtered off and washed with 10 mL of heptane. The organic phase is concentrated in vacuum to yield 265.4 mg of crude material.
The crude product is purified by column chromatography on silicagel (10 g) with heptane/ethyl acetate (5:1) to give in the purest fractions 140.7 mg of the desired nitro compound **43** (yield 48%) as a colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm) rotamers
0.87 (d, *J*=6 Hz, 6H, CH_{3iPr}), 1.47 - 1.57 (m, 1H, C<u>H</u>-CH_{iPr}), 1.65 - 1.79 (m, 1H, CH_{iPr}), 1.78 - 1.90 (m, 1H, <u>H</u>CHCH_2NO_2), 1.97-2.05 (m, 1H, <u>H</u>CHCH_2NO_2), 3.86 - 3.95 (m, 1H, <u>H</u>CH-O), 3.97 - 4.08 (m, 1H, HC<u>H</u>-O), 4.18 (d, *J*=6 Hz, 2H, CH_2-N), 4.45 - 4.71 (m, 2H, CH_2NO_2), 7.24 (d, *J*=7 Hz, 2H, CH_{arom}) 7.30 (d, *J*=7 Hz, 2H, CH_{arom}), 7.65 (s, 1H, NH)

^{13}C NMR (101 MHz, DMSO-d_6) δ_C (ppm)
18.97 (CH_{3iPr}), 19.20 (CH_{3iPr}), 25.91 (<u>C</u>$H_2CH_2NO_2$), 28.01 (CH_{iPr}), 40.34 (CH CH_{iPr}), 43.73 (CH_{2Benz}), 64.45 (CH_2OH), 74.20 (CH_2NO_2), 126.74 (CH_{arom}), 126.96 (CH_{arom}), 128.23 (CH_{arom}), 139.79 (C_{arom}), 156.43 (C=O)

<u>IR</u>: (FTIR-microscopy in transmission)
3334-3416 (NH), 3032 ($CH_{aromatic}$), 2962 (C-H_{aliph}), 1704 (C=$O_{carbamate}$), 1605-1455 (Phenyl), 1552 (NO_{2vas}), 1525 (Amide II), 1384 (NO_{2vs}), 1244 (C-O), 739-699 (C-$H_{\delta aromatic\ monosubst.}$)

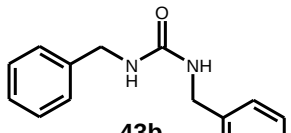
<u>MS</u>: MH^+ =295

<u>HRMS</u> $C_{15}H_{21}O_5N$ (0.3 ppm/MH+): $[MH]^+$= 296.15902, cal. 296.15925, $C_{15}H_{22}O_5N$

<u>HPLC method</u>: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 6.9 min

R_f (heptane/ethyl acetate, 1:1) = 0.63

Spectroscopic data of N,N-dibenzylurea **<u>43b:</u>**
CAS Number: 1466-67-7



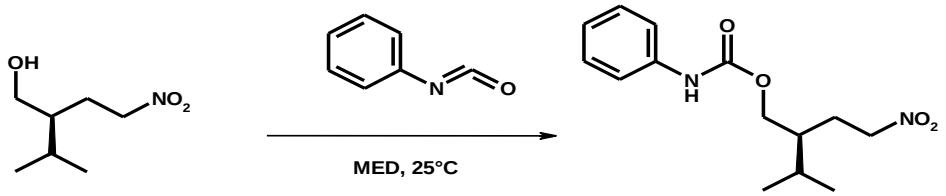
<u>43b</u>
MW: 240.31

^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm)
4.25 (s, 4H, CH_{2benz}), 6.46 (t, 2H, NH), 7.15-7.38 (m, 10H, CH_{arom}),

<u>IR</u>: (FTIR-microscopy in transmission)
3325 (NH), 3031 ($CH_{aromatic}$), 1628 (C=O_{urea}), 1573 (Amide II, Phenyl), 1494-1454 (Phenyl), 751-697 (C-$H_{\delta aromatic\ monosubst.}$)

<u>MS</u>: MH^+ =241.1

phenyl-carbamic acid (S)-3-methyl-2-(2-nitro-ethyl)-butyl ester 42



(S)-8
MW: 161.20

(S)-42
MW: 280.33

329.1 mg of **8** (2.04 mmol, 1.00 eq.) are diluted in 0.8 mL of dry dichloromethane at room temperature (21°C) and 245.2 mg of phenylisocyanate (2.06 mmol, 1.0 eq.) are added. The reaction mixture is then warmed to 25°C and stirred at 25°C over 18 hours. Precipitation of N,N-diphenyl urea **42b** is observed. The reaction mixture is then cooled down to room temperature, the precipitate filtered off and washed with 3 mL of dichloromethane. The organic phase is concentrated in vacuum to yield 379 mg of crude material.
The crude product is purified by column chromatography on silicagel (20 g) with heptane/ethyl acetate (5:1) to give in the purest fractions 227.3 mg of the desired nitro compound **42** (yield 40%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm)
0.91 (dd, J_1= 7 Hz, J_2= 2Hz, 6H, CH_{3iPr}), 1.52 - 1.67 (m, 1H, C<u>H</u>-CH_{iPr}), 1.75 - 1.96 (m, 2H, CH_{iPr}, <u>H</u>C<u>H</u>CH_2NO_2), 1.99 - 2.16 (m, 1H, HC<u>H</u>CH_2NO_2), 3.98 - 4.06 (m, 1H, <u>H</u>CH-O), 4.08 - 4.21 (m, 1H, HC<u>H</u>-O), 4.57 - 4.75 (m, 2H, CH_2NO_2), 6.95 - 7.02 (m, 1H, CH_{arom}), 7.27 (t, J=8 Hz, 2H, CH_{arom}), 7.46 (d, J=8 Hz, 2H, CH_{arom}), 9.56 (s, 1H, NH)

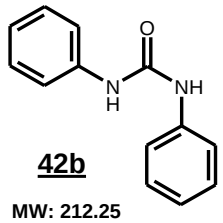
<u>IR</u>: (FTIR-microscopy in transmission)
3326 (NH), 3138($CH_{aromatic}$), 2963 (C-H_{aliph}), 1714 (C=$O_{carbamate}$), 1601-1445 (Phenyl), 1555 (Amide & NO_{2vas}), 1384 (NO_{2vs}), 1221 (C-O), 755-693(C-$H_{\delta aromatic}$),

<u>MS</u>: MH^+ = 281, M+Na^+ = 303
MH^- = 279

<u>HPLC method</u>: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 7.4 min

R_f (heptane/ethyl acetate, 5:1) = 0.14

Spectroscopic data of N,N-diphenylurea **<u>42b:</u>**
CAS Number: 102-07-8



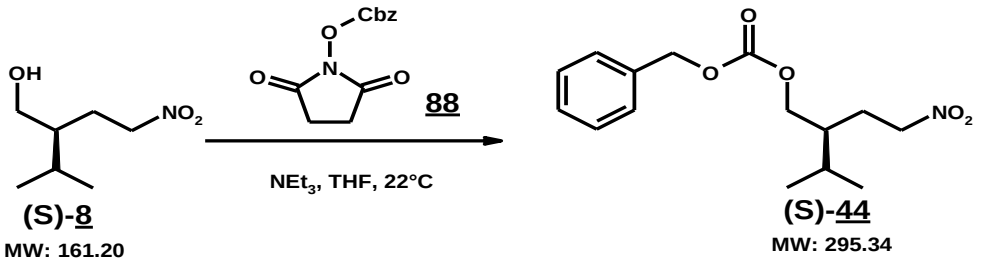
<u>42b</u>
MW: 212.25

^{1}H NMR (600 MHz, DMSO-d_6) δ_H ppm
7.98 (t, J=8 Hz, 2H, CH_{arom}), 7.27 (t, J=8 Hz, 4H, CH_{arom}), 7.45 (t, J=8 Hz, 4H, CH_{arom}), 8.68 (s,2H, NH)

IR: (FTIR-microscopy in transmission)
3327-3291 (NH), 3036 ($CH_{aromatic}$), 1650 ($C=O_{urea}$), 1556 (Amide II), 1498-1448 (Phenyl), 753-696 ($C-H_{\delta aromatic\ monosubst.}$)

MS: MH^+ =213.1

carbonic acid benzyl ester (S)-3-methyl-2-(2-nitro-ethyl)-butyl ester 44



170.1 mg of nitroalcohol **8** (1.06 mmol, 1.00 eq.) are diluted in 1 mL of dry tetrahydrofuran at room temperature (22°C). 1.24 g of benzyl *N*-succinimidyl carbonate (4.95 mmol, 4.9 eq.) and 1.0237 g of triethylamine (10.10 mmol, 10.0 eq.) are added dropwise at room temperature. The reaction mixture is then warmed to 25°C and allows stirring at 25°C over 2.5 days. The reaction mixture is then cooled down to room temperature and diluted with 10 mL of *tert*-butyl methyl ether yielding to the precipitation of a white solid (side products), which is then filtered off and washed with 10 mL of *tert*-butyl methyl ether. The organic phase is extracted three times with 15 mL of citric acid (until a pH of 7) and with 15 mL of demineralized water. The organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 414.6 mg of crude material.

The crude product is purified by column chromatography on silicagel (20 g) with heptane/ethyl acetate (9:1) to give in the pure fraction 149.5 mg of the desired nitro compound **44** (yield 48%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm)
0.95 (dd, J_1= 8 Hz, J_2= 5Hz, 6H, CH_{3iPr}), 1.57 - 1.73 (m, 1H, C<u>H</u>-CH_{iPr}), 1.73 - 1.91 (m, 1H, CH_{iPr}), 1.93 - 2.06 (m, 1H, <u>H</u>CHCH_2NO_2), 2.11 - 2.34 (m, 1H, HC<u>H</u>CH_2NO_2), 4.07 (dd, J_1= 11 Hz, J_2=7 Hz, 1H, <u>H</u>CH-O), 4.24 (dd, J_1= 11 Hz, J_2=5 Hz , 1H, HC<u>H</u>-O), 4.37 - 4.58 (m, 2H, CH_2NO_2), 5.17 (s, 2H, CH_{2Benz}), 7.29 - 7.51 (m, 5H, CH_{arom})

^{13}C NMR (101 MHz, DMSO-d_6) δ_C (ppm)
18.96 (CH_{3iPr}), 19.05 (CH_{3iPr}), 25.45 (<u>C</u>$H_2CH_2NO_2$), 27.86 (CH_{iPr}), 68.08 (CH_2-O), 68.90 (<u>C</u>H_2-O-C=O), 73.91 (CH_2NO_2), 128.15 (CH_{arom}), 128.35 (CH_{arom}), 128.41 (CH_{arom}), 128.50 (CH_{arom}), 135.51 (C_{arom}), 154.38 (C=O)

IR: (FTIR-microscopy in transmission)
3035-3091 ($CH_{aromatic}$), 2963-2877 ($C-H_{aliph}$), 1746 (Phenyl), 1746 ($C=O_{carbonate}$), 1554 (NO_{2vas}), 1498 (Phenyl), 1386 (NO_{2vs}), 1264 ($C-O_{carbonate}$), 1029 ($C-H_{\delta aromatic}$), 754-741 ($C-H_{\delta aromatic}$), 689 ($Phenyl_{\delta}$)

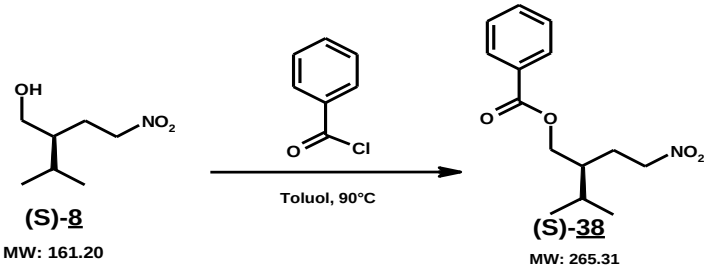
MS: (EI^+) MH^+ = 296.3

HRMS ($C_{15}H_{22}O_5N$, 0.7 ppm/MH+): [M+H] += 296.14902, cal. 296.14925, $C_{15}H_{22}O_5N$

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 7.9 min

Rf (Hexan/Ethyl acetate 9:1) = 0.47

benzoic acid (S)-3-methyl-2-(2-nitro-ethyl)-butyl ester 38



9.2 g of benzoyl chloride (65.5 mmol, 1.05 eq.) are diluted in 35 mL of toluene at room temperature under Ar atmosphere. A solution of 10.01 g of **8** (62.1 mmol, 1.00 eq.) in 3 mL of toluene is added dropwise to the mixture at room temperature. The red solution is then warmed to 92°C and stirred at 92°C over 2 hours turning into a black solution. The formed HCl_{gaz} is quenched in an external trap with a solution of aqueous sodium hydroxide (1M). 0.8 mL of benzoyl chloride (6.9 mmol, 0.11 eq.) are then added to the mixture. The reaction mixture is stirred over night at 92°C (14 hours 30 min.) and then cooled down to room temperature. 45 mL of brine are added to the toluene phase and both phases are separated. The organic phase is again extracted with 20 mL of brine. The organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 13.42 g of crude material (95%).

The crude product is purified by column chromatography on silicagel (200 g) with heptane/ethyl acetate (5:1) to give in the pure fractions 7.92 g of the desired nitro compound **38** (yield 48%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm)
0.89 - 1.01 (m, 6H, CH_{3iPr}),1.60 - 1.69 (m, 1H, CH_{3iPr}), 1.72 - 1.88 (m, J_1= 7Hz, J_2= 5Hz, 1H, C<u>H</u>-CH_{iPr}), 1.92 - 2.07 (m, 1H, <u>H</u>CHCH_2NO_2), 2.19 (m, 1H, HC<u>H</u>CH_2NO_2), 4.07 (dd, J_1= 11 Hz, J_2= 7Hz, 1H, <u>H</u>CH-O), 4.24 (dd, J_1= 11Hz, J_2= 5Hz, 1H, HC<u>H</u>-O), 4.37 - 4.58 (m, 2H, CH_2NO_2), 7.31 - 7.46 (m, 5H, CH_{arom})

^{13}C NMR (101 MHz, $CDCl_3$) δ_C (ppm)
19.11-19.26 (CH_{3iPr}), 25.86 ($CH_2CH_2NO_2$), 28.30 (CH_{iPr}), 64.97 (CH_2-O), 74.00 (CH_2NO_2), 129.06-129.21 (CH_{arom}), 129.63 (C_{arom}), 165.61 (CH_{arom}), 165.61 (C=O)

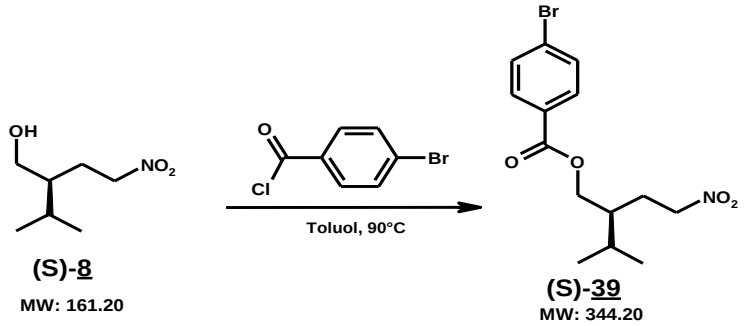
IR: (FTIR-microscopy in transmission)
3065 ($CH_{aromatic}$), 2963-2877 (C-H_{aliph}), 1717 (C=O_{ester}), 1602 (Phenyl), 1553 (NO_{2vas}), 1383 (NO_{2vs}), 1273 (C-O_{ester}),1113 (C-O), 712-688 (C-$H_{\delta aromatic\ monosubst.}$),

MS: (EI$^+$) MH^+ = 266.3, M+NH_4^+ = 283

HRMS ($C_{14}H_{19}O_4N$, 0.7 ppm/MH+): $[M+H]^+$= 266.13848, cal. 266.13869, $C_{14}H_{20}O_4N$

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 7.0 min

4-bromo-benzoic acid (S)-3-methyl-2-(2-nitro-ethyl)-butyl ester 39



5.00 g of **8** (31.0 mmol, 1.00 eq.) are diluted in 20 mL of toluene at room temperature (22°C) and 8.81 g of bromo benzoyl chloride (40.3 mmol, 1.3 eq) are added to the mixture. The yellow suspension is then warmed to 92°C and allows stirring at 92°C over night (22 hours 35 min.), turning into a yellow solution. The formed HCl_{gaz} is quenched in an external trap with a solution of aqueous sodium hydroxide (1M). The reaction mixture is then cooled down to room temperature. 40 mL of brine are added to the toluene phase and both phases are separated ($pH_{aqueous\ phase}$=2). The organic phase is again extracted with 60 mL ($pH_{aqueous\ Phase}$=4), 50 mL ($pH_{aqueous\ phase}$=6) and 40 mL of brine ($pH_{aqueous\ phase}$=7). The organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 10.17 g of crude material (95%).

The crude product is purified by column chromatography on silicagel (300 g) with heptane/ethyl acetate (5:1) to give in the pure fractions 4.65 g of the desired nitro compound **39** (yield 69%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm)
0.93 (m, 6H, CH_{3iPr}), 1.57 - 1.76 (m, 1H, C<u>H</u>-CH_{iPr}), 1.77 - 1.88 (m, 1H, CH_{iPr}), 1.89 - 2.02 (m, 1 H, <u>H</u>CHCH_2NO_2), 2.02 - 2.16 (m, 1H, HC<u>H</u>CH_2NO_2), 4.17 - 4.27 (m, 1H, <u>H</u>CH-O), 4.27 - 4.35 (m, 1H, HC<u>H</u>-O), 4.64 - 4.70 (m, 2H, CH_2NO_2), 7.73 - 7.80 (m, 2H, CH_{arom}), 7.86 - 7.93 (m, 2H, CH_{arom})

^{13}C NMR (101 MHz, $CDCl_3$) δ_C (ppm)
19.14 (CH_{3iPr}), 19.39 (CH_{3iPr}), 25.85 ($CH_2CH_2NO_2$), 28.30 (CH_{iPr}), 40.04 (<u>C</u>HCH_{iPr}), 65.29 (CH_2-O), 74.01 (CH_2NO_2), 127.43 (Br-C_{arom}), 128.88 (C_{arom}), 131.09 (CH_{arom}), 131.95 (CH_{arom}), 165.01 (C=O)

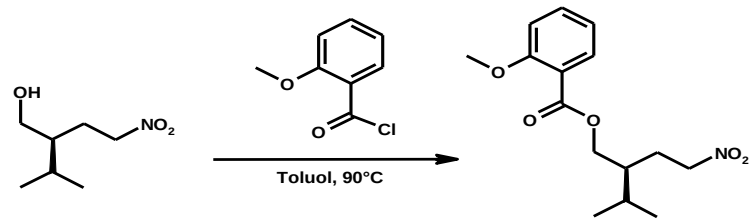
<u>IR</u>: (FTIR-microscopy in transmission)
3094 ($CH_{aromatic}$), 2962-2876 (C-H_{aliph}), 1720 (C=O_{ester}), 1581 (Phenyl), 1553 (NO_{2vas}), 1398-1384 (NO_{2vs}; $(CH_3)_{2d}$), 1272 (C-O_{ester}),1103 (C-O), 1012 (CH_{arom}), 848 (C-$H_{\delta aromatic.}$)

<u>MS</u>: MH^+ = 345

<u>HRMS</u> ($C_{14}H_{18}O_4NBr$, 0.5 ppm/MNH_4+): $[M+NH_4]^+$= 361.07558, cal. 361.07575, $C_{14}H_{22}O_4N_2Br$

<u>HPLC method</u>: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 8.9 min

2-methoxy-benzoic acid (S)-3-methyl-2-(2-nitro-ethyl)-butyl ester 41



(S)-8
MW: 161.20

(S)-41
MW: 295.34

2.51 g of **8** (15.6 mmol, 1.00 eq.) are diluted in 15 mL of toluene at room temperature and 2.68 g of o-methoxy benzoyl chloride (15.7 mmol, 1.3 eq) are added to the mixture. The yellow solution is then warmed to 92°C and stirred at 92°C over 2.5 days turning into a black solution. The formed HCl_{gaz} is quenched with/within a solution of aqueous sodium hydroxide (1M). The reaction mixture is then cooled down to room temperature. 30 mL of demineralized water are added to the toluene phase and both phases are separated ($pH_{aqueous\ phase}$=3). The organic phase is again extracted with 20 mL ($pH_{aqueous\ phase}$=4), and two times with 30 mL of demineralized water ($pH_{aqueous\ phase}$=6). The organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 4.06 g of crude material (88%).

The crude product is purified by column chromatography on silicagel (150 g) with heptane/ethyl acetate (4:1) to give in the pure fractions 2.85 g of the desired nitro compound **41** (yield 62%) as a yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm)
1.01 (dd, J_1= 6 Hz, J_2= 5Hz, 6H, CH_{3iPr}), 1.67 - 1.80 (m, 1H, CH_{iPr}), 1.80 - 1.93 (m, 1H, C<u>H</u>-CH_{iPr}), 2.01 - 2.17 (m, 1H, HC<u>H</u>CH_2NO_2), 2.17 - 2.48 (m, 1H, <u>H</u>CHCH_2NO_2), 3.91 (s, 3H, OCH_3), 4.20 (dd, J_1=11 Hz, J_2= 7 Hz, 1H, <u>H</u>CH-O), 4.42 (dd, J_1=11 Hz, J_2= 4 Hz, 1H, HC<u>H</u>-O) ,4.48 - 4.70 (m, 2H, CH_2NO_2), 6.94 - 7.10 (m, 2H, CH_{arom}), 7.38 - 7.54 (m, 1H, CH_{arom}), 7.79 (dd, J_1=7 Hz, J_2= 2 Hz, 1H, CH_{arom})

^{13}C NMR (101 MHz, $CDCl_3$) δ_C (ppm)
19.15-19.18 (CH_{3iPr}), 25.93 ($CH_2CH_2NO_2$), 28.19 (CH_{iPr}), 56.63 (OCH_3), 64.89 (CH_2-O), 73.97 (CH_2NO_2), 112.50 (CH_{arom}), 120.07 (C_{arom}), 130.72 (CH_{arom}), 133.59 (CH_{arom}), 158.16 (C_{arom}- OCH_3), 165.84 (C=O)

IR: (FTIR-microscopy in transmission)
3079 ($CH_{aromatic}$), 2963 (C-H_{aliph}), 2841 (OCH_3), 1704 (C=O), 1602(Phenyl), 1555 (NO_{2vas}), 1384 (NO_{2vs}), 1031-1253 (Ph-O, C-O), 757 (C-$H_{\delta aromatic}$)

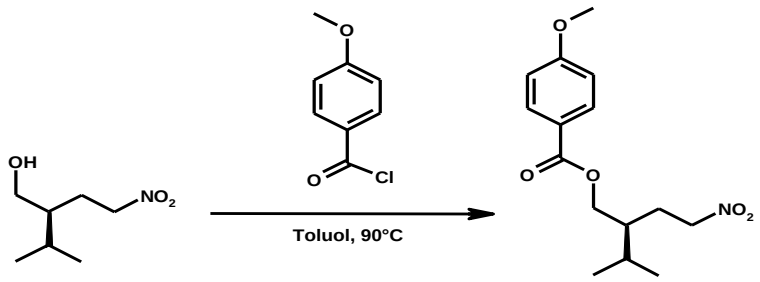
MS: (EI^+) MH^+ = 296, $M+Na^+$ = 318
(EI^-)$M+HCOO^-$ = 340

HRMS ($C_{15}H_{21}O_5N$, 0.2 ppm/MH+): $[M+H]^+$= 296.14942, cal. 296.14925, $C_{15}H_{22}O_5N$

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 7.4 min

Rf (heptan/ethyl acetate 4:1)=0.21

4-methoxy-benzoic acid (S)-3-methyl-2-(2-nitro-ethyl)-butyl ester <u>40</u>



(S)-<u>8</u>
MW: 161.20

(S)-<u>40</u>
MW: 295.34

5.03 g of **<u>8</u>** (31.2 mmol, 1.00 eq.) are diluted in 50 mL of toluene at room temperature and 5.33 g of *p*-methoxy benzoyl chloride (30.2 mmol, 0.9 eq) are added to the mixture. The orange solution is then warmed to 92°C and stirred at 92°C over 24 hours turning into a black solution. The formed HCl_{gaz} is quenched in an external trap with a solution of aqueous sodium hydroxide (1M). The reaction mixture is then cooled down to room temperature. 50 mL of demineralized water are added to the toluene phase and both phases are separated ($pH_{aqueous\ phase}$=4). The organic phase is again extracted twice with 60 mL of demineralized water ($pH_{aqueous\ phase}$=6). The organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 8.11 g of crude material (89%).

The crude product is purified by column chromatography on silicagel (150 g) with heptane/ethyl acetate (4:1) to give in the pure fractions 5.15 g of the desired nitro compound **<u>40</u>** (yield 56%) as a yellow oil.

^{1}<u>H NMR</u> (400 MHz, DMSO) δ_H (ppm)
0.92 (t, *J*=6 Hz, 6H, CH_{3iPr}), 1.67 (ddd, J_1= 8 Hz, J_2=5 Hz, J_3=5 Hz, 1H, CH_{iPr}), 1.82 (td, J_1= 7Hz, J_2= 5 Hz, 1H, C<u>H</u>-CH_{iPr}), 1.90-1.99 (m, 1H, HC<u>H</u>CH_2NO_2), 2.08 (ddd, J_1= 14 Hz, J_2= 7 Hz, J_3= 5 Hz, 1H, <u>H</u>$CHCH_2NO_2$), 3.83 (s, 3H, OCH_3), 4.15-4.21 (m, 1H, <u>H</u>CH-O), 4.25-4.29 (m, 1H, HC<u>H</u>-O), 4.63-4.70 (m, 2H, CH_2NO_2), 7.04-7.06 (m, 2H, CH_{arom}), 7. 89-7.93 (m, 2H, CH_{arom})

^{13}<u>C NMR</u> (150 MHz, $CDCl_3$) δ_C (ppm)
19.10-19.26 (CH_{3iPr}), 25.91 ($CH_2CH_2NO_2$), 28.32 (CH_{iPr}), 55.48 (OCH_3), 64.82 (CH_2-O), 74.02 (CH_2NO_2), 114.03 (CH_{arom}), 121.84 (C_{arom}), 131.17 (CH_{arom}), 163.14 (C_{arom}- OCH_3), 165.28 (C=O)

<u>IR</u>: (FTIR-microscopy in transmission)
3080 ($CH_{aromatic}$), 2963 (C-H_{aliph}), 2842 (OCH_3), 1712 (C=O), 1607 (Phenyl), 1554 (NO_{2vas}), 1029 (Phenyl), 1383 (NO_{2vs}), 1275-1285, 1029 (Ph-O, C-O), 849 (C-$H_{\delta aromatic}$),

<u>MS</u>: MH^+ = 296.3

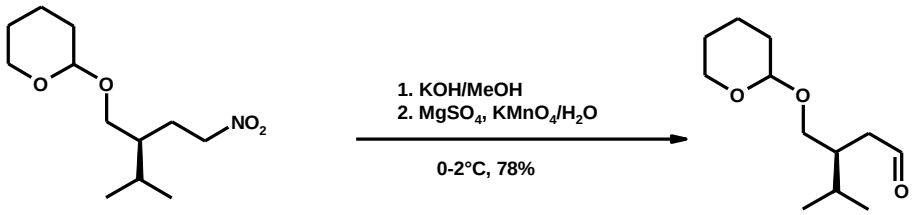
<u>HRMS</u> ($C_{15}H_{21}O_5N$, 0.7 ppm/MH+): $[M+H]^+$= 296.14948, cal. 296.14925, $C_{15}H_{22}O_5N$

<u>HPLC method</u>: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 7.4 min

Rf (heptan/ethyl acetate 4:1)=0.22

I.3.2. (S)-aldehyde derivatives

(S)-4-methyl-3-(tetrahydro-pyran-2-yloxymethyl)-pentanal 45



(S)-32
MW: 245.32

(S)-45
MW: 214.31

To a mechanically stirred solution of 4.85 g of **32** (19.9 mmol, 1 eq.) in methanol (140 mL) is added dropwise, at 0 °C under an atmosphere of argon, over a period of 2h a freshly prepared methanolic (200 mL) solution of KOH (pallets) (1.35 g, 24.9 mmol, 1.2 eq.). After stirring for an additional 23 min, 178 mg $MgSO_4$, (1.5 mmol, 0.07 eq.) are added. A freshly prepared solution of $KMnO_4$ (2.15 g, 13.6 mmol, 0.7 eq.) and water (300 mL) is added dropwise, with vigorous stirring, over 2h (at a rate that maintained the reaction temperature at 0-2°C). Upon complete addition, the reaction mixture is stirred for an additional 2h at 0°C and then filtered over a layer of celite. The collected material is washed with toluene (3 x 50 mL), triturated with an additional 200 mL of toluene, and refiltered over a new layer of celite. The filtrates and washings are combined and washed with 200 mL brine. The aqueous layer is extracted four times with 200 mL of toluene. The organic phases are combined, dried over $MgSO_4$, and concentrated in vacuum (bath temperature not permitted to exceed 35 °C). The yellow liquid is then dried again in vacuum to yield 3.36 g (78%) of **45**.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ_H (ppm)
0.94 (m, 6H, CH_{3iPr}), 1.48-1.82 (m, 9H, 3*$CH_{2THP,}$ CH_{iPr}), 2.18-2.24 (m, 1H, C<u>H</u>CH_{iPr}), 2.31-2.43 (m, 2H, CH_2C=O), [3.84-3.89 (m), 3.73-3.84 (m), 3.61-3.65 (m), 3.49-3.54 (t), 3.42 (dd, *J*=9Hz), 3.18 (dd, *J*=9Hz)] (CH_2-0, CH_2-O_{THP}), 4.59 (t, J=3Hz, 0.5H, CH-O_{THP}), 4.52 (t, 0.5H, CH-O_{THP}), 9.74-9.77 (dd, J *3*Hz, 1H, HC=O)

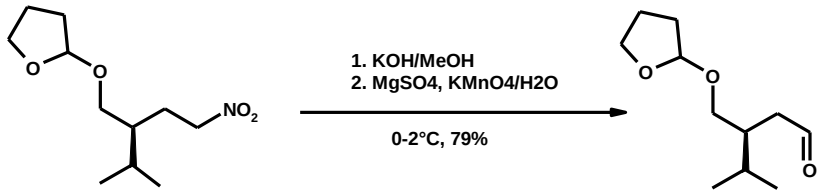
^{13}C-NMR (101 MHz, DMSO-d^6) δ_C (ppm)
19.15-19.23 (CH_{3iPr}) , 24.91 (CH_{2THP}), 27.34 (CH_{2THP}), 28.85 (CH_{iPr}), 30.09 (CH_{2THP}), 41.07 (<u>C</u>H-CH_{iPr}), 61.43-61.74 (CH_{2THP}-O), 68.32-68.44 (CH_2-O), 98.15 (CH_{THP}), 203.07 (C=O)

IR: (FTIR-microscopy in transmission)
2956 (C-H), 1726 (C=O aldehyde), 1122 (C-O-C), 1033 (C-O)

MS: $[M+H]^+$ = 215
HR-MS: no response by EI/CI-MS

GC: column Optima-1MN, 25mx0.32mmx0.35µm, Hydrogen flow: 30.0 mL/min, Air flow: 400.0 mL/min, Helium flow: 20.0 mL/min, 75 to 200°C in 10 min, 3min at 200°C, 200 to 300°C in 10 min, 2min50 at 300°C, t_R = 13.41 min

(S)-4-methyl-3-(tetrahydro-furan-2-yloxymethyl)-pentanal 46



(S)-33
MW: 231.29

(S)-46
MW: 200.28

To a mechanically stirred solution of 2.32 g of **33** (10.0 mmol, 1 eq.) in methanol (70 mL) is added dropwise, at 0 °C under an atmosphere of argon, a freshly prepared methanolic (100 mL) solution of KOH (pallets) (0.75 g, 13.4 mmol, 1.3 eq.) over a period of 1h. After stirring for an additional 15 min, 89.5 mg $MgSO_4$, (7.3 mmol, 0.07 eq.) are added. Then a freshly prepared solution of $KMnO_4$ (1.24 g, 7.8 mmol, 0.7 eq.) in water (150 mL) is added dropwise, with vigorous stirring, over 1 hour 40 min (at a rate that maintained the reaction temperature at 0-2°C). Upon complete addition, the reaction mixture is stirred over 2 hours 35 min at 0°C and then filtered over a layer of celite. The collected material is washed with toluene (3 X 25 mL), triturated with an additional 100 mL of toluene, and refiltered over a new layer of celite. The filtrates and washings are combined and washed with 100 mL of brine. The aqueous layer is extracted four times with 100 mL of toluene. The organic phases are combined, dried over $MgSO_4$, and concentrated in vacuum (bath temperature not permitted to exceed 35 °C). The yellow liquid was then dried in vacuum to yield 1.58 g (78%) of **46**.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ_H (ppm)
0.92 (m, 1H), 1.76-1.95 (m, 5H, $CH_{2THF,}$ CH_{iPr}), 2.12-2.20 (m, 1H, C<u>H</u>CH_{iPr}), 2.33-2.37 (m, 2H, CH_2C=O), 3.42 (dd, *J*=9 Hz), 3.18-3.22 (m)](CH_2O, CH_2O_{THF}), 3.55 (t, *J*= 9Hz), 5.02-5.06 (m, 1H, CH_{THF}), [3.81-3.88 (m), 3.76 (dd, *J*=9Hz), 9.71 (dt, J 4Hz, 1H, HC=O)

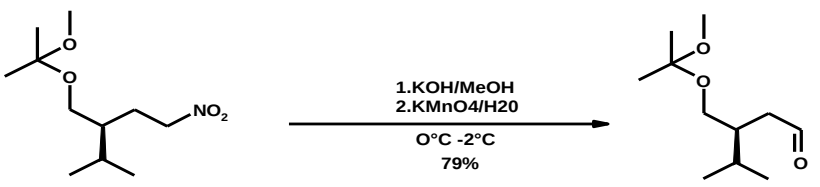
^{13}C-NMR (150 MHz, $CDCl_3$) δ_C (ppm)
18.31-19.22 (CH_{3iPr}), 24.68 (CH_{2THF}), 28.45 (CH_{iPr}), 30.09 (CH_{2THF}), 42.61 (<u>C</u>H_2-HC=O, C<u>H</u>CH_{iPr}), 61.29 (CH_{2THP}-O), 68.63 (CH_2-O), 98.00 (CH_{THF}), 202.53 (C=O)

IR: (FTIR-microscopy in transmission)
2960 (C-H), 2723 (CH aldehyde), 1725 (C=O aldehyde), 1102 (C-O-C), 1039 (C-O)

MS: $[M+H]^+$ = 201

HR-MS: no response by EI/CI-MS

(S)-3-(1-methoxy-1-methyl-ethoxymethyl)-4-methyl-pentanal 47



(S)-36
MW: 233.31

(S)-47
MW: 202.30

To a mechanically stirred solution of 4.93 g of **36** (21.1 mmol, 1.00 eq.) in methanol (180 mL) is added dropwise at 0 °C under an atmosphere of argon over a period of 1h a freshly prepared methanolic (215 mL) solution of KOH (pallets) (1.44 g, 24.3 mmol, 1.15 eq.). After stirring for an additional 20 min, 194.0 mg $MgSO_4$, (1.6 mmol, 0.07 eq) are added. Then a freshly prepared solution of $KMnO_4$ (2.33 g, 14.7 mmol, 0.7 eq.) and water (320 mL) is added dropwise, with vigorous stirring, over 1 hour 20 min (at a rate that maintained the reaction temperature at 0-2°C). Upon complete addition, the reaction mixture is stirred for an additional 40 min at 0°C and then filtered over a layer of celite. The collected material is washed four times with 100 mL of toluene. The filtrates and washings are combined, and washed with 200 mL of brine (200 mL). The aqueous layer is extracted three times with 200 mL of toluene. The organic phases are combined, dried over $MgSO_4$, and concentrated in vacuum (bath temperature not permitted to exceed 35 °C) to yield 3.32 g (79%) of **47**.

^{1}H-NMR: (400 MHz, $CDCl_3$) δ_H (ppm)
0.85 (dd, J_1=13Hz, J_2=7Hz, 6H, CH_{3iPr}), 1.21 (d, J=3Hz, 6H, CH_3), 1.66 - 1.80 (m, 1H, CH_{iPr}), 1.99 - 2.09 (m, 1H, C<u>H</u>CH_{iPr}), 2.16 - 2.27 (m, 1H, <u>H</u>CHC=O), 2.34 - 2.42 (m, 1H, HC<u>H</u>C=O), 3.05 (s, 3H, O CH_3), 3.12 - 3.19 (m, 1H, <u>H</u>CHC-O), 3.29 - 3.34 (m, 1H, HC<u>H</u>C-O), 9.63 (s, 1H, HC=O)

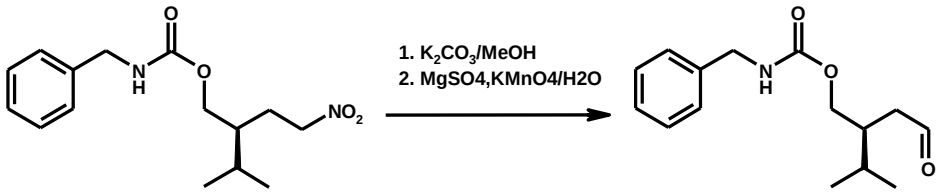
^{13}C NMR (101 MHz, DMSO-d_6) δ_C (ppm)
18.94 (CH_{3iPr}), 19.91 (CH_{3iPr}), 24.06 (CH_{3MIP}), 24.13 (CH_{3MIP}), 28.14 (CH_{iPr}), 43.33 (<u>C</u>H_2C=O), 47.89 (OCH_{3MIP}), 61.55 (CH_2-O), 99.45 (C_{MIP}), 203.03 (C=O)

IR: (FTIR-microscopy in transmission)
2960 (C-$H_{aliph.}$), 2877 (CH_{3vs}), 2829 (O-CH_3), 2723 (aldehyde), 1726 (C=$O_{aldehyde}$), 1467 (CH_δ), 1370 ($(CH_3)_{2\delta}$), 1214-1048(C-O)

MS: LC/MS (ESI) no response
GC/MS (EI) no response
HR-MS: no response by EI/CI-MS

GC: column Optima-1MN, 25mx0.32mmx0.35µm, Hydrogen flow: 30.0 mL/min, Air flow: 400.0 mL/min, Helium flow: 20.0 mL/min, 75 to 200°C in 10 min, 3min at 200°C, 200 to 300°C in 10 min, 2min50 at 300°C, t_R = 10.4 min

benzyl-carbamic acid (S)-3-methyl-2-(2-oxo-ethyl)-butyl ester 52



66.0 mg of nitro compound **43** (0.22 mmol, 1.0 eq.) are diluted in 1 mL of methanol at room temperature under Ar. The light yellow solution is cooled down to 0°C and 172.1 mg of K_2CO_3 (1.2 mmol, 5.7 eq.) are added, followed by 5.1 mg of $MgSO_4$ (0.04 mmol, 0.2 eq.). A solution of 26.6 mg of

$KMnO_4$ (0.17 mmol, 0.7 eq.) in 5 mL of demineralized water is then added dropwise over 4 min resulting in the precipitation of MnO_2. The reaction mixture is allowed to stir at 0°C over a period of 24 min.
5 mL of toluene are added to the reaction mixture over stirring and the resulting suspension is filtered over a layer of celite. The collected material is washed twice with 10 mL of toluene. The filtrates and washings are combined and extracted twice with 15 mL of brine. The organic layer is dried over $MgSO_4$ and concentrated in vacuum to yield 32.0 mg of colourless oil (55%) **52**.

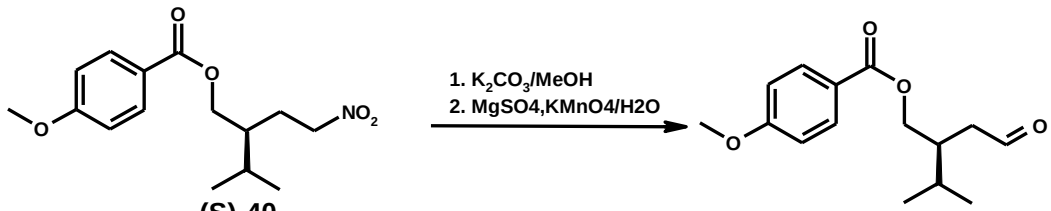
^{1}H NMR (400 MHz, DMSO-d_6) δ_H ppm
0.81 - 0.91 (m, 6H, CH_{3iPr}), 1.67 - 1.83 (m, 1H, CH_{iPr}), 2.07 - 2.20 (m, , 1 H, C<u>H</u>CH_{iPr}), 2.25 - 2.46 (m, 2H, C<u>H$_2$</u>CHO), 3.76 - 3.91 (m, 1H, <u>H</u>CH-O), 3.94 - 4.04 (m, 1H, HC<u>H</u>-O), 4.16 (d, *J*=6 Hz, CH_{2Benz}), 7.19 - 7.40 (m, 5H, CH_{arom}), 9.62 - 9.84 (m, 1H, HC=O)

<u>IR</u>: (FTIR-microscopy in transmission)
3339 (NH), 3032 ($CH_{aromatic}$), 2961 (C-H_{aliph}), 2727 (Aldehyde), 1717 ($C=O_{aldehyde,\ carbamate}$), 1585-1455 (Phenyl), 1526 (Amide sec.), 1246-1137-1042 (C-O), 739-699 (C-$H_{\delta aromatic\ monosubst}$)

<u>MS</u>: MH^+ = 264, $M+Na^+$ = 286

<u>HPLC method</u>: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 7.1 min

4-methoxy-benzoic acid (S)-3-methyl-2-(2-oxo-ethyl)-butyl ester <u>51</u>



(S)-<u>40</u>
MW: 295.33

(S)-<u>51</u>
MW: 264.32

294.8 mg of **<u>40</u>** (0.99 mmol, 1.0 eq.) are diluted in 10 mL of methanol under Ar atmosphere at room temperature (22°C). The yellow solution is cooled down to 0°C and 809.6 mg of K_2CO_3 (5.85 mmol, 5.9 eq.) are added. 23.8 mg of $MgSO_4$ (0.19 mmol, 0.2 eq.) are added to the suspension. A freshly prepared solution of 116.7 mg of $KMnO_4$ (0.74 mmol, 0.7 eq.) in 22 mL of demineralized water is then added dropwise over a period of 11 min resulting in the precipitation of MnO_2. The reaction mixture is allowed to stir at 0°C over a period of 14 min.
40 mL of toluene are added to the reaction mixture over stirring and the resulting suspension is filtered over a layer of celite to remove MnO_2. The collected material is washed with 60 mL of toluene. The filtrates and washings are combined and extracted four times with 50 mL of brine (pH of the aqueous layer decreases from 10 to 7). The organic layer is dried over $MgSO_4$ and concentrated in vacuum to yield 213.0 mg of colourless liquid **<u>51</u>** (80%).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm)
0.91 (t, J_1=7 Hz, 6H, CH_{3iPr}), 1.81 (td, J_1=7 Hz, J_2=5 Hz, 1H, CH_{iPr}), 2.23 - 2.62 (m, 1H, C<u>H</u>CH_{iPr}), 3.14 - 3.38 (m, 2H, C<u>H$_2$</u>CO), 3.83 (m, 3H, OCH_3), 4.12 (dd, J_1=11 Hz, J_2=7 Hz, 1H, <u>H</u>CH-O), 4.27 (dd, J_1=11 Hz, J_2=5 Hz, 1H, HC<u>H</u>-O), 6.62 - 7.26 (m, 2H, CH_{arom}), 7.65 - 8.00 (m, 2H, CH_{arom}), 9.72 (s, 1H, <u>H</u>C=O)

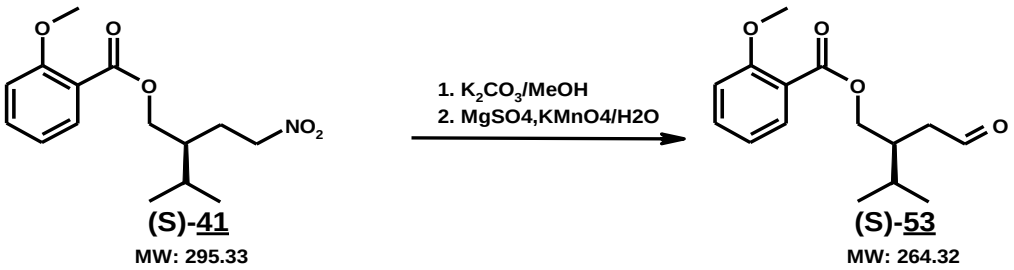
^{13}C NMR (101 MHz, DMSO-d_6) δ_C (ppm)
19.10 (CH_{3iPr}), 19.64 (CH_{3iPr}), 28.38 (CH_{iPr}), 37.59 ($\underline{C}HCH_{iPr}$), 42.86 ($\underline{C}H_2CO$), 55.50 (OCH_3), 65.53 (CH_2O), 114.04 (CH_{arom}), 121.80 (CH_{arom}), 131.21 (CH_{arom}) 163.16 (O-C_{arom}), 165.27 (C=O), 203.01 (HC=O)

IR: (FTIR-microscopy in transmission)
3081 ($CH_{aromatic}$), 2962 (C-H_{aliph}), 2841 (OCH_3), 1713 (C=O), 1607-1512 (Phenyl), 1275 (C_{arom}-O, C-O), 1257 (C-O), 849 (C-$H_{\delta aromatic}$)

MS: MH^+ = 265, $M+Na^+$ = 287

HRMS ($C_{15}H_{20}O_4$, 0.2 ppm/MH+): $[M+H]^+$= 265.14336, cal. 265.14344, $C_{15}H_{21}O_4$

2-Methoxy-benzoic acid (S)-3-methyl-2-(2-oxo-ethyl)-butyl ester 53



(S)-41 **MW: 295.33** **(S)-53** **MW: 264.32**

295.3 mg of **41** (1.00 mmol, 1.0 eq.) are diluted in 10 mL of methanol under Ar atmosphere at room temperature (22°C). The yellow solution is cooled down to 0°C and 803.5 mg of K_2CO_3 (5.81 mmol, 5.8 eq.) and 23.6 mg of $MgSO_4$ (0.19 mmol, 0.2 eq.) are added to the suspension. A fresh prepared solution of 123.4 mg of $KMnO_4$ (0.78 mmol, 0.8 eq.) in 22 mL of demineralized water is then added dropwise over a period of 17 min, resulting in the precipitation of MnO_2. The reaction mixture is allowed to stir at 0°C over a period of 3 min.
30 mL of toluene are added to the reaction mixture over stirring and the resulting suspension is filtered over a layer of celite to remove MnO_2. The collected material is washed with 50 mL of toluene. The filtrates and washings are combined and extracted three times with 50 mL of brine (pH of the aqueous layer decreases to 6-7) and once with 20 mL of demineralized water. The organic layer is dried over $MgSO_4$ and concentrated in vacuum to yield 217 mg of **53** as a colourless liquid (82%).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm)
0.85 - 0.98 (m, 6H, CH_{3iPr}), 1.80 (td, J_1=7 Hz, J_2=5 Hz, 1H, CH_{iPr}), 2.25 (td, J_1=7 Hz, J_2=5 Hz, 1 H, $C\underline{H}CH_{iPr}$), 2.39 - 2.61 (m, 2H, $C\underline{H}_2CO$), 3.80 (s, 3H, OCH_3), 4.10 (dd, J_1=11 Hz, J_2=7 Hz, 1H, $\underline{H}CH$-O), 4.23 (dd, J_1=11 Hz, J_2=5 Hz, 1H, $HC\underline{H}$-O), 7.00 (td, J_1=7 Hz, J_2=1Hz, 1H, CH_{arom}), 7.13 (d, J=8 Hz, 1H, CH_{arom}), 7.53 (ddd, J_1= 9Hz, J_2=7 Hz, J_3=2 Hz, 1H, CH_{arom}), 7.61 (dd, J_1=7 Hz, J_2=2 Hz, 1H, CH_{arom}), 9.70 (s, 1H, HC=O)

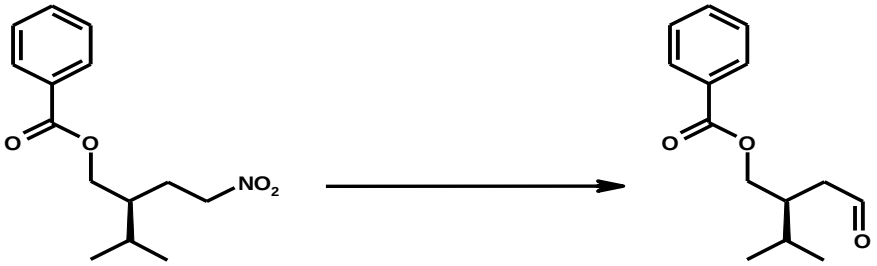
^{13}C NMR (101 MHz, DMSO-d_6) δ_C (ppm)
18.74 (CH_{3iPr}), 19.24 (CH_{3iPr}), 28.50 (CH_{iPr}), 38.12 ($\underline{C}HCH_{iPr}$), 41.50 ($\underline{C}H_2CO$), 53.08 (OCH_3) 64.40 (CH_2O), 112.54 (CH_{arom}), 119.61 (C_{arom}), 130.68 (CH_{arom}), 133.61 (CH_{arom}) 158.23 (O-C_{arom}), 165.69 (C=O), 203.08 (HC=O)

IR: (FTIR-microscopy in transmission)
3079 ($CH_{aromatic}$), 2962 (C-H_{aliph}), 2840 (OCH_3), 1725 (C=O), 1601-1466 (Phenyl), 1253 (C_{arom}-O, C-O), 1080 (C-O), 757 (C-$H_{\delta aromatic}$)

MS: $[M+H]^+$ = 265, $M+Na^+$ = 287

HRMS ($C_{15}H_{20}O_4$, 0.7 ppm/MH+): $[M+H]^+$= 265.14324, cal. 265.14344, $C_{15}H_{21}O_4$

benzoic acid (S)-3-methyl-2-(2-oxo-ethyl)-butyl ester 49



500.2 mg of **38** (1.88 mmol, 1.0 eq.) are diluted in 14 mL of methanol under Ar atmosphere at room temperature (22°C). The yellow solution is cooled down to 0°C and 1.5072 g of K_2CO_3 (5.7 mmol, 5.7 eq.) and 31.7 mg of $MgSO_4$ (0.26 mmol, 0.14 eq.) are added to the suspension. A freshly prepared solution of 252.3 mg of $KMnO_4$ (1.6 mmol, 0.8 eq.) in 35 mL of demineralized water is then added dropwise over a period of 19 min resulting in the precipitation of MnO_2. The reaction mixture is allowed to stir at 0°C over a period of 5 min.
The reaction mixture is filtered over a layer of celite and the collected material is washed with 50 mL of toluene. The filtrates and washings are combined and extracted once with 10 mL and three times with 20 mL of brine. The organic layer is dried over $MgSO_4$ and concentrated on vacuum to yield 370 mg of a liquid **49** (84%).

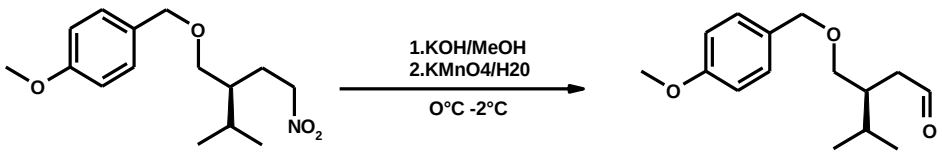
^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm)
0.87 - 0.98 (m, 6H, CH_{3iPr}), 1.79-1.87 (m, 1H, C<u>H</u>-CH_{iPr}), 2.31-2.36 (m, 1H, C<u>H</u>CH_{iPr}), 2.40 - 2.66 (m, 2H, C<u>H</u>$_2$CO), 4.17 (dd, J_1=11 Hz, J_2=7Hz, 1H, <u>H</u>CH-O), 4.32 (dd, J_1=11 Hz, J_2=5Hz, 1H, HC<u>H</u>-O), 7.53 (t, J=7Hz, 2H, CH_{arom}), 7.60 - 7.75 (m, 1H, CH_{arom}), 7.87 - 8.04 (m, 2H, CH_{arom} H), 9.65 - 9.87 (m, <u>H</u>C=O)

^{13}C NMR (150 MHz, DMSO-d_6) δ_C (ppm)
18.83 (CH_{3iPr}), 19.30 (CH_{3iPr}), 28.39 (CH_{iPr}), 37.85 (<u>C</u>HCH_{iPr}), 43.31 (<u>C</u>H_2CO), 65.69 (CH_2O), 127.97 (CH_{arom}), 129.17 (C_{arom}), 132.78 (CH_{arom}) 158.23 (O-C_{arom}), 166.04 (C_{arom}-C=O), 241.03 (HC=O)

IR: (FTIR-microscopy in transmission)
3065-3035 ($CH_{aromatic}$), 2962-2877 (C-H_{aliph}), 2725 (Aldehyde), 1721 (C=O), 1584 (Phenyl), 1390-1312 ($CH_{\delta tertiary}$), 1274 (C-O), 1080 (C-O), 712 (C-$H_{\delta aromatic,\ monosubs.}$)

MS: (EI^+) $[M+Na]^+$ = 257, $M+NH_4^+$ = 283

(S)-3-(4-Methoxy-benzyloxymethyl)-4-methyl-pentanal 34



(S)-34-a
MW: 281.35

(S)-34
MW: 250.34

1.497 g of nitro compound **34-a** (5.3 mmol, 1.0 eq.) is diluted in 45 mL of methanol under Ar atmosphere at room temperature (22°C). The yellow solution is cooled down to 0°C and a solution of 368.2 mg of KOH (6.5 mmol, 1.2 eq.) in 50 mL of methanol are added drop wise over a period of 10 min. 52.6 mg of $MgSO_4$ (0.43 mmol, 0.08 eq.) are added to the reaction mixture. A fresh prepared solution of 592.4 mg of $KMnO_4$ (3.7 mmol, 0.8 eq.) in 80 mL of demineralized water is then added dropwise over a period of 25 min yielding to the precipitation of MnO_2. The reaction mixture is allowed to stir at 0°C over a period of 10 min.
The reaction mixture is diluting over stirring with 10 mL of toluene and is filtered over a layer of celite. The collected material is washed four times with 100 mL of toluene. The filtrates and washings are combined and extracted two times with 200 mL of brine whereas the resulting aqueous phases are extracted three times with 200 mL of toluene. The combined organic layers are dried over $MgSO_4$ and concentrated on vacuum to yield 1.01 g of a colourless liquid **34** (76%).

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ_H (ppm)
0.89 (dd, J_1= 10 Hz, J_2= 7 Hz, 6H, CH_{3iPr}), 1.74-1.82 (m, 1H, CH_{iPr}), 2.13 - 2.26 (m, 1 H, C<u>H</u>CH_{iPr}), 2.39 (dd, J_1= 6 Hz, J_2= 2 Hz, 2H, C<u>H</u>$_2$CO), 3.30 (t, *J*=9 Hz, 1H, <u>H</u>CH-O), 3.51 (dd, J_1= 9 Hz, J_2= 5 Hz, 1H, HC<u>H</u>-O), 3.81 (s, 3H, OCH_3), 4.39 (s, 2H, CH_{2Benz}), 6.78 - 6.98 (m, 2H, CH_{arom}), 7.21-7.24 (m, 2H, CH_{arom}), 9.63 - 9.91 (s, 1H, HC=O)

^{13}C NMR (101 MHz, DMSO-d_6) δ_C (ppm)
18.73 (CH_{3iPr}), 19.79 (CH_{3iPr}), 28.71 (CH_{iPr}), 38.96 (<u>C</u>HCH_{iPr}), 43.51 (<u>C</u>H_2CO), 54.95 (OCH_3) 70.98 (CH_2O), 71.91 (CH_{2Benz}), 112.45 (CH_{arom}), 128.49 (CH_{arom}), 130.41 (C_{arom}), 158.64 (O-C_{arom}), 203.06 (HC=O)

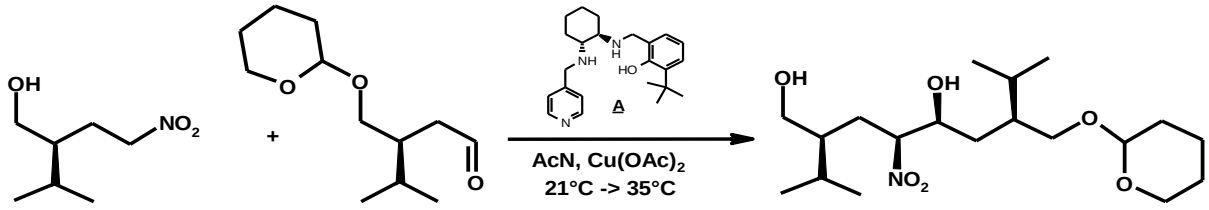
IR: (FTIR-microscopy in transmission)
2959 (C-H_{aliph}), 2838(OCH_3), 2725 (Aldehyde), 1723 (C=O), 1613-1514 (Phenyl), 1368 ($(CH_3)_{2\delta}$), 1087-1036 (C-O), 821 (C-$H_{\delta aromatic\ para\ subst.}$)

MS: $M+NH_4^+$ = 268

I.3.3. Henry products

(2S,4S,5S,7S)-2-isopropyl-8-methyl-4-nitro-7-(tetrahydropyran-2-yloxymethyl)-nonane-1,5-diol 54

Methode 1



(S)-8 MW: 161.20 | **(S)-45** MW: 214.31 | **(S,S,S,S)-54** MW: 375.52 + other Stereoisomers

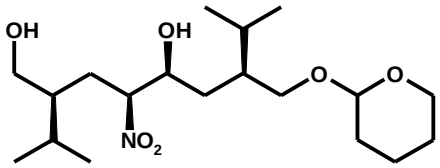
34.3 mg of the ligand **A** (0.09 mmol, 0.02 eq.) are dissolved at 21°C in 1.4 mL of acetonitrile and 19.2 mg of copper (II) acetate monohydrate (0.09 mmol, 0.02 eq.) are added to the solution. After 30 min, 938.1 mg of nitro compound **8** (6.09 mmol, 1.3 eq.) and 1.01 g of aldehyde **45** (4.7 mmol, 1.0 eq.) are added at 22°C to the green reaction mixture. The reaction mixture is heated to 35°C and is stirred over 5.5 days.

The reaction mixture is cooled down to room temperature and diluted in 100 mL of a mixture of hexan/demineralized water/methanol (70:20:10 v/v/v), yielding to the precipitation of a green solid. The layers are separated and the aqueous phase is extracted again once with 75 mL and two times with 25 mL of dichloromethane. Both organic phases are dried over $MgSO_4$ and concentrated on vacuum to yield 670.0 mg of a green oil (containing the nitro diol in mixture with the starting nitro compound **54** and aldehyde **45**) and 640.0 mg of a green oil (containing the nitro diol **54** in mixture with **8**).

The diastereoisomeric ratio measured on CHIRALPAK AD-H (mixture of hexan/isopropanol/methanol/ethanol 973:9:9:9, 1 mL/min, at 40°C) shows the presence of four diastereoisomers with a ratio of 4:10:11:**75**.

The crude material (640 mg) is purified by column chromatography on silicagel (40 g) with heptane/ethyl acetate (4:1) to give in the pure fractions 456.0 mg of the desired nitro compound **54** (yield 26%) as a yellow oil containing two diastereoisomers the (S,S,S,S,S) and (R,S,S,S,S) isomers and 185.3 mg of a yellow oil (10%) as a mixture of diastereoisomers with a ratio of 24:20:2:38.

Spectroscopic data of (S,S,S,S)-54



(S,S,S,S)-54
MW: 375.51

^{1}H NMR (600 MHz, dmso-d^6) δ_H (ppm) (mixture of 2 diastereoisomers)
0.75-0.91 (m, 12H, CH_{3iPr}), 1.13-1.86 (m, 14H, C<u>H</u>CH_{iPr}, CH_{iPr}, CH_{2THP}, CH_2O, CH_2), 3.13-3.48 (m, 6H, CH_2-O-THP, CH_2-O, CH_2-O_{THP}), 4.47-4.66 (m, 3H, CH-NO_2, OH, CH_{THP}), 5.23-5.36 (m, 1H, OH)

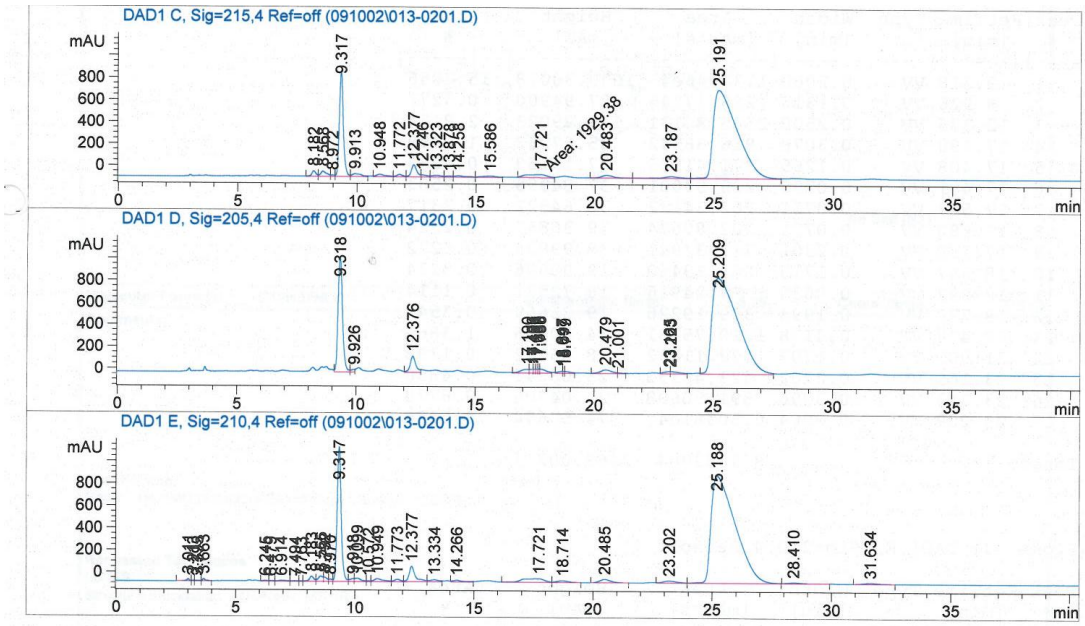
^{13}C NMR (151 MHz, DMSO-d_6) δ_C (ppm) (mixture of 2 diastereoisomers)
18.42 (CH_{3iPr}), 19.07 (CH_{3iPr}), 19.30-20.05 (CH_{2THP}), 20.22 (CH_{3iPr}), 20.31 (CH_{3iPr}), 25.18 (br. s., 1 C), 25.24 (CH_{2THP}), 27.89, 28.73, 28.96, 29.24, 30.37, 31.30, 31.49 (CH_2-$CHNO_2$, CH_{iPr}), 32.48 (CH_2-CHOH), 39.92 ($CHCH_{iPr}$), 42.79 ($CHCH_{iPr}$), 61.06 (CH_2-O_{THP}), 67.57 (CH_2-OH), 68.00 (CH_2-O-THP), 70.60-71.03 (CH-OH), 93.27 (CH-NO_2), 97.83-98.22 (CH-O_{THP})

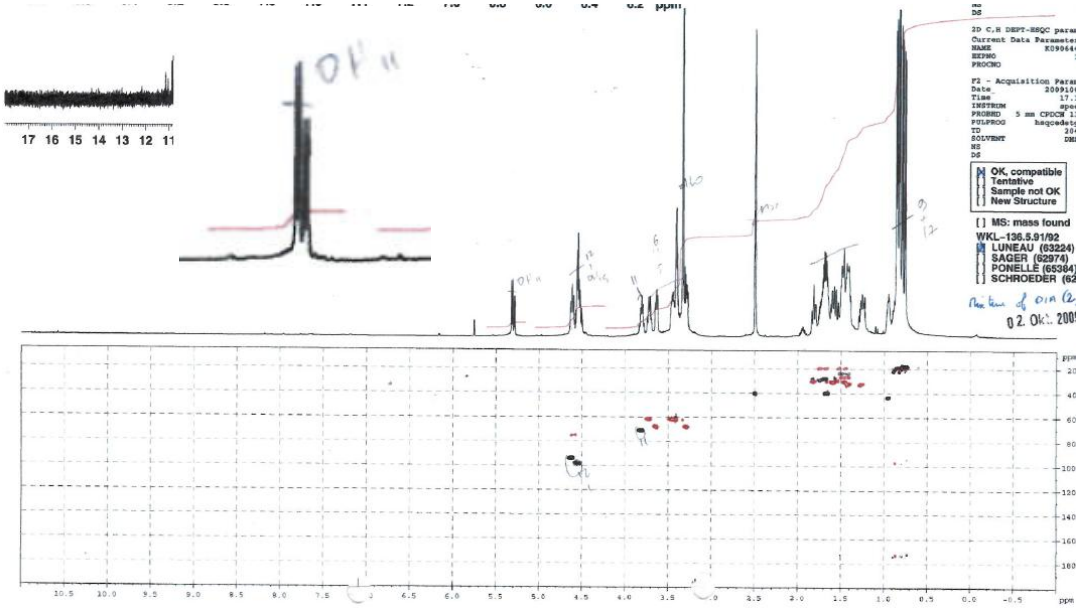
IR: (FTIR-microscopy in transmission)
3406 (OH), 2957-2875 (C-H_{aliph}), 1553 (NO_{2vas}), 1467-1385 (CH_δ), 1370 (NO_{2vs}), 1119-1062 (C-O), 1024 (C-OH)

MS: MH+ = 376, $M+NH_4^+$ = 393

HRMS ($C_{19}H_{38}O_6N$, 0.3 ppm/MH+): $[M+H]^+$= 376.26926, cal. 376.26937, $C_{19}H_{38}O_6N$

Chirale HPLC (CHIRALPAK AD-H with a mixture of hexan/isopropanol/methanol/ethanol 973:9:9:9, 1 mL/min, at 40°C) and ^{1}H NMR (600 MHz, dmso-d^6) of (S,S,S,S)-**54**:





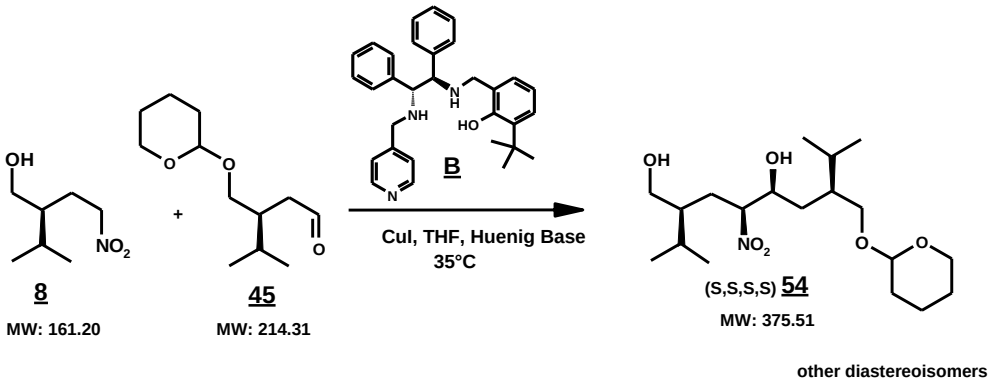
Spectroscopic data of 54, as a mixture of diastereoisomers

^{1}H NMR (600 MHz, dmso-d^6) δ_H (ppm) (mixture of 6 diastereoisomers)
0.71-0.90 (m, 12H, CH_{3iPr}), 1.23-1.92 (m, 14H, C<u>H</u>CH_{iPr}, CH_{iPr}, CH_{2THP}, CH_2O, CH_2), [3.23-3.46 (m, 4H), 3.62-3.71 (m, 1H), 3.71-3.74 (m, 1H) CH_2-O-THP, CH_2-O, CH_2-O_{THP}], 3.76-3.82 (m, 1H, CH-OH), 4.50-4.66 (m, 3H, CH-NO_2, OH, CH_{THP}), 5.26-5.29 (d, J=9 Hz, 1H, OH), 5.29-5.31 (d, J=9 Hz, 1H, OH)

IR: (FTIR-microscopy in transmission)
3406 (OH), 2968-2875 (C-H_{aliph}), 1550 (NO_{2vas}), 1467-1386 (CH_δ), 1370 (NO_{2vs}), 1120-1075-1062 (C-O), 1025 (C-OH)

MS: MH+ = 376, M+NH_4^+ = 393 (mixture of stereoisomers)

Methode 2



840.1 mg of the ligand **B** (2.8 mmol, 0.06 eq.) are dissolved at 21°C in 3.0 mL of THF and 866.7 mg of copper (I) iodide in 15 mL THF (4.5 mmol, 0.10 eq) are added. After 20 min, 400 µL of diisopropyl ethyl amine (2.3 mmol, 0.5 eq) are added and the mixture is allowed to stir at 30°C for 27 min. A solution of 9.92 g of aldehyde **45** (46.3 mmol, 1.00 eq) in 8 mL of THF and 12.63 g of nitro compound

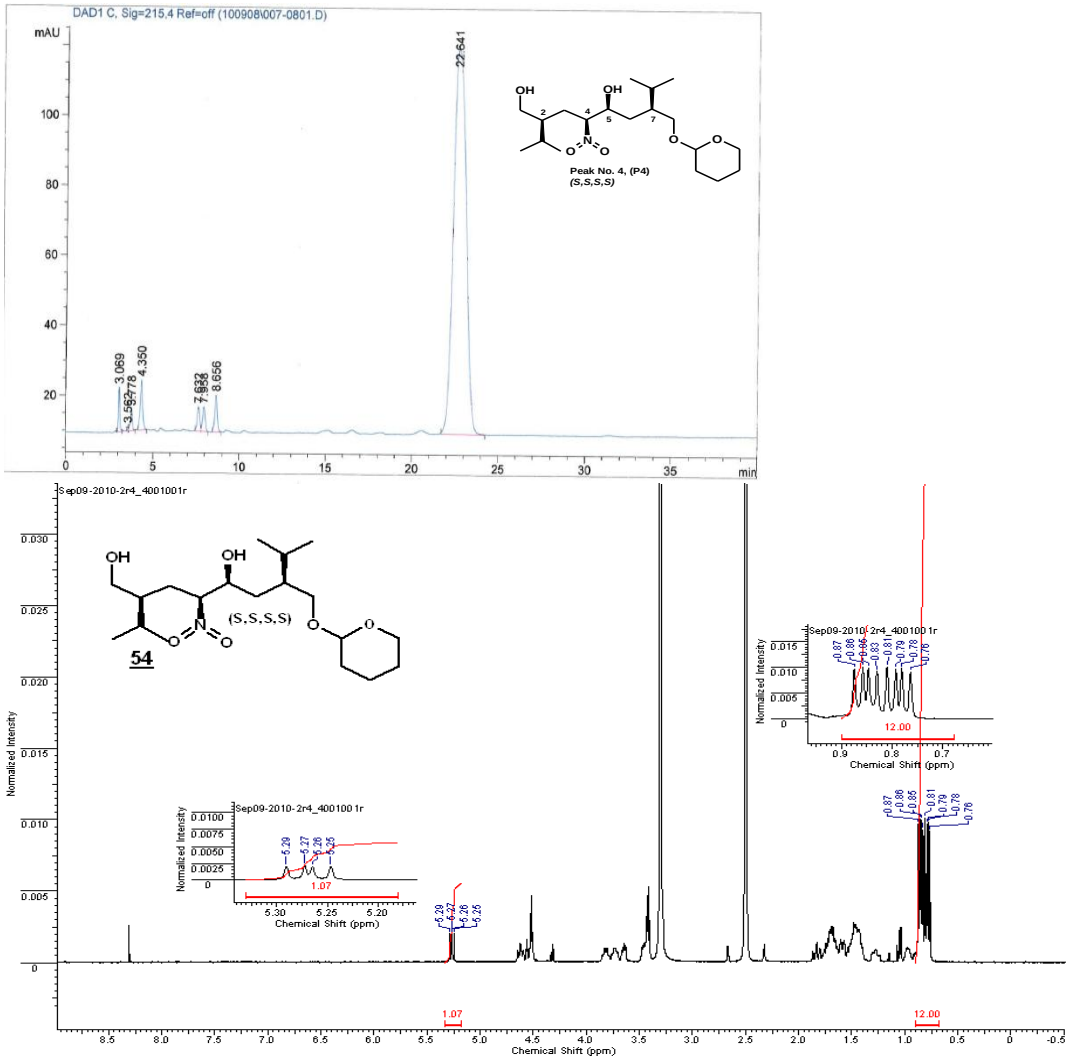
8 (78.3 mmol, 1.70 eq.) are added at 30°C to the green reaction mixture. The reaction mixture is stirred over 2.5 days.
The reaction mixture is cooled down to room temperature and diluted in 300 mL of a mixture of hexan/demineralized water/methanol (70:20:10 v/v/v), yielding to the precipitation of a green solid. The layers are separated and the organic phase is extracted again twice with 100 mL of dichloromethane. Both organic phases are dried over $MgSO_4$ and concentrated on vacuum to yield 6.23 g of a green oil (containing the nitro diol in mixture with the starting material **8** and aldehyde **45**) and 10.1 g of a green oil (containing the nitro diol **54** in mixture with **8**).
The determination of the diastereoisomeric ratio measured on CHIRALPAK AD-H (mixture of hexan/isopropanol/methanol/ethanol 973:9:9:9, 1 mL/min, 40°C) shows the presence of four diastereoisomers with a ratio of 13:11:19:**57**.

10.01 g of the crude material are purified by chromatography on CHIRALPAK AD-H (30*250 nm) with CO_2/isopropanol (8:2) and a flow of 120 g/min to yield in the pure fractions 1.20 g of **54** (yield 12%) as a yellow oil containing 98% of the (S,S,S,S) configured **54** (as 50:50 ratio of (R,S,S,S,S) and (S,S,S,S,S) isomers).

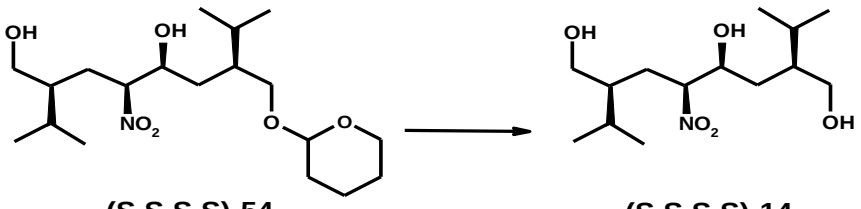
^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm) (mixture of 2 diastereoisomers)
0.83 (m,12H, CH_{3iPr}), 1.23-1.89 (m, 14H, C<u>H</u>CH_{iPr}, CH_{iPr}, CH_{2THP}, CH_2O, CH_2), [3.38 - 3.51 (m, 4H), 3.62 - 3.69 (m, 1H), 3.69 - 3.77 (m, 1 H) CH_2-O-THP, CH_2-O, CH_2-O_{THP}], 3.78 - 3.88 (m, 1H, CH-OH), 4.49 - 4.68 (3H, CH-NO_2, OH, CH_{THP}), 5.20 - 5.31 (m, 1H, OH)

^{13}C NMR (151 MHz, DMSO-d_6) δ_C (ppm) (mixture of 2 diastereoisomers)
18.42 (CH_{3iPr}), 19.07 (CH_{3iPr}), 19.31-20.05 (CH_{2THP}), 20.23 (CH_{3iPr}), 20.29 (CH_{3iPr}), 25.18 (br. s., 1 C), 25.24 (CH_{2THP}), 27.89, 28.73, 28.80, 29.25, 30.41, 31.57 (<u>C</u>H_2-$CHNO_2$, CH_{iPr}), 32.48 (<u>C</u>H_2-CHOH), 39.92 (<u>C</u>HCH_{iPr}), 42.79 (<u>C</u>HCH_{iPr}), 61.06 (CH_2-O_{THP}), 67.03 (CH_2-OH), 68.09 (CH_2-O-THP), 70.62-70.97 (<u>C</u>H-OH), 93.36 (CH-NO_2), 97.84-98.23 (CH-O_{THP})

Chirale HPLC (CHIRALPAK AD-H with a mixture of hexan/isopropanol/methanol/ethanol 973:9:9:9, 1 mL/min, at 40°C) and ^{1}H NMR (600 MHz, dmso-d^6) of (S,S,S,S)-**54**:



(2S,4S,5S,7S)-2,7-diisopropyl-5-nitro-octane-1,4,8-triol 14



(S,S,S,S)-54
MW: 375.52

(S,S,S,S)-14
MW: 291.39

66 mg of nitro aldol (S,S,S,S)-**54** (0.17 mmol, 1.0 eq.) are dissolved at 21°C in 1 mL of methanol and 1.5 mg of *p*-toluene sulfonic acid (0.04 mmol, 0.3 eq.) is added to the solution. After stirring at room temperature over 2 hours, the reaction mixture is diluted in 4 mL of dichloromethane. The organic phase is extracted with 2 mL of an aqueous solution of $NaHCO_3$ (10%), and the resulting aqueous layer is extracted two times with 4 mL of dichloromethane.
The organic phase is dried over $MgSO_4$ and concentrated in vacuum to give nitro diol **14** (86% yield).

^{1}H NMR (600 MHz, DMSO-d^{6}) δ_H (ppm)
0.75-0.85 (m, 12H, CH_{3iPr}), 0.86-0.97 (m, 1H, C<u>H</u>CH_{iPr}), 1.17-1.95 (m, 14H, C<u>H</u>CH_{iPr}, CH_{iPr}, C<u>H$_2$</u>CHO, CH_2CHNO_2), 3.37-3.42 (m, 4H, CH_2-OH), 3.69-3.79 (m, 1H, CH-OH), 4.45-4.47 (m, 1H, OH), 4.55-4.58 (m, 1H, OH), 4.65-4.67 (m, 1H, $CHNO_2$), 5.25 (d, J=9Hz, 1H, OH)

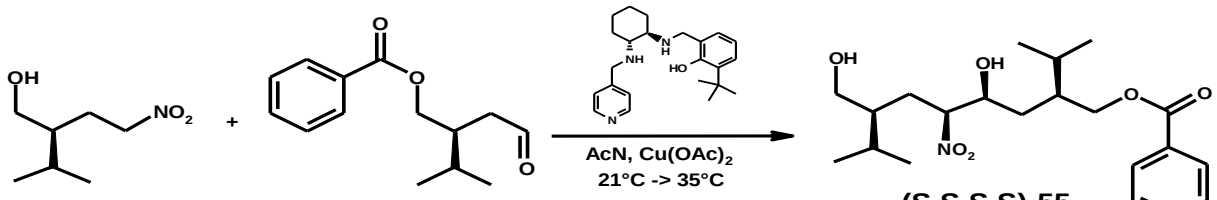
^{13}C NMR (101 MHz, DMSO-d_6) δ_C (ppm)
18.57 (CH_{3iPr}), 18.89 (CH_{3iPr}), 20.10 (CH_{3iPr}), 20.34 (CH_{3iPr}), 27.88 (CH_{iPr}), 28.07 (CH_{iPr}), 28.62 (<u>C</u>H_2CHNO_2), 31.39 (HOC-<u>C</u>H_2-CH- CH_{iPr}), 41.36 (<u>C</u>H- CH_{iPr}), 42.80 (<u>C</u>H- CH_{iPr}), 61.00 (CH_2-OH), 70.51 (CH_2-OH), 74.67 (CH-OH), 93.46 (CH-NO_2)

IR: (FTIR-microscopy in transmission)
3358 (NH), 2960-2876 (C-H_{aliph}), 1555 (NO_{2vas}), 1466(CH_δ), 1371 (NO_{2vs}), 1043 (C-OH)

MS: MH+ = 292, M+NH_4^+ = 309

HRMS ($C_{14}H_{30}O_5N$, 0.5 ppm/MH+): $[M+H]^+$= 292.2169, cal. 292.21185, $C_{14}H_{30}O_5N$

benzoic acid (2S,4S,5S,7S)-4-hydroxy-7-hydroxymethyl-2-isopropyl-8-methyl-5-nitro-nonyl ester <u>55</u>



(S)-<u>8</u>
MW: 161.20

(S)-<u>49</u>
MW: 234.30

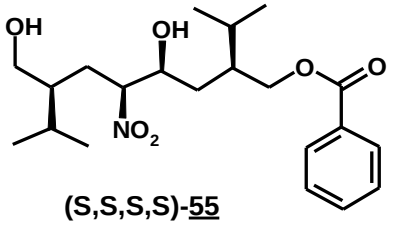
(S,S,S,S)-<u>55</u>
MW: 395.50
+ other stereoisomers

29.9 mg of the ligand (0.08 mmol, 0.09 eq.) are dissolved at 21°C in 1 mL of acetonitrile and 15.6 mg of copper (II) acetate monohydrate (0.08 mmol, 0.09 eq.) are added to the solution. After 35 min, 180.3 mg of aldehyde **<u>49</u>** (0.77 mmol, 1.0 eq.) and 115.3 mg of nitro compound **<u>8</u>** (0.72 mmol, 0.9 eq.) are added at 22°C to the green reaction mixture. The reaction mixture is heated to 35°C and is stirred over 7 days.
The diastereoisomeric ratio is measured on CHIRALPAK AD-H (mixture of hexan/isopropanol/methanol/ethanol 973:9:9:9, 1 mL/min, 40°C) and shows the presence of four picks 7:7:27:**59**.
The reaction mixture is cooled down to room temperature and diluted in 55 mL of a mixture of hexan/demineralized water/methanol (40:10:5v/v/v) yielding to the precipitation of a green solid. The layers are separated and the aqueous phase is extracted again three times with 10 mL of dichloromethane. Both organic phases are dried over $MgSO_4$ and concentrated on vacuum to yield 188.1 mg of a green oil (containing the nitro diol **<u>55</u>** in mixture with the starting nitro compound **<u>8</u>** and aldehyde **<u>49</u>**) and 175.3 mg of a green oil (containing the nitro diol **<u>55</u>** in mixture with the starting nitro compound **<u>8</u>**).
The diastereoisomeric ratio measured on CHIRALPAK AD-H (mixture of hexan/isopropanol/methanol/ethanol 973:9:9:9, 1 mL/min, 40°C) reveals the presence of four diastereoisomers with a ratio of 7:7:27:**59.**

The crude material is purified by column chromatography on silicagel (3 g) with heptane/ethyl acetate (4:1) to give in the pure fractions 48.3 mg of the desired compound **<u>55</u>** (yield 16%) as a

yellow oil containing the single (S,S,S,S) isomer and 63.1 mg of a yellow oil (20 %) as a mixture of diastereoisomers.

Spectroscopic data of (S,S,S,S)-55



(S,S,S,S)-55

^{1}H NMR (400 MHz, DMSO-d^6) δ_H (ppm)
0.61 - 0.69 (m, 12H, CH_{3iPr}), 0.69 - 0.78 (m, 3H, CH_{3iPr}), 0.75 - 0.88 (m, 1H, C<u>H</u>CH_{iPr}), 0.89 - 0.99 (m, 6H, CH_{3iPr}), 1.21 - 1.98 (m, 7H, CH_2CHCO, CH_2CHNO_2, 2*CH_{iPr}, C<u>H</u>CH_{iPr}), 3.34 - 3.49 (m, 2H, CH_2-OH), 3.78 - 3.92 (m, 1H, CH-O), 4.25 - 4.34 (m, 1H, <u>H</u>CH-O-) 4.34 - 4.45 (m, 1H,HC<u>H</u>-O-), 4.45 - 4.54 (t, *J*=5Hz, 1H, OH), 4.57 - 4.73 (m, 1H, $CHNO_2$), 5.29 - 5.49 (d, J= 7Hz,1H, OH), 7.44 - 7.56 (m, 2H, CH_{arom}), 7.61 - 7.76 (m, 1H, CH_{arom}), 7.88 - 8.05 (m, 2H, CH_{arom})

^{13}C NMR (151 MHz, DMSO-d_6) δ_C (ppm)
18.29 (CH_{3iPr}), 19.43 (CH_{3iPr}), 20.16 (CH_{3iPr}), 27.82 (CH_{iPr}), 28.69 (<u>C</u>H_2-$CHNO_2$), 29.34 (CH_{iPr}), 31.61 (<u>C</u>H_2-CHOH), 38.93 (<u>C</u>HCH_{iPr}), 42.73 (<u>C</u>HCH_{iPr}), 61.13 (CH_2-OH), 64.68 (CH_2-OH, CH_2-O), 70.43 (CH-OH), 93.15 (CH-NO_2), 128.88 ($CH_{arom.}$), 129.15 (CH_{arom}), 129.80 (C_{arom}), 133.44 (CH_{arom}), 165.77 (C=O)

<u>IR</u>: (FTIR-microscopy in transmission)
3456 (OH), 3066-3034 (C-H_{arom}), 2960 (C-H_{aliph}), 2876 ($CH_{3\delta s}$), 1703 (C=O_{ester}), 1584-1452 (Phenyl), 1553 (NO_{2vas}), 1372 (NO_{2vs}), 1277 (C-O_{ester}), 1115 (C-O, C-OH), 713 (Phenyl$_{\delta monosub}$, CH_{δ})

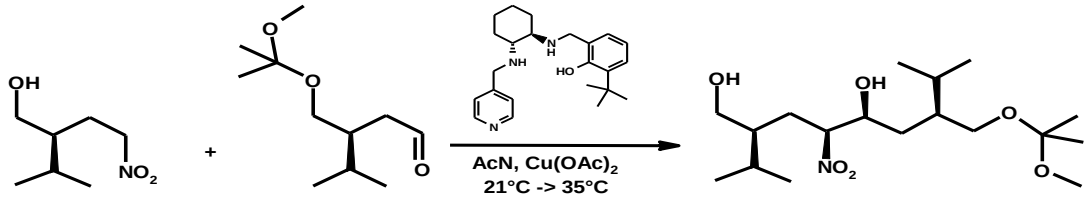
<u>MS</u>: (EI$^+$) MH^+= 396
(EI$^-$) MH^-= 394

<u>HRMS</u> ($C_{21}H_{34}O_5N$, 0.08 ppm/MH+): $[M+H]^+$= 396.23810, cal. 396.23807, $C_{21}H_{34}O_5N$

Spectroscopic data of 55, as a mixture of diastereoisomers

^{1}H NMR (400 MHz, dmso-d^6) δ_H (ppm) (mixture of diastereoisomers)
0.66 - 1.03 (m, 13H, C<u>H</u>CH_{iPr}, 3*CH_{3iPr}), 1.12 - 1.97 (m, 7H, CH_2CHCO, CH_2CHNO_2, 2*CH_{iPr}, C<u>H</u>CH_{3iPr}), 3.33 - 3.47 (m, 2H, CH_2-OH), 3.78 - 4.06 (m, 1H, CH-O), 4.23 - 4.46 (m, 1H, <u>H</u>CH-O-) 4.34 - 4.45 (m, 1H,HC<u>H</u>-O-), 4.48 - 4.55 (m, 1H, OH), 4.55 - 4.74 (m, 1H, $CHNO_2$), 5.40 - 5.44 (d, J= 7Hz, OH_{Dia1}), 5.45 - 5.48 (d, J= 6.5Hz, OH $_{Dia2}$), 7.51-7.55 (m, 2H, CH_{arom}), 7.61 - 7.69 (m, 1H, CH_{arom}), 7.94-7.98 (m, 2H, CH_{arom})

(2S,4S,5S,7S)-2-isopropyl-7-(1-methoxy-1-methyl-ethoxymethyl)-8-methyl-4-nitro-nonane-1,5-diol 56



(S)-8
MW: 161.20

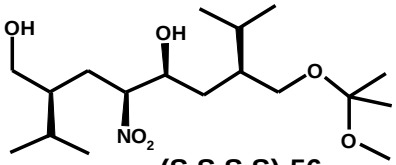
(S)-47
MW: 202.30

(S,S,S,S)-56
MW: 363.50
+ other Stereoisomers

36.6 mg of the ligand (0.10 mmol, 0.02 eq.) are dissolved at 21°C in 1.5 mL of acetonitrile and 19.9 mg of cupper (II) acetate monohydrate (0.10 mmol, 0.02 eq.) are added to the solution. After 30 min, 1.001 g of aldehyde **47** (4.9 mmol, 1.0 eq.) and 1.048 g of nitro compound **8** (6.5 mmol, 1.3 eq.) are added at 22°C to the green reaction mixture. The reaction mixture is heated to 35°C and is stirred over 4 days.
The diastereoisomeric ratio measured on CHIRALPAK AD-H (40°C, 93:7 hexane/isopropanol, isocratic, 2 mL/min) shows the presence of three major picks 25:17:**58.**
Analytic measurement also shows a convertion rate of 65% and the presence of 25% of deprotected Henry product.
The reaction mixture is cooled down to room temperature and diluted in 100 mL of a mixture of hexan/demineralized water/methanol (70:20:10 v/v/v) yielding to the precipitation of a green solid. The layers are separated and the aqueous phase is extracted again once with 75 mL and twice with 25 mL of dichloromethane. Both organic phases are dried over $MgSO_4$ and concentrated on vacuum to yield 870 mg of a green oil (containing **56** in mixture with the starting nitro compound **8** and aldehyde **36**) and 770 mg of a green oil (containing **56** in mixture with the deprotected starting material).
The residue (870 mg) is diluted in 100 mL of a mixture of hexan/demineralized water/methanol (70:25:5 v/v/v). The layers are separated and the organic phase is washed twice with 50 mL of demineralized water. The hexan phase is dried over $MgSO_4$ and concentrated on vacuum to yield 590 mg of a green oil (containing **56** in mixture with the starting nitro compound **8** and aldehyde **47**), whereas the aqueous phase is extracted three times with 50 mL of dichloromethane. The resulting organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 156 mg of a green oil.
Chiral HPLC analysis measured on CHIRALPAK AD-H (mixture of hexan/isopropanol/methanol/ethanol 973:9:9:9, 2 mL/min, at 40°C) reveals the presence of three signals with a ratio of 25:17:**58**

The crude material (590 mg) is purified by column chromatography on silicagel (30 g) with heptane/ethyl acetate/triethylamine (3:1) to give in the pure fractions 112 mg of the desired nitro compound **56** (yield 6%) as a yellow oil containing the (S,S,S,S) and 262.3 mg of a yellow oil (15%) as a mixture of diastereoisomers (14:64:22).

Spectroscopic data of 56



(S,S,S,S)-56

^{1}H NMR (600 MHz, dmso-d^6) δ_H (ppm)
0.53-0.86 (m, 12H, CH_{3iPr}), 0.96-0.98 (m, 1H, CH_2O-CH-CH_{iPr}), 1.26 (S, 6H, CH_{3MIP}), 1.36-1.38 (m, 1H, HCHCHNO$_2$), 1.55 - 1.85 (m, 6H, CH_2CHCO, HCHCHNO$_2$, 2*CH_{iPr}, CHCH$_{iPr}$), 3.11 (s, 3H, CH_{3MIP}), 3.25 (d, J= 2Hz, 2H, CH_2O_{MIP}), 3.30 - 3.45 (m, 2H, CH_2-O), 3.71 - 3.81 (m, 1H, CH-O), 4.57 (m, 1H, $CHNO_2$), 4.65 (t, *J*=6 Hz, 1H, OH), 5.11 (d, J= 6 Hz,1H, OH)

IR: (FTIR-microscopy in transmission)
3406 (OH), 2959 (C-H_{aliph}), 1555 (NO_{2vas}), 1466 (CH_δ), 1371 (NO_{2vs}), 1152 (C-O, C-OH), 1049 (C-OH)

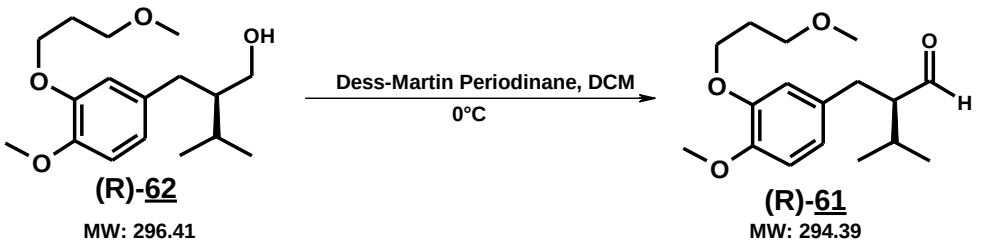
MS: (EI$^+$) $M_{-MIP}H^+$= 291
(FIA) M+NH_4^+=381.3

Rf (heptane/ethyl acetate/triethylamine 3:1) =0.19

I.4. Atom economy strategy for the preparation of Aliskiren

I.4.1. Preparation of racemic-59

(R)-2-[4-methoxy-3-(3-methoxy-propoxy)-benzyl]-3-methyl-butyraldehyde 61
CAS Number: 1027979-11-8
First described by : S.M.A. De Wildeman, H.M.M.G Straatman, G.K.M. Verzijl, V. Vermote, A.H.M. De Vries, WO **2009**-007460
L. Heng, S. Xia, C. He, **2008**, CN 101284769



(R)-62 **(R)-61**
MW: 296.41 **MW: 294.39**

20.0 g of **62** (67.5 mmol, 1.0 eq.) are dissolved at room temperature in 300 mL of methylene chloride. 32.2 g of Dess-Martin reagent (19.7 mmol, 0.3 eq.) are added at 10°C in 5 portions to the yellow mixture over a period of 5 min. The resulting white suspension is allowed to warm to room temperature and is stirred for 2 hours, until total conversion of the starting material (HPLC control).
The reaction mixture is concentrated on vacuum (the bath temperature is 25°C). 200 mL of *t*-butyl methyl ether are added to the residue, resulting in the precipitation of a white solid, which is filtered off and washed with 100 mL of *t*-butyl methyl ether. The organic phase is extracted four times with 500 mL of a solution of 1:1 (v/v) of aqueous $Na_2S_2O_3$ (10%) and saturated aqueous $NaHCO_3$. The organic layer is washed again with 500 mL of brine and 500 mL of water. The organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 19.4 g of crude product **61** (98%) as a yellow liquid.

Determination of the enantiomeric ratio by HPLC with a CHIRALCEL OD-H columm at λ = 215 nm (Hex/iPrOH = 9:1, 0.5 mL/min, 20°C) reveals the presence of 98% of the (R)-enantiomer of **61** at 39.5 min and of 2 % of the (S)-enantiomer of **61** at 41.3 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm)
1.03 (dd, J_1=7 Hz, J_2=4Hz, 6H, CH_{3iPr}), 2.03 - 2.14 (m, 3H, CH_{2MOP}, CH_{iPr}), 2.41 - 2.52 (m, 1H, CH_{iPr}), 2.70 (dd, J_1=14 Hz, J_2=5 Hz, HCH_{benz}), 2.92 (dd, J_1=14 Hz, J_2=9 Hz, 1H, HCH_{benz}), 3.36 (s, 3H, CH_3O_{MOP}), 3.57 (t, J=6 Hz, 2H, OCH_{2MOP}), 3.82 (s, 3H, CH_3O), 4.09 (t, J=6Hz, 2H, CH_2O_{MOP}), 6.66 - 6.70 (m, 2H, H_{arom}), 6.75 - 6.79 (m, 1H, H_{arom}), 9.68 (d, J=2 Hz, 1H, CH=O)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C (ppm)
20.04 (CH_{3iPr}), 20.23 (CH_{3iPr}), 28.62 (CH_{iPr}), 29.88 (CH_{2MOP}), 32.01 (CH_{2benz}), 56.33 ($CH_{iPr,\beta HC=O}$), 58.92 (OCH_3), 60.02 (OCH_{3MOP}), 64.83 (CH_{2MOP}), 69.63 (CH_{2MOP}), 112.24 (CH_{arom}), 114.52 (CH_{arom}), 121.34 (CH_{arom}), 132.46 (C_{arom}), 148.25 (C_{arom}), 148.72 (C_{arom}), 205.40 (CH=O)

IR: (FTIR-microscopy in transmission)
2933 (C-Haliphatic), 2834 ($OCH_3\nu_s$), 2726 (C-H aldehyde), 1722 (C=O, aldehyde), 1590 (phenyl), 1517 (phenyl), 1262 (Ph-O), 1140 (C-O-C), 1027 (C-O), 866-809 (C-Haliph)

MS: (ES^+); [M+NH_4^+] = 312.2, [M+Na^+] = 317.3

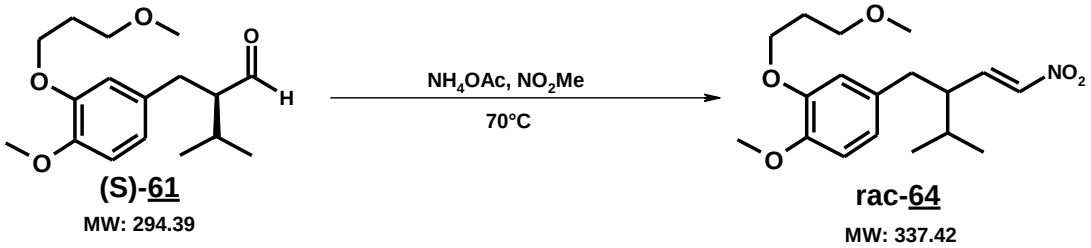
HRMS($C_{17}H_{26}O_4$,0.14 ppm) [M+NH_4] $^+$= 312.21698, cal. 312.21694, $C_{17}H_{30}O_4N$

α_D (1% CHCl3, 1dm, 20°C) = -52.2° (436 nm), -22.5° (546 nm), -18.6° (578 nm), -17.4° (589 nm)

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220 nm. tr= 6.2 min

Rf (hexan/ethyl acetate 1:1) = 0.53

4,2-isopropyl-4-nitro-but-3-enyl)-1-methoxy-2-(3-methoxy-propoxy)-benzene rac-64



(S)-61
MW: 294.39

rac-64
MW: 337.42

103.4 mg of compound **61** (0.35 mmol, 1.0 eq.) are added to 306.5 mg of nitromethane (5.01 mmol, 14.7 eq.) at room temperature. The yellow mixture is stirred over a period of 5 min, and 46.9 mg of ammonium acetate (0.60 mmol, 1.7 eq.) are added at room temperature. The reaction mixture is heated to 70°C and stirred at 70°C for 13 hours. The reaction is then quenched at room temperature by addition of 15 mL of demineralized water. The aqueous layer is then extracted three times with 25 mL of toluene. The resulting organic phase is extracted with 40 mL of demineralized water, and 40 mL of brine. The toluene phase is dried over $MgSO_4$ and concentrated in vacuum to yield 137.9 mg of crude product **64** as a yellow oil. Compound **64** which is almost pure according to the ^{1}H NMR, and is used without further purification in the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm)
0.93 - 1.03 (dd, 6H, CH_{3iPr}), 1.86 (dq, J_1=12 Hz, J_2=7 Hz, 1H, CH_{iPr}), 2.05 - 2.14 (m, 2H, CH_{2MOP}), 2.28 - 2.39 (m, 1H, CH_{iPr}), 2.57 (dd, J_1=13 Hz, J_2=9 Hz, 1H, HCH_{benz}), 2.87 (dd, J_1=13 Hz, J_2=5 Hz, 1H, HCH_{benz}),

3.37 (s, 3 H, $\underline{CH_3}O_{MOP}$), 3.54 - 3.61 (m, 2H, $O\underline{CH_2}_{MOP}$), 3.84 (s, 3H, $\underline{CH_3}O$), 4.03 - 4.13 (m, 2H, $\underline{CH_2}O_{MOP}$), 6.59 - 6.80 (m, 4H, C=$\underline{CH}$ & H_{arom}), 7.13 (dd, J_1=13 Hz, J_2=10 Hz, 1H, $\underline{HC}$=C)

$^{13}\underline{C\ NMR}$ (101 MHz, $CDCl_3$) δ_C (ppm)
18.70 ($\underline{CH_3}_{iPr}$), 20.86 ($\underline{CH_3}_{iPr}$), 29.58 ($\underline{CH}_{iPr}$), 31.17 ($\underline{CH_2}_{MOP}$), 37.74 ($\underline{CH_2}_{benz}$), 47.95 ($\underline{CH}CH_{iPr}$), 56.01 ($O\underline{CH_3}$), 58.66 ($O\underline{CH_3}_{MOP}$), 66.20 ($\underline{CH_2}O_{MOP}$), 69.32 ($\underline{CH_2}O_{MOP}$), 111.87 (CHarom), 114.16 (CHarom), 121.18 (CHarom), 131.39 (Carom), 139.99 (CH=CH), 143.78 (CH=CH), 148.17 (Carom), 148.43 (Carom)

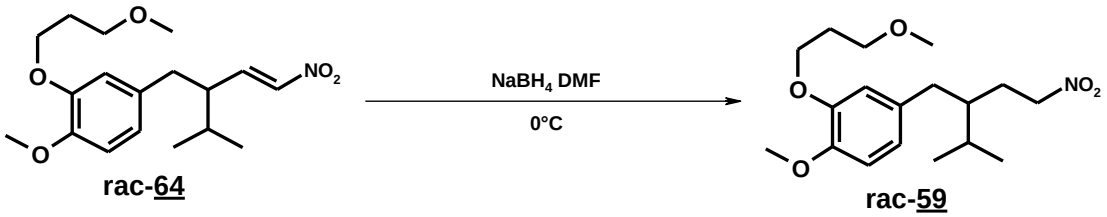
IR: (FTIR-microscopy in transmission)
3099 (C-Harom), 2960-2932-2875 (C-Haliphatic), 2835 (OCH_3), 1644 (C=C), 1518 (NO_2, ν_{as}), 1350 (NO_2, ν_s), 1260 (Ph-O), 1140 (C-O-C), 1027 (C-O), 805 (C-Haliph.)

MS: (ES^+); [M-H^+] = 338.4, [M+NH_4] $^+$= 355.3
(ES^-); [M-H^+] = 336.3

HRMS($C_{18}H_{27}O_5N$, 0.5 ppm): [M-H] $^+$ = 338.19601, cal. 338.19620, $C_{18}H_{28}O_5N$

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220 nm. tr= 7.7 min

1-methoxy-2-(3-methoxy-propoxy)-4-[3-methyl-2-(2-nitro-ethyl)-butyl]-benzene rac-59



rac-64
MW: 337.42

rac-59
MW: 339.44

129.3 mg (0.38 mmol, 1.0 eq.) of crude racemic nitroalkene **64** are dissolved at room temperature in 2 mL of DMF. The resulting solution is cooled down to 0°C and 114.2 mg (3.1 mmol, 7.9 eq.) of sodium borohydride are added in three portions. The reaction mixture is stirred at 0°C over a period of 90 min, and then quenched at room temperature with 3 mL of aqueous HCl (1M). The aqueous layer is then extracted three times with 25 mL of toluene, and the resulting organic phase is then washed with 40 mL of demineralized water, and 40 mL of brine. The toluene phase is dried over $MgSO_4$ and concentrated in vacuum to yield 125.0 mg of crude **59**.
The crude product is purified by column chromatography on silicagel (0.040-0.063 nm) (10 g) with heptan: ethyl acetate (6:1) to give in the pure fractions 60.3 mg of nitro compound **59** (48% starting from aldehyde **61**, 2 steps) as a colorless oil.
The enantiomeric ratio measured on CHIRALCEL OD-H (20°C, 93:7 hexane/isopropanol, 1 mL/min) proves a ratio of 50:50 of both enantiomers (S-enantiomer at 11.3 min, R-enantiomer at 16.9 min).

$^1\underline{H\ NMR}$ (400 MHz, $CDCl_3$-*d*) δ_H (ppm)
0.79 - 0.99 (dd, J_1=6 Hz, 6H, $\underline{CH_3}_{iPr}$), 1.54 - 1.62 (m, 1H, $\underline{CH}_{iPr}$), 1.74 (dddd, J_1=10 Hz, J_2=7Hz, J_3=3 Hz, 1H, $\underline{CH}_{iPr}$), 1.80 - 1.95 (m, 1H, $HCHCH_2NO_2$) 2.00 - 2.10 (m, 1H, $\underline{HC}HCH_2NO_2$) 2.07 - 2.18 (m, 2 H, $\underline{CH_2}_{MOP}$), 2.34 (dd, J_1=14 Hz, J_2=6 Hz, 1H, $\underline{HC}H_{benz}$), 2.67 (dd, J_1=14 Hz, J_2=6 Hz, 1H, $H\underline{CH}_{benz}$), 3.37 (s, 3H, $O\underline{CH_3}_{MOP}$), 3.55 - 3.67 (m, 2H, $\underline{CH_2}O_{MOP}$), 3.85 (s, 3H, $O\underline{CH_3}$), 4.07 - 4.17 (m, 2H, $\underline{CH_2}O_{MOP}$), 4.21 (t, J_1=7 Hz, 2H, $\underline{CH_2}NO_2$), 6.65 - 6.75 (m, 2H, H_{arom}), 6.77 - 6.91 (m, 1H, H_{arom})

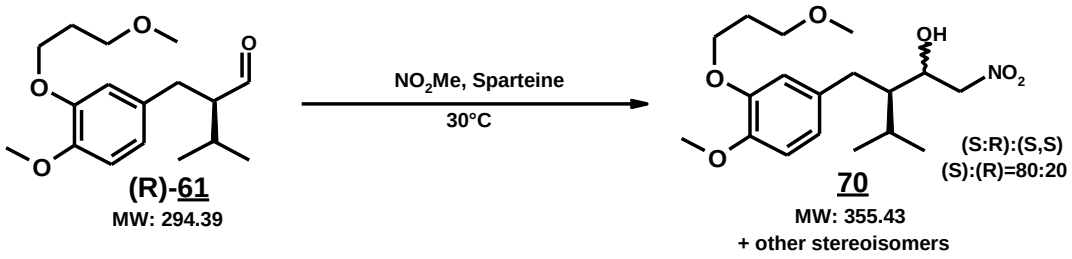
^{13}C NMR (101 MHz, $CDCl_3$) δ_C (ppm)
18.57 ($\underline{CH_3}_{iPr}$), 18.93 ($\underline{CH_3}_{iPr}$), 28.48 ($\underline{CH}_{iPr}$), 29.55 ($\underline{CH_2}_{MOP}$), 29.72 ($CH_2\underline{CH_2}NO_2$), 36.77 ($\underline{CH_2}_{benz}$), 43.25 ($\underline{CH}CH_{iPr}$), 56.09 ($O\underline{CH_3}$), 58.68 ($O\underline{CH_3}_{MOP}$), 66.20 ($\underline{CH_2}O_{MOP}$), 69.39 ($\underline{CH_2}O_{MOP}$), 74.67 ($\underline{CH_2}NO_2$), 111.99 (CH_{arom}), 114.17 (CH_{arom}), 121.13 (CH_{arom}), 133.01 (C_{arom}), 148.02 (C_{arom}), 148.56 (C_{arom})

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220 nm. tr= 7.8 min

R_f (hexan/ethyl acetate 1:1) = 0.75

I.4.1. Preparation of enantiopure 59

(R)-3-[4-methoxy-3-(3-methoxy-propoxy)-benzyl]-4-methyl-1-nitro-pentan-2-ol 70 method 1



(R)-61
MW: 294.39

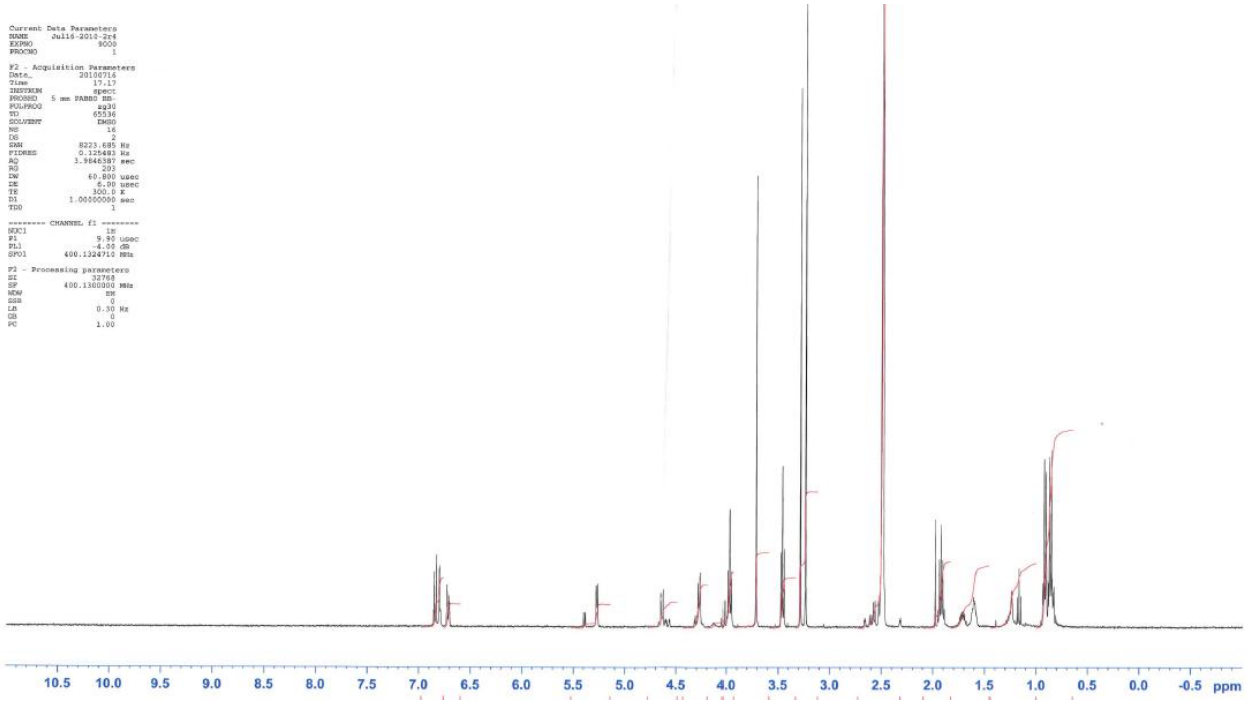
70
MW: 355.43
+ other stereoisomers

19.9 g of compound **61** (67.6 mmol, 1.0 eq.) are added to 25.86 g of nitromethane (423.6 mmol, 6.2 eq.) at room temperature. 4.63 g of sparteine (19.7 mmol, 0.3 eq.) are added dropwise to the orange mixture for 10 min. The resulting brown solution is stirred at 30°C (IT) for 1 hour 30 min (90% conversion, HPLC control). The reaction mixture is diluted at room temperature with 200 mL of ethyl acetate. The organic phase is extracted with 600 mL of water ($pH_{aq.\ Phase}$ = 9), 500 mL aqueous citric acid solution (10%) ($pH_{aq.\ Phase}$ = 3), and three times with 1L of demineralized water ($pH_{aq.\ Phase}$ = 5) until complete extraction of nitromethane from the organic layer. The ethyl acetate phase is dried over $MgSO_4$ and concentrated in vacuum to yield 19.2 of crude product **70** in mixture with 30% of unreacted aldehyde **61** (yield 60% according to NMR spectrum).
The diastereoisomeric ratio measured on CHIRALCEL OD-H (20°C, 93:7 hexane/isopropanol, isocratic, 1mL/min) is 78% of diastereoisomer 4 / 19 % of diastereoisomer 3 / 3% diastereoisomers 1,2.

The crude product is purified two times by column chromatography on silicagel (0.040-0.063 nm) (400g and 200g) with heptan:ethyl acetate (4:1) to give in the pure fractions 10.2 g of Henry product **70** (42% isolated yield) and 4.4 g of a mixture of compounds **61** and **70** as a yellow oil.
The enantiomeric ratio measured on CHIRALCEL OD-H (20°C, 97:3 hexane/isopropanol, isocratic, 1mL/min) is 78% of diastereoisomer 4 / 19 % of diastereoisomer 3 / 3% diastereoisomer 1,2.
A part of the diastereoisomeric mixture is purified by chromatography on CHIRALPAK AD (heptan/ethanol/methanol, 90:5:5, 400 mL/min) to yield the diastereoisomer 3 as single isomer with 93% purity and the diastereoisomer 4 as single isomer with 98% purity.

Spectroscopic data of 70 as isomeric mixture:

^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm), mixture of diasteroisomers
0.80 - 0.96 (m, 6H, CH_{3iPr}), 1.60 (bm, 1H, C<u>H</u>-CH_{iPr}), 1.72 (bm, 1H, CH-$CH_{iPrDia4}$), 1.89-1.96 (m, C<u>H</u>$_2$$CH_2OCH_{3MOP,}$ $CH_{3iPrDia3}$), 2.52 - 2.63 (m, 2H, CH_{2benz}), 3.24 (s, $OCH_{3MOPDia3}$), 3.29 (s, $OCH_{3MOPDia4}$), 3.46 (t, *J*=6 Hz, 2H, CH_2-O_{MOP}), 3.72 (s, 3H, OCH_3), 3.97 (t, *J*=6 Hz, 2H, CH_2-O_{MOP}), 4.14 (br. s., C<u>H</u>-OH_{Dia3}), 4.25 - 4.34 (m, HC<u>H</u>NO_2, C<u>H</u>-OH_{Dia4}), 4.55 - 4.62 (m, 1H, <u>H</u>$CHNO_{2Dia3}$), 4.64 (d, *J*=9 Hz, <u>H</u>$CHNO_{2Dia4}$), 5.27 (d, *J*=5 Hz, OH_{Dia4}), 5.40 (d, *J*=6 Hz, OH_{Dia3}), 6.69 - 6.75 (m, 1H, H_{arom}), 6.78 - 6.82 (m, 1H, H_{arom}), 6.83 - 6.87 (m, H_{arom})



^{13}C NMR (101 MHz, $CDCl_3$) δ_H ppm
20.16 (m, CH_{3iPr}), 20.33 (m, CH_{3iPr}), 21.63 ($CH_{3iPrDia3}$), 27.45 ($CH_{iPrDia3}$), 29.61 ($CH_{iPrDia4}$), 31.37 ($CH_{2benzDia3}$), 31.96 ($CH_{2benzDia4}$), 49.18 (C<u>H</u>-$CH_{iPrDia3}$), 49.48 (C<u>H</u>-$CH_{iPrDia4}$), 56.07 (OCH_3), 58.68 (OCH_{3MOP}), 65.98 (CH-OH_{Dia3}), 66.20 (CH-OH_{Dia4}), 69.34 (CH_2-O_{MOP}), 69.85 (CH_2-O_{MOP}), 80.56 ($CHNO_2$), 112.00 (CH_{arom}), 114.31 (CH_{arom}), 120.94 ($CH_{aromDia3}$), 121.20 ($CH_{aromDia4}$), 133.49 (C_{arom}), 148.04 (C_{arom}-OCH_{3MOP}), 148.58 (C_{arom}-OCH_3)

<u>IR</u>: (FTIR-microscopy in transmission)
3506 (OH), 2933 (C-Haliphatic), 2836 (OCH_3,ν_s), 1556 (NO_2, ν_{as}), 1385 (NO_2, ν_s), 1261 (Ph-O), 1140 (C-O-C), 1027 (C-O)

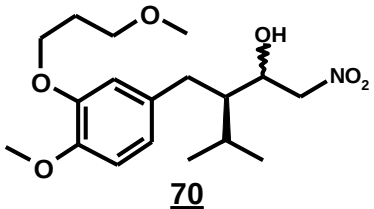
<u>MS</u>: (ES^+); [M-H^+] = 356.4
(ES^-); [M-H^-] = 354.4

<u>HR-MS</u>($C_{18}H_{29}O_6N$, 0.12 ppm): [M+H] $^+$= 356.20627, cal. 356.20677, $C_{18}H_{30}O_6N$

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 6.1 min (Diastereoisomer 1), tr = 6.2 min (Diastereoisomer 2)

Rf (hexan/ethyl acetate 4:1) = 0.44

Spectroscopic data of 70-Diastereoisomer 3 (P3):

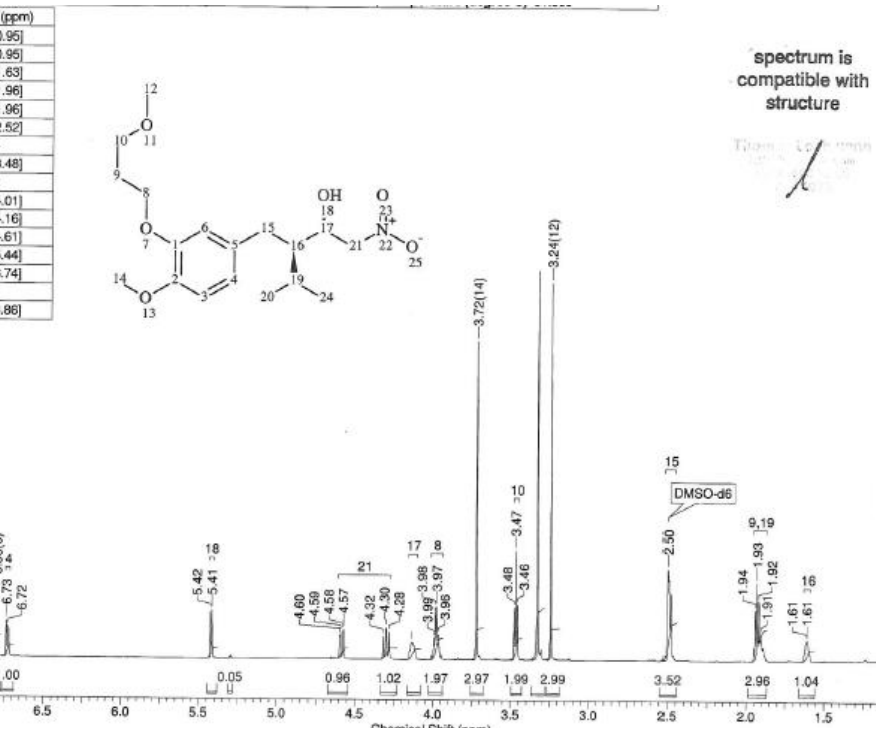


70

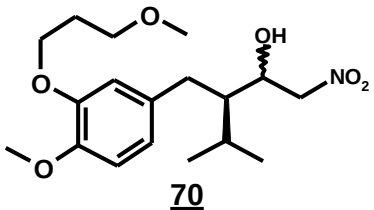
^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm),
0.89 - 0.98 (m, 6H, CH_{3iPr}), 1.63 (bm, 1H, CH-CH_{iPr}), 1.88 - 1.99 (m, $CH_2CH_2OCH_{3MOP,}$ 3H, CH_{iPr}), 2.51 - 2.54 (m, 2H, CH_{2benz}), 3.26 (OCH_{3MOP}), 3.49 (t, *J*=6 Hz, 2H, CH_2-O_{MOP}), 3.74 (s, 3H, OCH_3), 3.96 - 4.04 (m, 2H, CH_2-O_{MOP}), 4.11 - 4.18 (br. s., CH-OH), 4.28 - 4.36 (m, 1H, $HCHNO_2$), 4.60 (dd, J_1=12 Hz, J_2=2Hz, 1H, $HCHNO_2$), 5.44 (d, *J*=6 Hz, 1H, OH_{Dia3}), 6.75 (d, *J*=8 Hz, 1H, H_{arom}), 6.82 (s, 1H, H_{arom}), 6.87 (d, *J*=8 Hz, 1H, H_{arom})

MS: (ES^+); [$M+NH_4^+$] = 373.4

No.	Atom	Exp. Shift (ppm)
1	20	[0.89 .. 0.95]
2	24	[0.89 .. 0.95]
3	16	[1.59 .. 1.63]
4	9	[1.87 .. 1.96]
5	19	[1.87 .. 1.96]
6	15	[2.45 .. 2.52]
7	12	3.24
8	10	[3.45 .. 3.48]
9	14	3.72
10	8	[3.93 .. 4.01]
11	17	[4.10 .. 4.16]
12	21	[4.27 .. 4.61]
13	18	[5.41 .. 5.44]
14	4	[6.71 .. 6.74]
15	6	6.80
16	3	[6.84 .. 6.86]



Spectroscopic data of 70-Diastereoisomer 4 (P4):

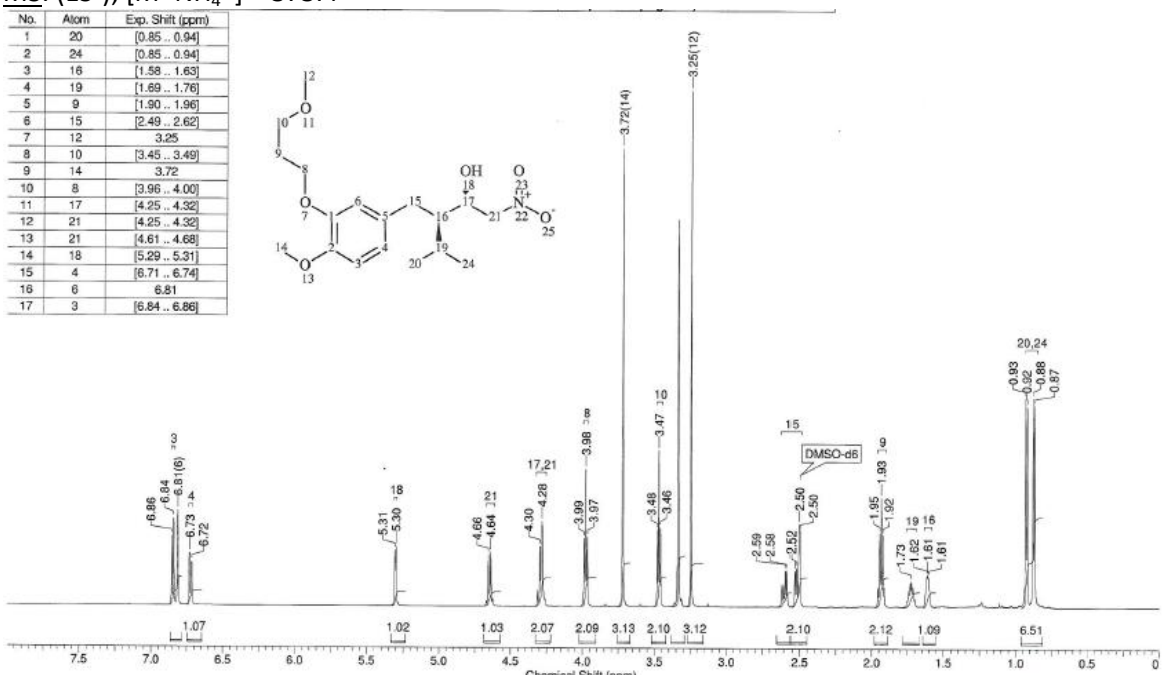


70

^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm),
0.83 - 0.96 (m, 6H, CH_{3iPr}), 1.55 - 1.65 (m, 1H, C<u>H</u>-CH_{iPr}), 1.70-1.75 (m, 1H, CH_{iPr}), 1.93 (m, 2H, $C\underline{H}_2CH_2OCH_{3MOP}$), 2.52 (d, *J*=7 Hz, 1H, <u>H</u>CH_{benz}), 2.58 (d, *J*=7 Hz, 1H, HC<u>H</u>$_{benz}$), 3.25 (OCH_{3MOP}), 3.47 (t, *J*=6Hz, 2H, CH_2-O_{MOP}), 3.72 (s, , 3H, OCH_3), 3.98 (t, *J*=6 Hz, 2H, CH_2-O_{MOP}), 4.28-4.29 (m, 2H, HC<u>H</u>NO_2, C<u>H</u>-OH), 4.65 (d, *J*=9 Hz, 1H, <u>H</u>$CHNO_2$), 5.30 (d, *J*=5 Hz, OH_{Dia4}), 6.72 (d, *J*=8 Hz, 1H, H_{arom}), 6.81 (s, 1H, H_{arom}), 6.85 (m, 1H, H_{arom})

MS: (ES^+); [M+NH_4^+] = 373.4

No.	Atom	Exp. Shift (ppm)
1	20	[0.85 .. 0.94]
2	24	[0.85 .. 0.94]
3	16	[1.58 .. 1.63]
4	19	[1.69 .. 1.76]
5	9	[1.90 .. 1.96]
6	15	[2.49 .. 2.62]
7	12	3.25
8	10	[3.45 .. 3.49]
9	14	3.72
10	8	[3.96 .. 4.00]
11	17	[4.25 .. 4.32]
12	21	[4.25 .. 4.32]
13	21	[4.61 .. 4.68]
14	18	[5.29 .. 5.31]
15	4	[6.71 .. 6.74]
16	6	6.81
17	3	[6.84 .. 6.86]



Method 2 (Table 9, Entry 1)

9.9 mg of the (R,R) ligand **A** (0.025 mmol, 0.05 eq.) are dissolved at 22°C in 0.5 mL of ethanol and 4.5 mg of cupper (II) acetate monohydrate (0.025 mmol, 0.05 eq.) are then added at 22°C. After 20 min, a solution of 67.7 mg of nitromethane **27** (1.1 mmol, 2.1 eq.) in 0.2 mL of ethanol and a solution of 150.3 mg of aldehyde **61 (**0.5 mmol, 1.0 eq.) in 0.3 mL of ethanol are added at 22°C to the green reaction mixture. The reaction mixture is heated to 35°C and is stirred at 35°C

The enantiomeric ratio measured on CHIRALCEL OD-H (20°C, 97:3 hexane/isopropanol, isocratic, 1mL/min) is 89% of diastereoisomer 4 / 1% of diastereoisomer 3 / 1% diastereoisomers 1,2.

Method 3 (Table 9, Entry 2)

9.6 mg of the (S,S) ligand **A** (0.025 mmol, 0.05 eq.) are dissolved at 22°C in 0.5 mL of ethanol and 4.5 mg of cupper (II) acetate monohydrate (0.025 mmol, 0.05 eq.) are then added at 22°C. After 20 min, a solution of 67.0 mg of nitromethane **27** (1.1 mmol, 2.1 eq.) in 0.2 mL of ethanol and a solution of 147.9 mg of aldehyde **61 (**0.5 mmol, 1.0 eq.) in 0.3 mL of ethanol are added at 22°C to the green reaction mixture. The reaction mixture is heated to 35°C and is stirred at 35°C.

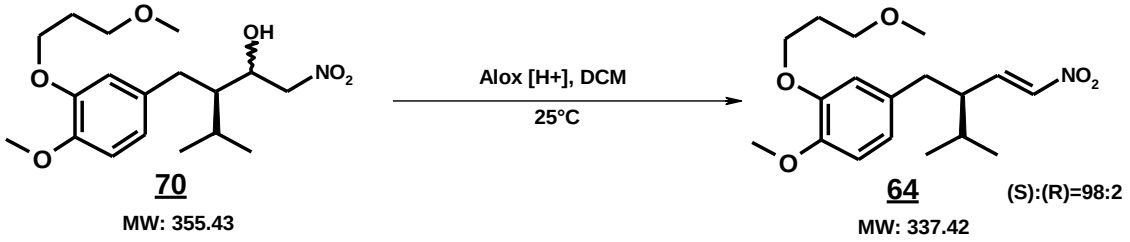
The enantiomeric ratio measured on CHIRALCEL OD-H (20°C, 97:3 hexane/isopropanol, isocratic, 1mL/min) is 77% of diastereoisomer 4 / 6% of diastereoisomer 3 / 1% diastereoisomers 1,2

Method 4 (Table 9, Entry 3)

9.4 mg of the (S,S) ligand **A** (0.025 mmol, 0.05 eq.) are dissolved at 22°C in 0.5 mL of ethanol and 4.7 mg of cupper (II) acetate monohydrate (0.025 mmol, 0.05 eq.) are then added at 22°C. After 20 min, a solution of 69.2 mg of nitromethane **27** (1.1 mmol, 2.1 eq.) in 0.2 mL of ethanol and a solution of 151.1 mg of aldehyde **61 (**0.5 mmol, 1.0 eq.) in 0.3 mL of ethanol are added at 22°C to the green reaction mixture. The reaction mixture is heated to 35°C and is stirred overnight.

((Z)-(R)-2-Isopropyl-4-nitro-but-3-enyl)-1-methoxy-2-(3-methoxy-propoxy)-benzene 64

Method 1



70
MW: 355.43

64 (S):(R)=98:2
MW: 337.42

To a solution of 10.2 g of compound **70** (28.7 mmol, 1.0 eq.) in 100 mL of dichloromethane are added at room temperature 15.2 g of Alox (Brockmann Activity I). After 30 min stirring at room temperature, 97% of the starting material is consumed, but nevertheless the resulting white suspension is stirred at room temperature over 3 days. The Alox is filtered off and washed with 100 mL of dichloromethane. The dichloromethane phase is concentrated in vacuum to yield 8.0 g of crude product **64** (yield 83%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm)
0.89 - 1.03 (dd, 6H, CH_{3iPr}), 1.76 - 1.94 (m, 1H, CH_{iPr}), 2.09 (quin, J_1=6 Hz, 2H, CH_{2MOP}), 2.26 - 2.42 (m, J_1= 10 Hz, J_2= 5 Hz, 1H, CH_{iPr}), 2.57 (dd, J_1= 14 Hz, J_2= 10 Hz, 1H, HCH_{benz}), 2.87 (dd, J_1=14 Hz, J_2=5 Hz, 1H, HCH_{benz}), 3.37 (s, 3H, CH_3O_{MOP}), 3.50 - 3.63 (m, 2H, OCH_{2MOP}), 3.84 (s, 3 H, CH_3O_{MOP}), 3.96 - 4.17 (m, 2H, CH_2O_{MOP}), 6.57 - 6.84 (m, 4H, C=CH & H_{arom}), 7.13 (dd, J_1=13 Hz, J_2=10 Hz, 1H, HC=C)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C (ppm)
148.43 (C_{arom}), 148.14 (C_{arom}), 143.78 (CH=CH), 140.01 (CH=CH), 131.39 (C_{arom}), 121.18 (CH_{arom}), 114.16 (CH_{arom}), 111.89 (CH_{arom}), 69.32 (CH_2O_{MOP}), 66.22 (CH_2O_{MOP}), 58.66 (OCH_{3MOP}), 56.01 (OCH_3), 47.98 ($CHCH_{iPr}$), 37.74 (CH_{2benz}), 31.19 (CH_{2MOP}), 29.59 (CH_{iPr}), 20.85 (CH_{3iPr}), 18.70 (CH_{3iPr})

MS: (ES^+); [M-H^+] = 338.4
(ES^-); [M-H^+] = 336.3

The enantiomeric ratio measured on CHIRALCEL OD-H (20°C, 93:7 hexane/isopropanol, isocratic, 1mL/min) is 98% of (S)-enantiomer and 2 % of (R)-enantiomer

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220 nm. tr= 7.7 min

Method 2 (Table 10, Entry 2)

To a solution of 100.1 mg of **70** (0.3 mmol) in 1 mL of 1,2-dichloroethane are added at room temperature 152.4 mg of Alox (Brockmann Activität I). The reaction mixture is stirred over night at 40°C.

Method 3 (Table 10, Entry 3)

To a solution of 102.7 mg of **70** (0.3 mmol) in 1 mL of 1,2-dichloroethane are added at room temperature 151.0 mg of Alox (Brockmann Activität I). The reaction mixture is stirred over 1hour 45 min at 60°C.

Method 4 (Table 10, Entry 4)

To a solution of 100.6 mg of **70** (0.3 mmol, 1.0 eq.) in 1 mL of 1,2-dichloroethane are added at room temperature 153.0 mg of $KHSO_4$ (1.12 mmol, 3.7 eq.). The reaction mixture is stirred over night at 25°C.

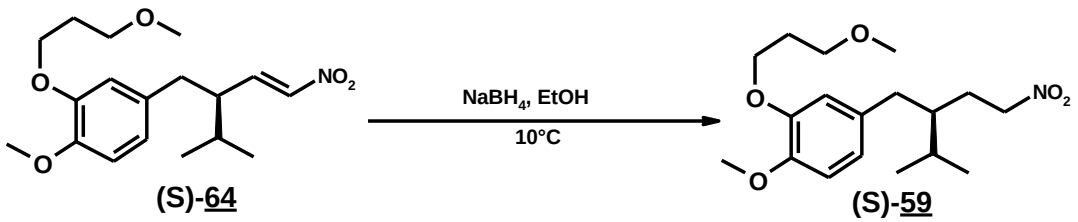
Method 5 (Table 10, Entry 5)

To a solution of 101.0 mg of **70** (0.3 mmol, 1.0 eq.) in 1 mL of 1,2-dichloroethane are added at room temperature 305.8 mg of $KHSO_4$ (1.12 mmol, 7.5 eq.). The reaction mixture is stirred over night at 25°C.

Method 6 (Table 10, Entry 6)

To a solution of 103.1 mg of **70** (0.3 mmol, 1.0 eq.) in 1 mL of 1,2-dichloroethane are added at room temperature 153.1 mg of SiO_2. The reaction mixture is stirred over night at 25°C.

1-methoxy-2-(3-methoxy-propoxy)-4-[(S)-3-methyl-2-(2-nitro-ethyl)-butyl]-benzene 59



(S)-64
MW: 337.42

(S)-59
MW: 339.44

5.05 g of compound **64** (15.0 mmol, 1.0 eq.) are diluted in 40 mL of abs. ethanol at room temperature. The reaction mixture is cooled down to 10°C, and 3.85 g of sodium borohydride (101.9 mmol, 6.8 eq.) are added portionswise over a period of 20 min. The reaction mixture is allowed to stir for 15 min until completion of the reaction (HPLC control), and 10 mL of toluene are added at room temperature. The reaction mixture is then quenched with 5 L of demineralized water (exothermic addition) and then diluted in 200 mL of a solution of 100 mL demineralized water and 100 mL of brine. The aqueous phase is extracted four times with 100 mL, five times with 200 mL once with 300 mL of toluene, three times with 50 mL of dichloromethane, and once with 200 mL of ethyl acetate. The combined organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 4.72 of crude product **59** (yield 93%) as slighty yellow oil.
A part of the crude product (3.51g) is purified by column chromatography on silicagel (0.040-0.063 nm) (60g) with heptan:ethyl acetate (4:1) to give in the pure fractions 1.21 g of nitro compound **59** as a colorless oil.

The enantiomeric ratio measured on CHIRALCEL OD-H (20°C, 93:7 hexane/isopropanol, isocratic, 1mL/min) is 98% of (S)-enantiomer and 2 % of (R)-enantiomer
^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm)
6.85 (d, *J*=8Hz, 1H, H_{arom}), 6.77 (s, 1H, H_{arom}), 6.68 (dd, J_1=8 Hz, J_2=1 Hz, 1H, H_{arom}), 4.46 (t, *J*=7 Hz, 2 H, CH_2NO_2), 3.99 (t, *J*=6 Hz, 2H, CH_2O_{MOP}), 3.74 (s, 3H, OCH_3), 3.47 (t, *J*=6 Hz, 2H, CH_2O_{MOP}), 3.25 (s, 3H, OCH_{3MOP}), 2.47 - 2.58 (m, 1H, HCH_{benz}), 2.38-2.41 (dd, J_1=13, J_2=7 Hz, 1H, HCH_{benz}), 1.94 (q, 3H, CH_{2MOP}, $HCHCH_2NO_2$), 1.72 (dd, J_1=14 Hz, J_2=7 Hz, 1H, $HCHCH_2NO_2$), 1.61 - 1.68 (m, 1H, CH_{iPr}) 1.53 (br. s., 1H, CH_{iPr}) 0.88 (dd, J_1=6 Hz, 6H, CH_{3iPr})

^{13}C NMR (101 MHz, $CDCl_3$) δ_C (ppm)
148.25 (C_{arom}), 147.69 (C_{arom}), 132.68 (C_{arom}), 120.80 (CH_{arom}), 113.84 (CH_{arom}), 111.67 (CHarom), 74.36 (CH_2NO_2), 69.06 (CH_2O_{MOP}), 65.88 (CH_2O_{MOP}), 58.36 (OCH_{3MOP}), 55.77 (OCH_3), 42.92 ($CHCH_{iPr}$), 36.46 (CH_{2benz}), 29.32 ($CH_2CH_2NO_2$), 29.21 (CH_{2MOP}), 28.15 (CH_{iPr}), 18.61 (CH_{3iPr}), 18.26 (CH_{3iPr})

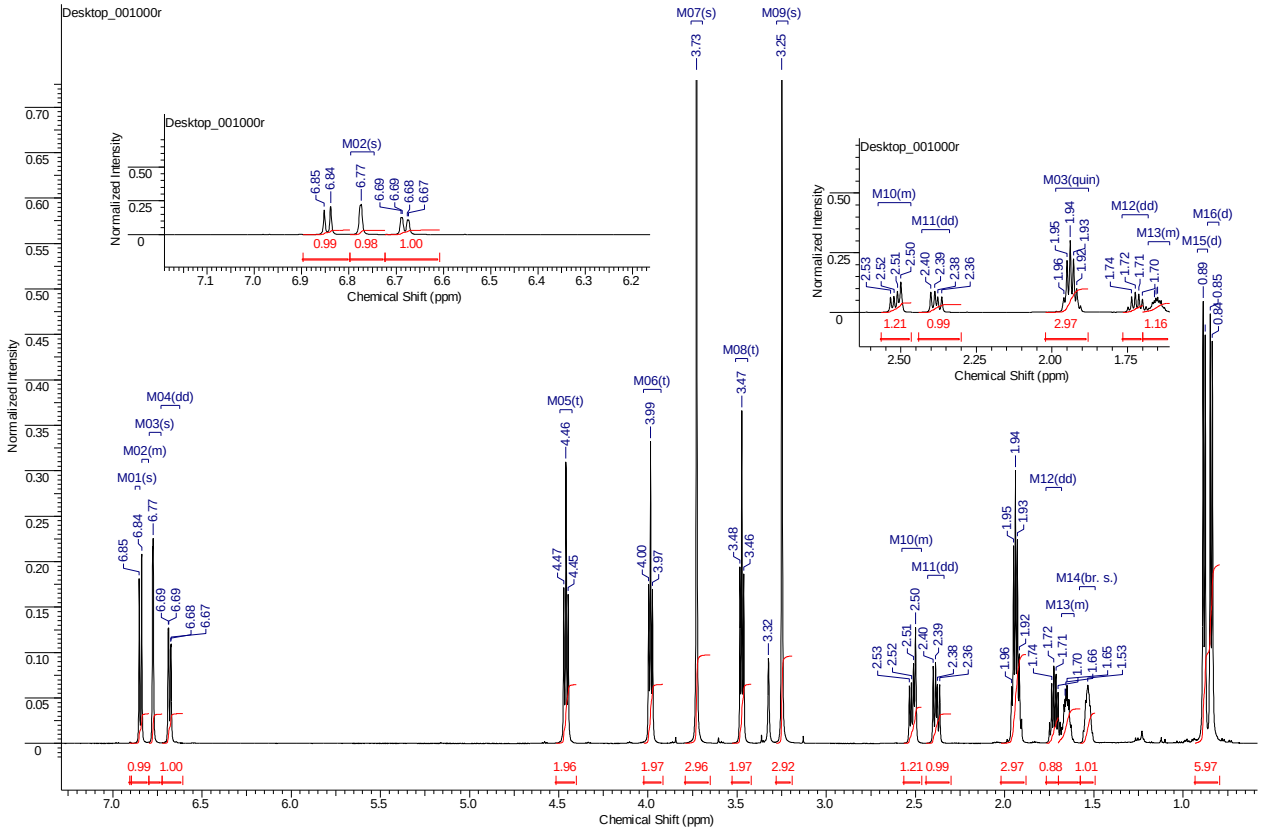
IR: (FTIR-microscopy in transmission) 2933 (C-Haliphatic), 2835 (OCH_3, ν_s), 1589 (Phenyl), 1554 (NO_2, ν_{as}), 1516(Phenyl), 1386 (NO_2, ν_s), 1237 (Ph-O), 1121 (C-O-C), 1028 (C-O)

MS: (ES^+); $[M-H^+]$ = 340.4, $[M+NH_4]^+$= 357.3
(ES^-); $[M-H^-]$ = 338.4

HRMS($C_{18}H_{29}O_5N$, 0.04 ppm/MH+): $[M-H^+]$ = 340.21198, cal. 340.21185, $C_{18}H_{30}O_5N$

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 7.8 min

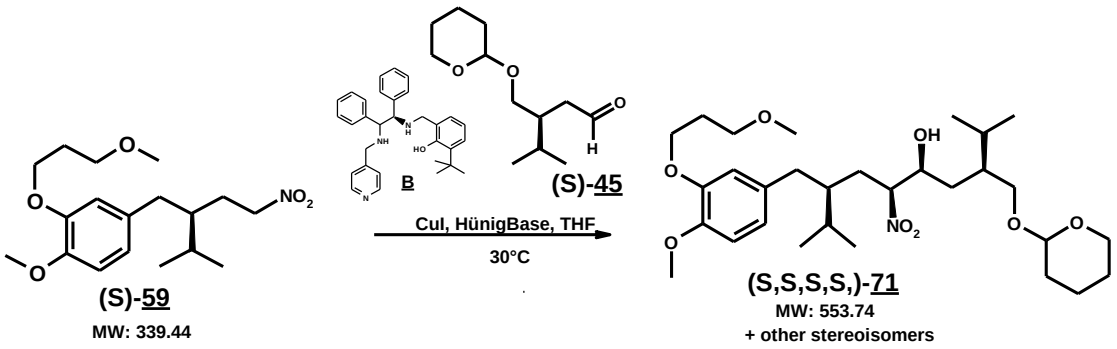
R_f (hexan/ethyl acetate 4:1) = 0.75



I.4.1. Preparation of 60

(3S,5S,6S,8S)-8-[4-methoxy-3-(3-methoxy-propoxy)-benzyl]-2,9-dimethyl-6-nitro-3-(tetrahydro-pyran-2-yloxymethyl)-decan-5-ol 71

Methode 1



51.9 mg of ligand (R,R)-**B** (0.11 mmol, 0.04 eq.) are diluted in 2 mL of THF at room temperature. After 12 min, 61.0 mg of CuI (0.32 mmol, 0.10 eq.) and 24.2 µL of Hünig base (0.08 mmol, 0.03 eq.), are added to the solution resulting in a slightly yellow suspension. The reaction is stirred for 45 min at 25°C, turning into a dark green suspension.

A solution of 1.009 g of nitro-compound **59** (2.9 mmol, 1.0 eq.) in 4 mL of THF and a solution of 850.8 mg of aldehyde component **45** (3.96 mmol, 1.3 eq.) in 4 mL of THF are added at room temperature. The reaction mixture is heated to 30°C and stirred at 30°C over a week. 213.3 mg of aldehyde

component **45** (0.19 mmol, 0.07 eq., bad quality, C=20%) are added to the reaction mixture, which is stirred over six days.

A pre-stirred (20 min at 25°C) suspension of 51.9 mg of ligand (0.11 mmol, 0.04 eq.), 81.0 mg of CuI (0.42 mmol, 0.14 eq.) and 12.2 µL of Hünig base (0.04 mmol, 0.01 eq.) in 500 µL of THF is added to reaction mixture at 30°C, followed by addition of 431.7 mg of a better quality of aldehyde **45** (2.01 mmol, 0.7 eq.). The reaction mixture is stirred over 2 days at 30°C. The reaction mixture is diluted in 10 mL of ethyl acetate at room temperature. The organic layer is washed two times with 50 mL of water, once with 60 mL of an aqueous solution of citric acid (10%), and again two times with 50 mL of water. The organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 2.575 g of crude product **71** in mixture with both reactants. The aqueous layer is extracted with 50 mL of dichloromethane. The organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 396.3 mg of crude product **71**.

Determination of the diastereoisomeric ratio of the crude material measured on CHIRALCEL OD-H (20°C, 93:7 hexane/isopropanol, isocratic, 1mL/min) reveals the presence of 66% of the major diastereoisomer.

The crude product (2.575 g) is purified by column chromatography on silicagel (0.040-0.063 nm) (75g) with heptan:ethyl acetate (4:1) to remove the unreacted starting material and give in the pure fractions 189.0 mg of **71** in mixture with nitro compound **59.**
The diastereoisomeric ratio of theses fractions measured on CHIRALCEL OD-H (20°C, 97:3, hexane/isopropanol, isocratic, 1mL/min) is 80 % of the major diastereoisomer.

588.0 mg of **71** (78% of major diastereoisomer, in mixture with nitro compound **59**) and 283 mg of **71** (66% of major diastereoisomer, in mixture with side product) are also isolated from this column chromatography.

The 189.0 mg of the purest fractions are purified again by column chromatography on silicagel (0.040-0.063 nm) (40g) with heptan:ethyl acetate (4:1), to give in the pure fractions 99.0 mg of **71** as isomeric mixture containing 80% of the major diastereoisomer and 74 mg of **71** as isomeric mixture containing 67% of the major diastereoisomer.

Yield: 40%

^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) (isomeric mixture)
0.69 - 0.76 (m, 1H, CH_{3iPr}), 0.76 - 0.89 (m, 10H, CH_{3iPr}), 0.90 - 0.96 (m, 1H, CH_{3iPr}) , 1.01 - 1.88 (m, 14H, $CH_{2\beta NO2}$, $CH_{2\alpha CH2OH}$, 3*CH_{2THP}, 2*CH_{iPr}, 2*$CHCH_{iPr}$), 1.89 - 1.98 (m, 2H, CH_{2MOP}), 2.16 (dd, J_1=13 Hz, J_2=9 Hz, 1H, HCH_{benz}), 2.35 - 2.48 (m, HCH_{benz}), 2.58 (dd, J_1=14 Hz, J_2=5Hz, , HCH_{benz}), 3.22 - 3.27 (m, 1H,CH_2OTHP), 3.43 (s, 3H, OCH_{3MOP}) 3.52 - 3.64 (m, 2 H), 3.37 - 3.43 (m, CH_{2THP}), 3.44 - 3.50 (m, 2H, CH_2O_{MOP}), 3.52 - 3.64 (m, 1H,CH_2OTHP), 3.72 (s, 3H, OCH_3), 3.73-3.75 (m, 1h, CHOH), 3.97 (t, J_1=6Hz, 2H, CH_2O_{MOP}), 4.08 - 4.16 (m, 1H, CH_{THP}), 4.41 - 4.58 (m, 1H, $CHNO_2$), 5.22 - 5.33 (m, 1H, OH), 6.52 - 6.72 (m, 1H, Harom), 6.75 (s, 1H, Harom) 6.77 - 7.05 (m, 1H, Harom)

^{13}C NMR (151 MHz, DMSO-d_6) δ_C (ppm) (isomeric mixture)
16.91-17.21-19.12-19.80-20.06 (CH_{3iPr}), 27.98 (CH_{iPr}), 25.18 (CH_{2THP}), 29.18 ($CH_{2MOP,}$ CH_2-$CHNO_2$, CH_2), 30.37 (CH_{2THP}), 31.56 (CH_{iPr}), 36.88 (CH_{2Bz}), 41.89 (CH-CH_{iPr}), 42.57 (CH-CH_{iPr}), 55.46 (O-CH_3), 58.01 (CH_{3MIP}), 61.07 (CH_2-OH), 65.27 (CH_{2MIP}), 68.65 (CH_{2MIP}), 70.63 (CH-OH), 93.64 (CH-NO_2), 98.23 (O-CH_{THP}), 111.80 ($CH_{arom.}$), 113.78 ($CH_{arom.}$), 120.93 ($CH_{arom.}$), 132.82 ($C_{arom.}$), 146.98 ($C_{arom.}$), 147.90 ($C_{arom.}$)

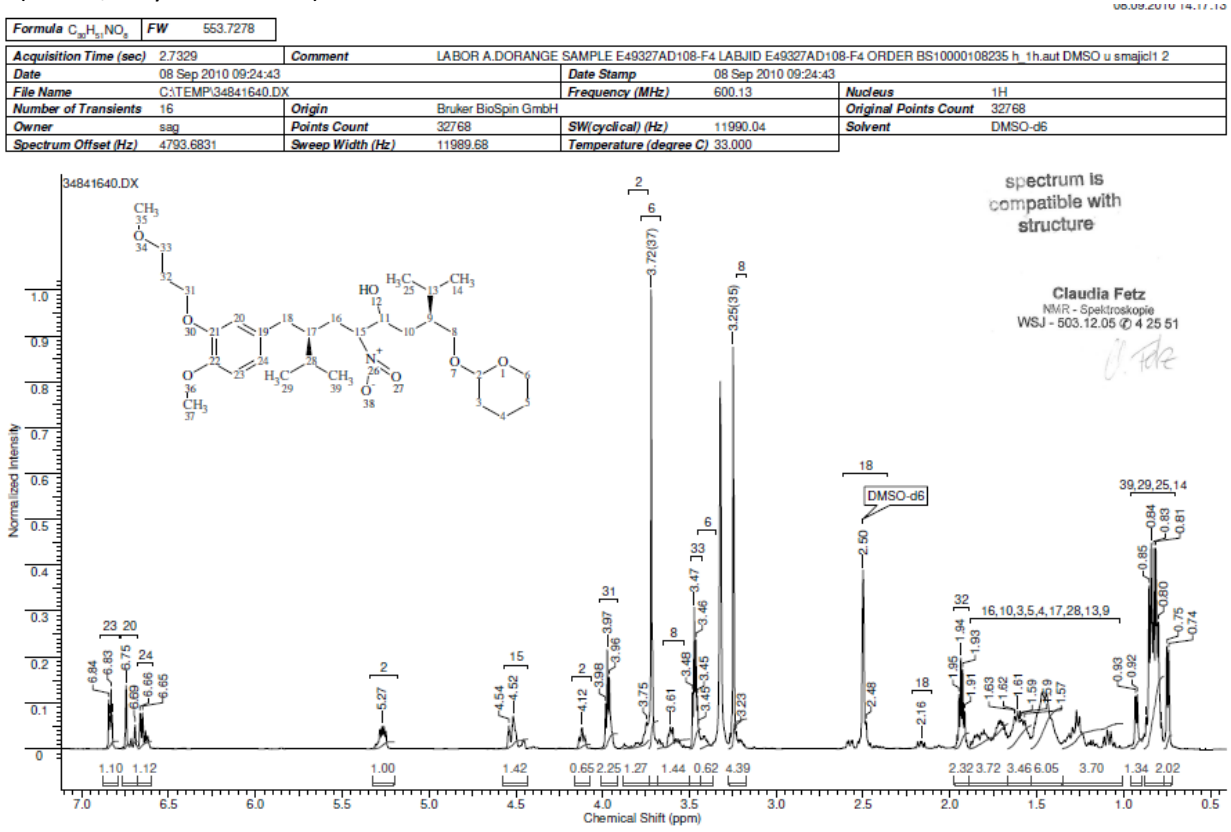
IR: (FTIR-microscopy in transmission)
3413 (OH), 2957 (C-Haliphatic), 1590-1516 (Phenyl), 1553 (NO_2, ν_{as}), 1386 (NO_2, ν_s), 1261 (Ph-O), 1121 (C-O-C), 1028 (C-O)

MS: (ES^+); $[M+NH_4^+]$ = 571.6, mixture of three isomers
(ES^-); $[M-h^-]$ = 552.5

HR-MS($C_{30}H_{51}O_8N$, 0.26 ppm): $[M+NH_4]^+$= 571.39529, cal. 571.39529, $C_{30}H_{55}O_8N_2$
$[M+Na]^+$= 576.35069, cal. 576.35034, $C_{30}H_{51}O_8NNa$

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 9.2 min (Diastereoisomer 1), tr = 9.4 min (Diastereoisomer 2), tr = 9.7 min (Diastereoisomer 2)

Rf (Hexan/Ethyl acetate 5:1) = 0.08



Methode 2 (Table 11, Entry 1)

To 15.4 mg of ligand (R,R)-**B** (0.03 mmol, 0.09 eq.) in 200 µL of dioxane are added at room temperature 10.5 mg of $Cu(OTf)_2$ (0.03 mmol, 0.09 eq.) and and 8 µL of Hünig base (0.04 mmol, 0.12 eq.). After 10 min, are added at 25°C a solution of 109.1 mg of nitro compound **59** (0.32 mmol, 1.00 eq.). in 700 µL of dioxan and a solution of 85.7 mg of aldehyde component **45** (0.39 mmol, 1.25 eq.) in 200 µL of dioxane. The reaction mixture is stirred at 25°C.
The diastereoisomeric ratio of theses fractions measured on CHIRALCEL OD-H (20°C, 97:3, hexane/isopropanol, isocratic, 1mL/min) is 72 % of the major diastereoisomer in a ratio of **72**:12:15.

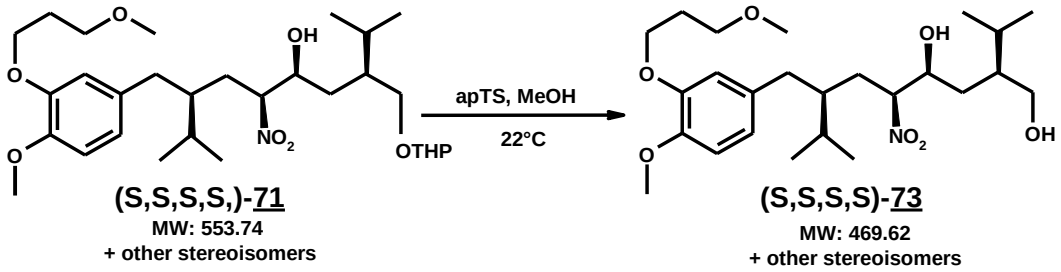
Methode 3 (**Table 11, Entry 2)**

108.1 mg of nitro compound **59** (0.31 mmol, 1.00 eq.) are diluted in 800 µL of ethanol. 81.6 mg of **45** (0.38 mmol, 1.23 eq.) and 20 µL of sparteine (0.1 mmol, 0.26 eq.). The reaction mixture is stirred at 25°C.
The diastereoisomeric ratio of theses fractions measured on CHIRALCEL OD-H (20°C, 97:3, hexane/isopropanol, isocratic, 1mL/min) is 72 % of the major diastereoisomer in a ratio of **50**:26:24.

Methode 3 (**Table 11, Entry 3)**

To 7.9 mg of Ligand (R,R)-**B** (0.017 mmol, 0.05 eq.) in 800 µL of THF are added at room temperature 2.0 mg of $CuOAc_2$ (0.017 mmol, 0.05 eq.) and 8 µL of Hünig base (0.04 mmol, 0.11 eq.). After 10 min, are added at 25°C a solution of 115.1 mg of nitro compound **59** (0.34 mmol, 1.00 eq.) in 200 µL of THF and 94.7 mg of **45** (0.44 mmol, 1.30 eq.). The reaction mixture is stirred at 25°C.
The diastereoisomeric ratio of theses fractions measured on CHIRALCEL OD-H (20°C, 97:3, hexane/isopropanol, isocratic, 1mL/min) is 72 % of the major diastereoisomer in a ratio of **67**:17:16.

(2S,4S,5S,7S)-2-isopropyl-7-[4-methoxy-3-(3-methoxy-propoxy)-benzyl]-8-methyl-5-nitro-nonane-1,4-diol 73



(S,S,S,S,)-71
MW: 553.74
+ other stereoisomers

(S,S,S,S)-73
MW: 469.62
+ other stereoisomers

210.8 mg of compound **71** (0.38 mmol, 1.0 eq.) are diluted in 4 mL of methanol at room temperature. 1.6 mg of p-toluenesulfonic acid monohydrate (0.008 mmol, 0.02 eq.) is added to the yellow solution at room temperature. After 45 min, 4.4 mg of p-toluenesulfonic acid monohydrate (0.023 mmol, 0.06 eq.) are added. The reaction mixture is allowed to stir for 5 hours and 1.1 mg of p-toluenesulfonic acid monohydrate (0.005 mmol, 0.01 eq.) is added, followed after one hour 30 min by addition of 3.1 mg of p-toluenesulfonic acid monohydrate (0.016 mmol, 0.04 eq.). After 30 min, all the starting material is consumed (HPLC control).
The reaction mixture is diluted with 10 mL of dichloromethane and the organic layer is washed with 10 mL of an aqueous solution of sodium bicarbonate (10%) (pH of the resulting aqueous phase is 9), with 10 mL of demineralized water (pH of the resulting aqueous phase is 6). The aqueous phase is extracted once with 10 mL of dichloromethane. The combined organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 659.0 mg of crude product **73.**

The crude product (659.0 mg) is purified by column chromatography on silicagel (0.040-0.063 nm) (40g) with heptan:ethyl acetate (3:1) to give in the pure fractions 138.5 mg of nitro-diol **73** (77%) as a colorless oil.

^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) (isomeric mixture)
0.71 - 0.89 (m, 12H, CH_{3iPr}), 0.99 - 1.15 (m, 1H, $CH_{2\alpha CH2OH}$), 1.19 - 1.33 (m, 2H, $CH_{2\alpha CH2OH}$, $CHCH_{iPr}$), 1.38 - 1.49 (m, 2H, $CHCH_{iPr}$, $CH_{2\beta NO2}$), 1.52 - 1.62 (m, 1H, CH_{iPr}), 1.65 - 1.84 (m, 1H, CH_{iPr}), 1.84 - 1.89 (m, 1H,

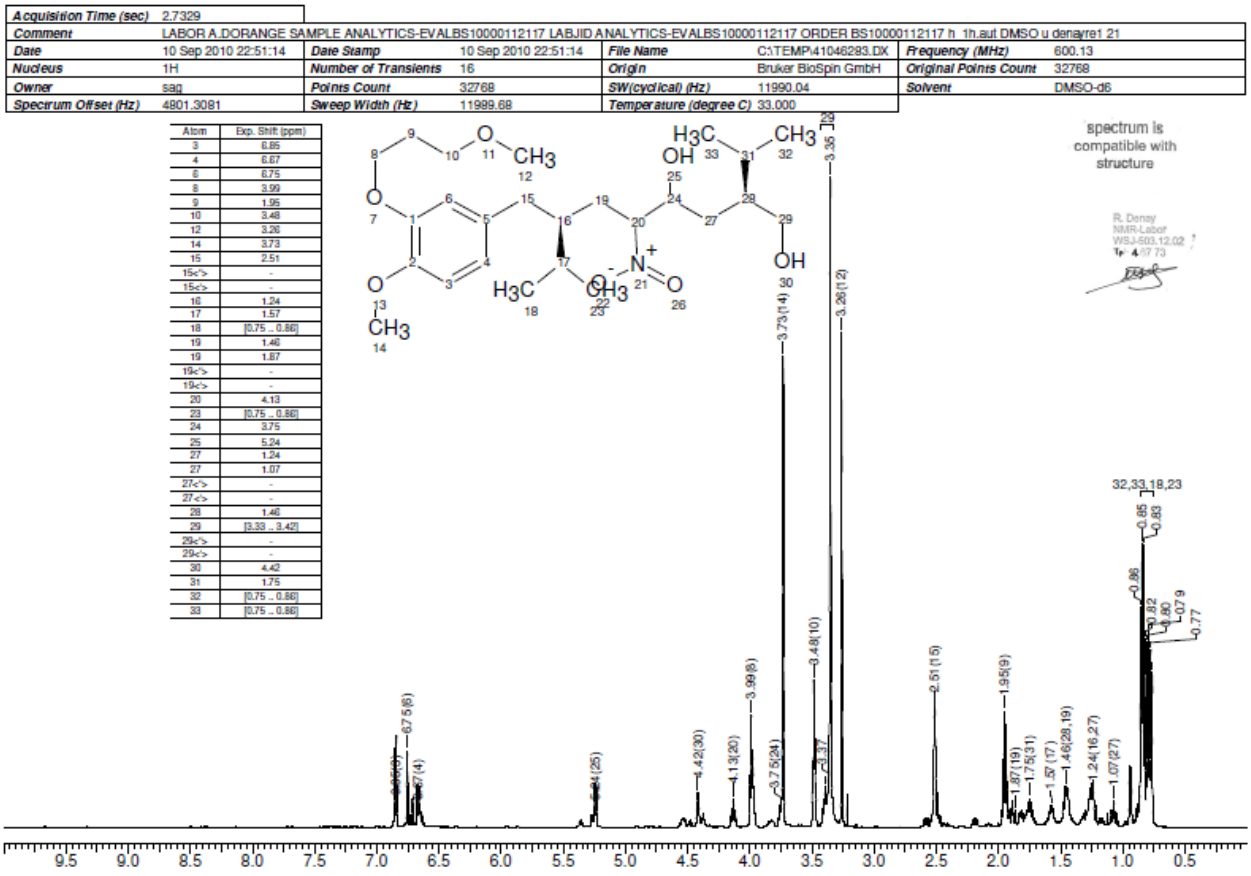
$\underline{CH_{2\beta NO2}}$), 1.93 (sxt, J_1=6 Hz, 2H, $\underline{CH_{2MOP}}$), 2.17 (dd, J_1=14 Hz, J_2=9Hz, 1H, H$\underline{CH_{benz}}$), 2.36- 2.63 (m, 1H, H$\underline{CH_{benz}}$), 3.25 (s, 3H, O$\underline{CH_{3MOP}}$), 3.26 - 3.42 (m, 2 H, $\underline{CH_2}$OH), 3.43 - 3.52 (m, 2H, $\underline{CH_2}O_{MOP}$), 3.73 (s, 3H, O$\underline{CH_3}$) 3.77 - 3.87 (m, 1H, $\underline{CH}$OH), 3.92 - 4.04 (m, 2H, $\underline{CH_2}O_{MOP}$), 4.07 - 4.17 (m, 1H, $\underline{CH}NO_2$), 4.34 - 4.58 (m, CH_2OH), 5.23 (d, J_1=6 Hz, CHOH), 5.26 (d, J_1=6 Hz, CHOH), 6.60 - 6.78 (m, 2H, Harom) 6.81 - 6.87 (m, 1H, Harom)

$^{13}\underline{C\ NMR}$ (151 MHz, DMSO-d_6) δ_C (ppm) (isomeric mixture)
17.07-18.77-19.86-20.50 (CH_{3iPr}), 27.98 (CH_{iPr}), 29.17 ($CH_{2MOP,}$ $\underline{CH_2}$-$CHNO_2$, CH_2), 31.29 (CH_{iPr}), 36.89 (CH_{2Bz}), 42.68 (CH-CH_{iPr}), 55.48 (O-CH_3), 58.03 (CH_{3MIP}), 61.01 (CH_2-OH), 65.28 (CH_{2MIP}), 68.66 (CH_{2MIP}), 70.27 (CH-OH), 93.92 (CH-NO_2), 111.84 ($CH_{arom.}$), 113.90 ($CH_{arom.}$), 121.06 ($CH_{arom.}$), 133.15 ($C_{arom.}$), 147.30 ($C_{arom.}$), 147.90 ($C_{arom.}$)

IR: (FTIR-microscopy in transmission)
3380 (OH), 2958-2933 (C-Haliphatic), 1590-1516 (Phenyl), 1553 (NO_2, ν_{as}), 1388 (CH_3, δ), 1370 (NO_2, ν_s), 1261 (Ph-O), 1121 (C-O-C), 1029 (C-O)

MS: (ES^+); [M-H^+] = 470, mixture of three isomers

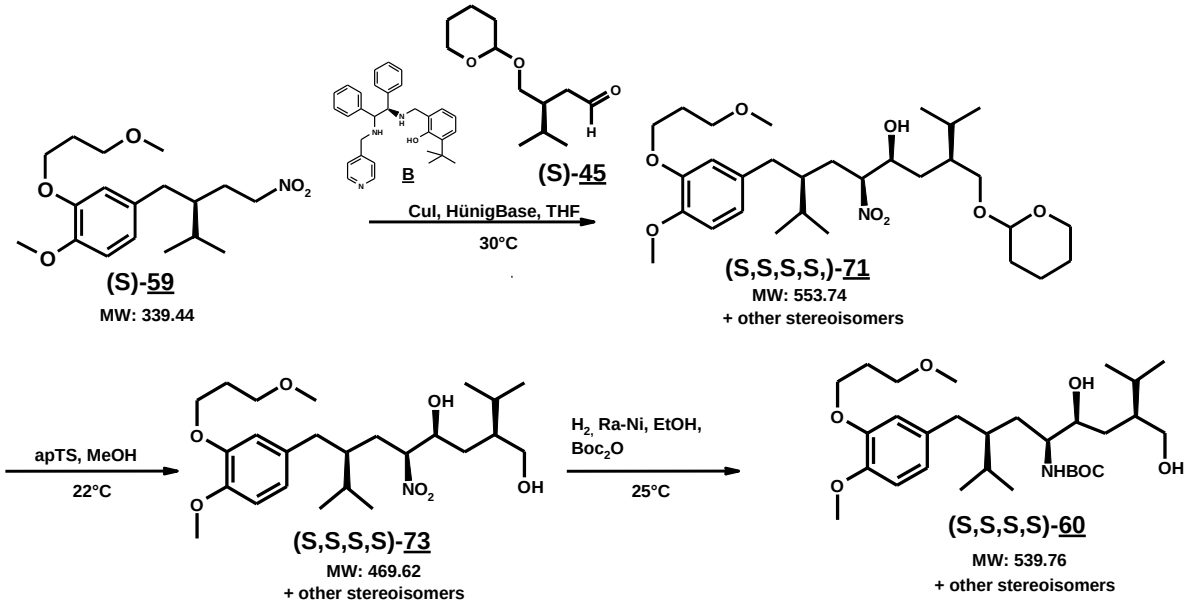
HRMS ($C_{25}H_{44}O_7N$, 0.2 ppm/MH+): [M+H] $^+$= 470.31131, cal. 470.31123, $C_{25}H_{44}O_7N$



HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 7.5 min

R_f (hexan/ethyl acetate 1:1) = 0.29

((1S,2S,4S)-2-hydroxy-4-hydroxymethyl-1-{(S)-2-[4-methoxy-3-(3-methoxy-propoxy)-benzyl]-3-methyl-butyl}-5-methyl-hexyl)-carbamic acid tert-butyl ester 60



5.7 mg of ligand (R,R)-**B** (0.01 mmol, 0.04 eq.) are diluted in 0.5 mL of THF at room temperature. After 15 min, 5.5 mg of CuI (0.03 mmol, 0.10 eq.) and 2 µL of Hünig base (0.008 mmol, 0.03 eq.), are added to the solution, resulting in a slightly yellow suspension. The reaction is stirred for 20 min at 25°C, turning into a dark green suspension.

A solution of 100.1 mg of nitro-compound **59** (0.3 mmol, 1.0 eq.) in 0.5 mL of THF and 121.6 mg of aldehyde component **45** (0.5 mmol, 1.6 eq.) are added at room temperature. The reaction mixture is heated to 35°C and stirred at 35°C over three days. The reaction mixture is cooled down to room temperature and diluted with 15 mL of dichloromethane. The organic layer is washed once with 20 mL and once with 10 mL of demineralized water. The organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 151.0 mg of crude product **71** in mixture with nitro-compound **59** (10%) and aldehyde component **45** (47%).

The diastereoisomeric ratio of the crude material measured on CHIRALCEL OD-H (20°C, 93:7 hexane/isopropanol, isocratic, 1mL/min) is 66% of the major diastereoisomer.

The crude product (151.0 mg) is diluted in 1 mL of methanol and 3.1 mg of p-toluenesulfonic acid monohydrate (0.016 mmol). The reaction mixture is stirred at room temperature over a period of 45 min, and 15 mL of demineralited water are added. The acidic aqueous phase is extracted twice with 20 mL of dichloromethane. The organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 107.0 mg of crude product **73.**

The crude product is purified again by column chromatography on silicagel (0.040-0.063 nm) (10g) with heptan:ethyl acetate (3:1) to give in the pure fractions 63.0 mg of **73** as isomeric mixture containing 58% of the major diastereoisomer.

63.0 mg of compound **73** (0.13 mmol, 1.0 eq.) are diluted in 2.2 mL of ethanol at room temperature. 31.3 mg of Boc_2O (0.14 mmol, 1.1 eq.) and 30.0 mg of $nickel_{raney}$ in suspension in water are added to the reaction mixture. The mixture is hydrogenated at normal pressure and room temperature over night (16 hours). The catalyst is filtered off and washed with 10 mL of ethanol. The solvent is removed in vacuum to give an oil which is purified by chromatography to remove the excess of Boc_2O.

The column chromatography on silicagel (0.040-0.063 nm) (15g) with heptan:ethyl acetate (2:1) gives in the pure fractions 28.0 mg of **60** (17%, over three steps) as a colorless oil.

The measurement of the diastereoisomeric excess on CHIRALCEL OD-H (20°C, 93:7 hexane/isopropanol, isocratic, 1mL/min) shows the presence of the desired (S,S,S,S)-diastereoisomer as the major one at 7.6 min.
The ^{1}H NMR spectrum (DMSO-d_6, 400 MHz) proves also the presence of a majority of diastereoisomer with the desired (S) stereochemistry on the amino group.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm)
0.65 - 0.89 (m, 12H, CH_{3iPr}), 1.15-1.43 (m, 4H, CH_2) 1.43 (s, 9H, CH_{3Boc}), 1.43-1.96 (m, CH_{iPr}, CH-CH_{iPr}, CH_{2MIP}), 2.15 - 2.70 (m, 2H, CH_{2Benz}), 3.26 (m, 3H. OCH_{3MIP}), 3.40 - 3.49 (m, 5H, CH_{2MIP}, CH_2O, CHO), (3.69-3.72 s, 3H, OCH_{3Dia}), 3.74 (s, 3H, OCH_3), 3.91 - 4.00 (m, 2H, CH_{2MIP}), 4.20 - 4.30 (m, 1H, C<u>H</u>NH_{Boc}), 4.22- 4.67 (m, C<u>H</u>NH_{BocDia}), 6.04 - 6.15 (m, 1H, NH_{Boc}), 6.41 - 6.49 (m, $NH_{BocDia2}$), 6.60 - 6.73 (m, 1H, CH_{arom}), 6.73 - 6.88 (m, 2H, CH_{arom})

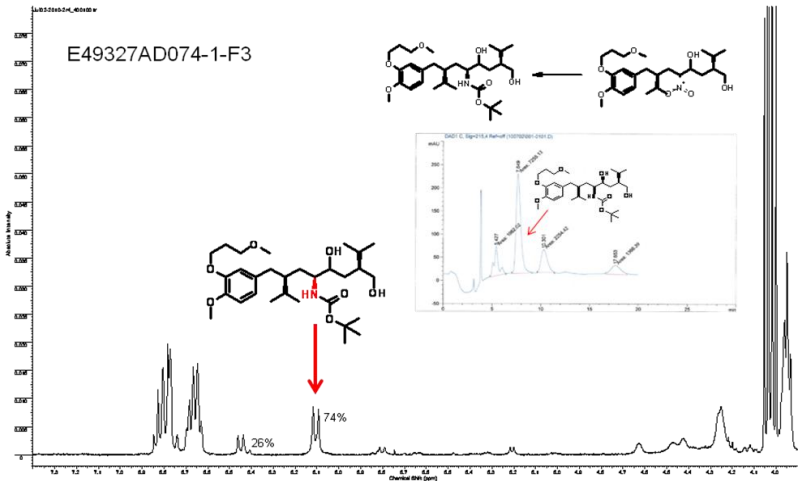
^{13}C NMR (151MHz, DMSO-d_6) δ_C (ppm)
18.33 (CH_{3iPr}), 20.48 (CH_{3iPr}), 27.58-28.30 (CH_{3Boc}), 29.18 (CH_{iPr}), 33.63 (<u>C</u>H_2), 34.94 (<u>C</u>H_2-CH-NH_{Boc}), 36.59 (CH_{2Bz}), 41.78 (<u>C</u>H-CH_{iPr}), 52.97 (CH-NH_{Boc}), 55.47 (CH_{3Boc}), 57.99 (CH_{3MOP}), 61.48 (CH_2-OH), 65.17 (CH_{2MOP}), 68.60 (CH_{2MOP}), 71.08 (CH-OH), 77.41 (C_{Boc}), 111.64 (CH_{arom}), 113.75 (CH_{arom}), 121.12 (CH_{arom}), 134.18 (C_{arom}), 146.98 (C_{arom}), 147.78 (CH_{arom}), 156.52 ($C{=}O_{Boc}$)

<u>LC-MS</u> : $M\text{-}H^+$= 540.4, $M+Na^+$=562.4

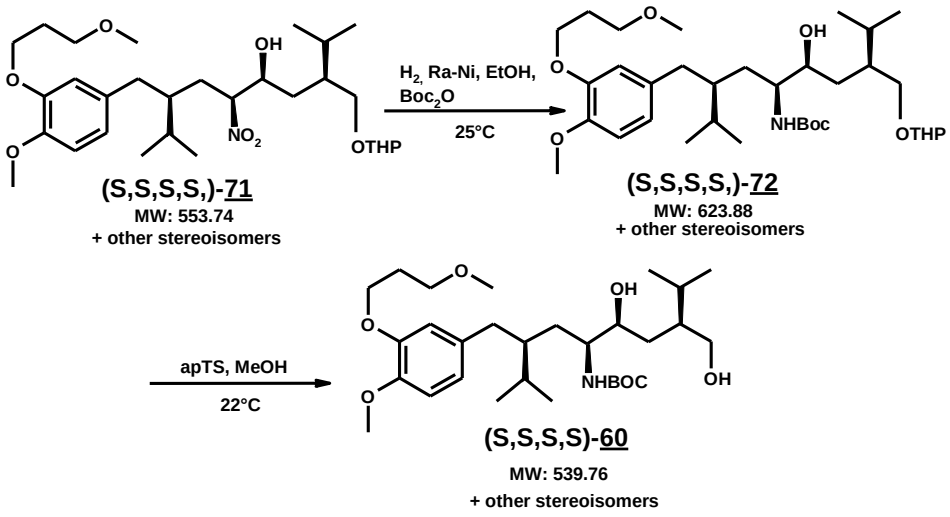
<u>HPLC method</u>: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 7.8 min

<u>HRMS</u> ($C_{30}H_{53}O_7N$, 0.5 ppm/MH+): $[M+H]^+$= 540.38922, cal. 540.38948, $C_{30}H_{54}O_7N$

Rf (hexan/ethyl acetate 2:1) = 0.11



((1S,2S,4S)-2-hydroxy-4-hydroxymethyl-1-{(S)-2-[4-methoxy-3-(3-methoxy-propoxy)-benzyl]-3-methyl-butyl}-5-methyl-hexyl)-carbamic acid tert-butyl ester 60

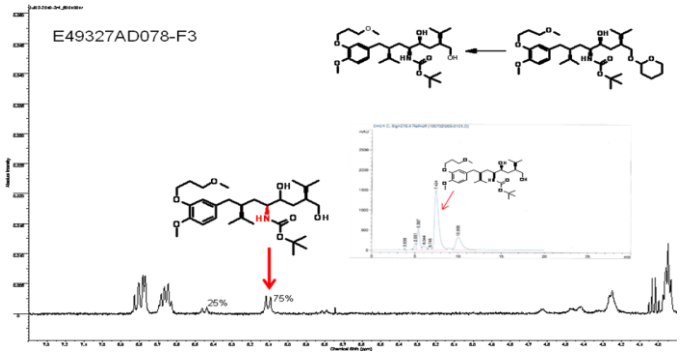


76.5 mg of compound **71** (0.14 mmol, 1.0 eq.) (containing the major diastereoisomer with a ratio of 60:20:20) are diluted in 2 mL of ethanol at room temperature. 35.2 mg of Boc_2O (0.16 mmol, 1.1 eq.) and 35.0 mg of $nickel_{raney}$ in suspension in water are added to the reaction mixture. The mixture is hydrogenated at normal pressure and room temperature over night (16 hours). The catalyst is filtered off and washed with 10 mL of ethanol. The solvent is removed in vacuum to give **72** in mixture with Boc_2O.

81.9 mg of compound **72** (0.13 mmol, 1.0 eq.) are diluted in 2 mL of methanol at room temperature. 16.5 mg of p-toluenesulfonic acid monohydrate (0.008 mmol, 0.07 eq.) are added at room temperature. The reaction mixture is allowed to stir for 55 min until completion of the reaction (HPLC control). The reaction mixture is diluted with 7 mL of dichloromethane and the organic layer is washed two times with 15 mL of demineralized water. The organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 68.1 mg of crude product **60** (97%).

The crude product (68.1 mg) is purified by column chromatography on silicagel (0.040-0.063 nm) (500 mg) with first, heptan:ethyl acetate (2:1) and then pure ethyl acetate to give in the pure fractions 31.0 mg of **60** (41% from Henry product **71**) as a colorless oil.

The measurement of the diastereoisomeric ratio on CHIRALCEL OD-H (20°C, 93:7 hexane/isopropanol, isocratic, 1mL/min) shows the presence of the desired diastereoisomer (S,S,S,S) as the major one at 7.6 min.
The ^{1}H NMR spectrum (DMSO-d_6, 400 MHz) proves also the presence of a majority of diastereoisomer with the desired (S) stereochemistry on the amino group.



^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm)
0.68 - 0.91 (m, 12H, CH_{3iPr}), 1.03-1.25 (m, 4H, CH_2), 1.43 (s, 9H, CH_{3Boc}), 1.43-1.96 (m, CH_{iPr}, CH-CH_{iPr}, CH_{2MIP}), 2.17 - 2.71 (m, 2H, CH_{2Benz}), 3.30 (s, 3H. OCH_{3MIP}), 3.37 - 3.457 (m, 5H, CH_{2MIP}, CH_2O, CHO), 3.76 (s, 3H, OCH_3), 3.90 - 4.00 (m, 2H, CH_{2MIP}), 4.23 - 4.36 (m, 1H, C<u>H</u>NH_{Boc}), 4.36- 4.69 (m, C<u>H</u>NH_{BocDia}), 6.05 - 6.16 (m, 1H, NH_{Boc}), 6.41 - 6.50 (m, $NH_{BocDia2}$), 6.74 - 6.86 (m, 1H, CH_{arom}), 6.73 - 6.88 (m, 2H, CH_{arom})

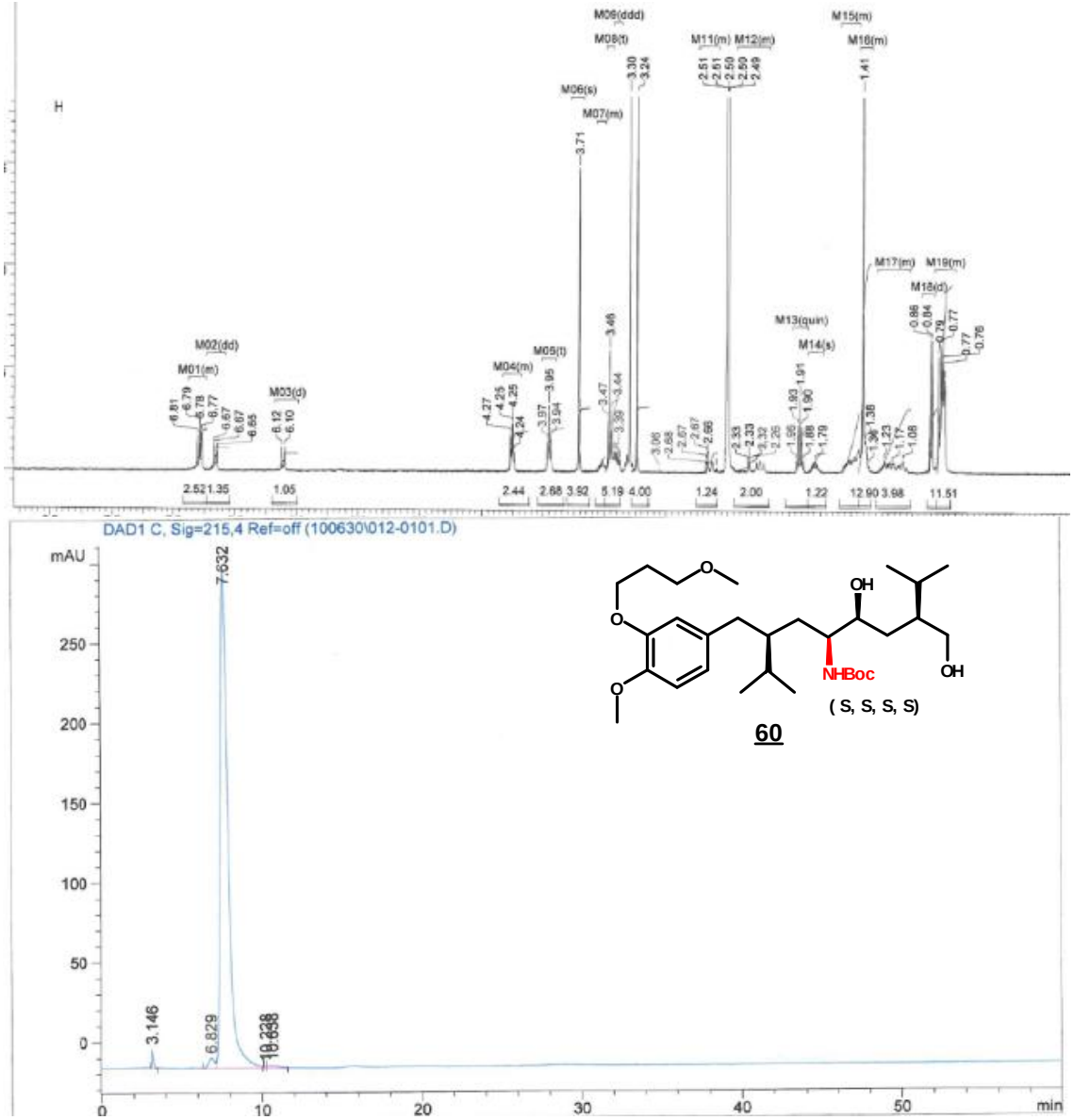
HRMS ($C_{30}H_{53}O_7N$, 0.9 ppm/MH+): $[M+H]^+$= 540.38995, cal. 540.38948, $C_{30}H_{54}O_7N$

LC-MS : $M\text{-}H^+$= 540.4, $M+Na^+$=562.4

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 7.8 min

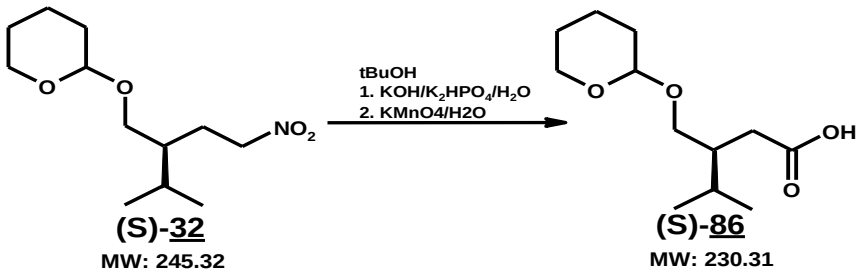
Rf (hexan/ethyl acetate 2:1) = 0.11

*[1]HNMR (DMSO-d6) and chiral HPLC (CHIRALPAK AD-H) of the (S,S,S,S) configured isomer of **60**. It was prepared in the laboratory by B. Berod from the API- intermediate **9***



I.5. Alternative synthesis: pathway A

(S)-4-methyl-3-(tetrahydro-pyran-2-yloxymethyl)-pentanoic acid 86



2.00 g of compound **32** (8.1 mmol, 1.0 eq.) are dissolved at room temperature under argon atmosphere in 38 mL of *t*-butanol. An aqueous solution of 1.31 g of potassium hydroxide (0.5M) (23.4 mmol, 2.8 eq.) 9 mL of methyl butene (83.4 mmol, 9.2 eq.) are added to the mixture. The exothermic addition of a solution of 1.22 g of $NaClO_2$ (13.5 mmol, 1.5 eq.) and of 1.87 g of KH_2PO_4 (83.4 mmol, 9.2 eq.) in 10 mL of demineralized water is performed at 0°C over a period of 5 min. The reaction mixture is allowed stir over 45 min until completion of the reaction (HPLC control). Both phases are then separated. The aqueous phase is acidified to pH 5 by addition of 15 mL of an aqueous solution of citric acid 10% and extracted twice with 30 mL of toluene. The organic phases are dried over $MgSO_4$ and concentrated in vacuum to yield 1.74 g of crude product **86** as a colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm) (mixture of diastereoisomers 1:1)
0.77 - 0.94 (m, 6H, CH_{3iPr}), 1.34 - 1.53 (m, 4H, 2*CH_{2THP}), 1.59 (m, 1H, CH_{iPr}), 1.65-1.82 (m, 2H, CH_{2THP}), 1.88-1.95 (m, 1H, C<u>H</u>-CH_{iPr}), 2.07 - 2.31 (m, 2H, C<u>H$_2$</u>CO_2H), [3.17-3.21 (m, 0.5H), 3.27-3.31 (m, 0.8H), 3.40-3.43 (m, 1H), 3.51-3.55 (m, 0.5H), 3.59-3.63 (m, 0.5H), 3.77-3.74 (m, 1H)] (CH_2-0, CH_2-O_{THP}), 4.51 (m, 1H, CH_{THP}), 11.98 (br. s., 1H, CO_2<u>H</u>)

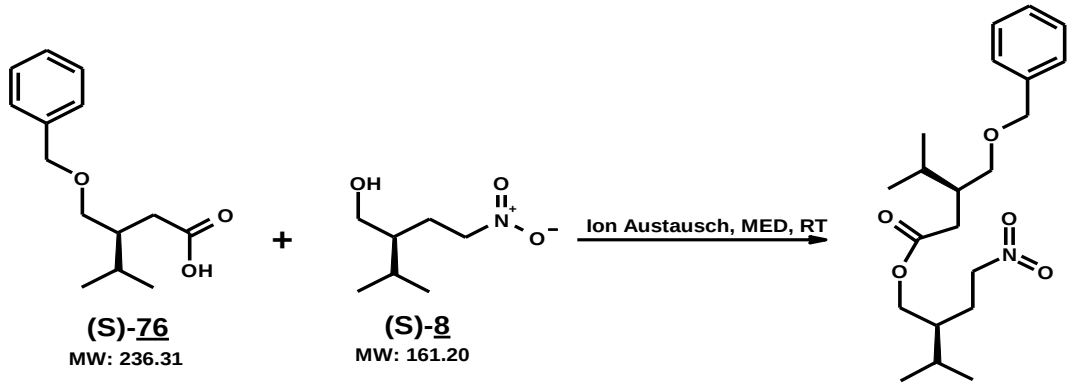
^{13}C NMR (101 MHz, DMSO-d_6) δ_C (ppm) (mixture of diastereoisomers 1:1)
18.87, 18.97, 19.01, 19.17,19.47,19.56 ($CH_{3iPr,}$ CH_{2THP}), 25.04 (CH_{2THP}), 27.83-28.04 (CH_{iPr}) 30.18 (CH_{2THP}), 33.28-33.56 (<u>C</u>H-CH_{iPr}), 40.52-40.60 (<u>C</u>H_2CO_2H, 61.07 (CH_2-O_{THP}), 67.54-67.64 (CH_2-0), 97.90-98.04 (CH_{THP}), 174.31 (CO_2H)

IR: (FTIR-microscopy in transmission)
3300-2600 (OH_{acid}), 2957 (C-$H_{aliphatic}$), 1708 (C=O_{acid}), 1388-1354 (C-$H_{3\delta}$), 1284 (C-O_{acid}), 1120-1024 (C-O)

MS: (ES$^+$) $[M+Na]^+$ = 253.4
$[M-H]^-$ = 229.3

HRMS ($C_{12}H_{22}O_4N$, 0.07 ppm/MH+): $[MH]^+$= 231.15910, cal. 231.15909, $C_{12}H_{23}O_4N$

(S)-3-benzyloxymethyl-4-methyl-pentanoic acid (S)-3-methyl-2-(2-nitro-ethyl)-butyl ester 82



(S)-76
MW: 236.31

(S)-8
MW: 161.20

(S,S)-82
MW: 379.50

1.06 g of acid **76** (4.5 mmol, 1.0 eq.) are dissolved at room temperature in 11 mL of dichloromethane. 8.92 mg of Amberlyst 15 are then added at room temperature. The reaction mixture is diluted in 6 mL of dichloromethane. After 7 min, 804.1 mg of nitro alcohol **8** (5.0 mmol, 1.1 eq.) are added and the reaction mixture is allowed to stir at room temperature over 5 days. 5 mL of dichloromethane are then added to the mixture and the Amberlyst 15 is filtered off and washed with 75 mL of dichloromethane. The organic phase is concentrated in vacuum to yield 1.63 g of crude product **82** as a yellow oil.
The crude product is purified by column chromatography on silicagel (30 g) with heptane/ethyl acetate (6:1) to give in the purest fractions 1.024 g of the desired ester (59%).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm)
0.75 - 0.91 (m, 12H, CH_{3iPr}), 1.37 - 1.56 (m, 1H, C<u>H</u>-CH_{iPr}), 1.64 - 1.88 (m, 3H, <u>H</u>CHNO_2,2*CH_{iPr}), 1.92 - 2.09 (m, 2H, C<u>H</u>-CH_{iPr}, HC<u>H</u>NO_2), 2.19 - 2.30 (m, 1H, <u>H</u>CH-C=O), 2.30 - 2.39 (m, 1H, HC<u>H</u>-C=O), 3.26 - 3.37 (m, 1H, <u>H</u>CH-O-CH_{2Benz}) 3.43 (dd, J_1=9 Hz, J_2=5Hz, 1H, HC<u>H</u>-O-CH_{2Benz}), 3.86 (dd, J_1=11 Hz, J_2=6 Hz, 1H, <u>H</u>CH-O-C=O), 3.95 - 4.05 (m, 1H, HC<u>H</u>-O-C=O), 4.42 (s, 2H, CH_{2Benz}), 4.49 - 4.68 (m, 2H, CH_2NO_2), 7.05 - 7.61 (m, 5H, CH_{arom})

^{13}C NMR (101 MHz, DMSO-d_6) δ_C (ppm)
19.01 (CH_{3iPr}), 19.05 (CH_{3iPr}), 19.53 (CH_{3iPr}), 25.89 (<u>C</u>H_2 CH_2NO_2), 28.11 (CH_{iPr}), 33.73 (<u>C</u>H_2C=O), 36.02 (CH_{iPr}), 39.85 (CH-CH_{iPr}), 40.88 (CH-CH_{iPr}), 64.33 (<u>C</u>H_2-O-C=O) 70.84 (<u>C</u>H_2-O-CH_{2Benz}), 72.10 (CH_{2Benz}), 74.01 (CH_2NO_2), 127.33 (CH_{arom}), 128.16 (CH_{arom}), 137.9 (C_{arom}), 172.71 (C=O),

<u>IR</u>: (FTIR-microscopy in transmission)
3031 (C-$H_{aromatic}$), 2962 (C-$H_{aliphatic}$), 1734 (C=O_{ester}), 1554 (NO_{2vas}), 1496 (phenyl), 1455 (phenyl), 1371 (NO_{2vs}), 1251 (C-O_{ester}), 1169-1104 (C-O), 1028 (C-$H_{\delta monosubst.}$), 738 (C-$H_{\delta monosubst.}$), 699 (Phenyl$_{\delta monosubst.}$),

<u>MS</u>: (ES^+) MH^+ = 380

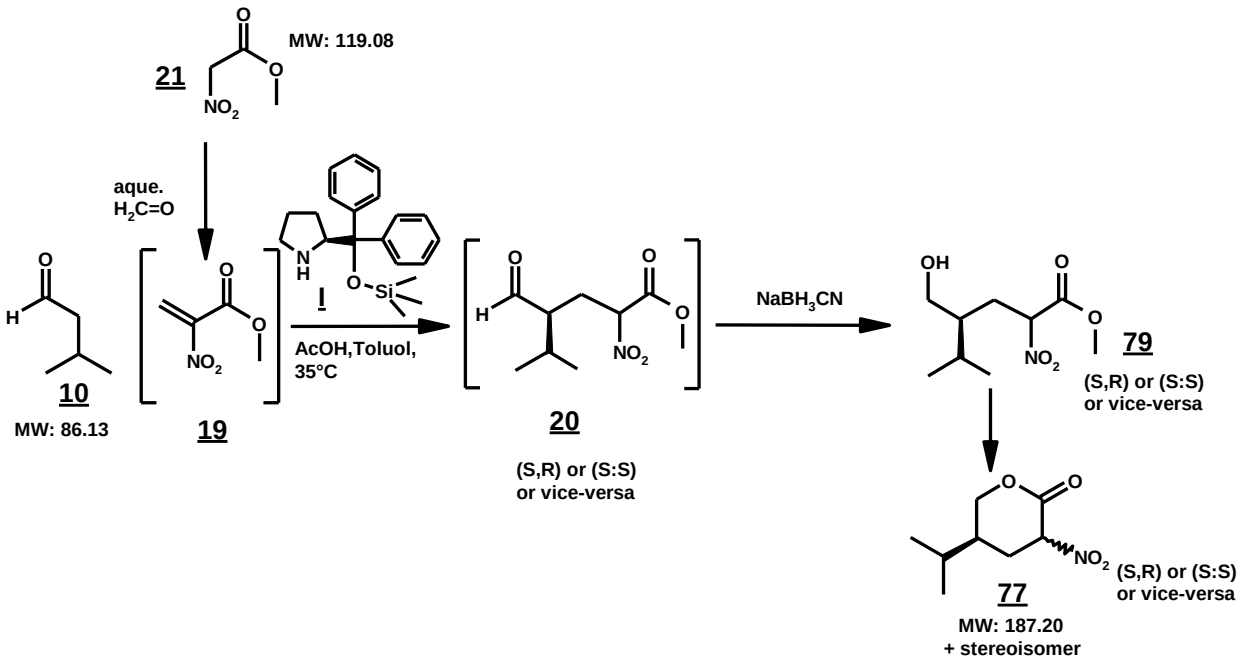
<u>HRMS</u> ($C_{21}H_{33}O_5N$, 0.2 ppm/MH+): $[MH]^+$= 380.24323, cal. 380.24315, $C_{21}H_{34}O_5N$

<u>HPLC method</u>: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 5.9 min

Rf (hexan/ethyl acetate 5:1) = 0.50

I.6. Alternative synthesis : pathway B

(S, R) and (S, S) -4-hydroxymethyl-5-methyl-2-nitro-hexanoic acid methyl ester 79; (S, R) and (S, S)-5-Isopropyl-3-nitro-tetrahydro-pyran-2-one 77

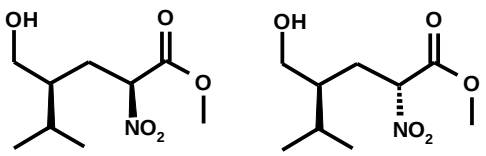


338.2 mg of (S)-diphenyl-prolinol-O-TMS-ether **I** (0.89 mmol, 0.08 eq.) are dissolved in 40 mL THF. 1.7 mL of acetic acid (30 mmol, 2.5 eq.) and 1.3 mL of isovaleraldehyde **10** (12 mmol, 1.0 eq.) are added to the mixture at room temperature. The mixture is then warmed to 35°C. A solution of 1.497 g of methyl nitroacetate **21** (12 mmol, 1.0 eq.) in 20 mL of THF and a solution of 1.124 g of formaldehyde (~37% in water) (13 mmol, 1.0 eq.) in 20 mL of THF are added simultaneously at 35°C for 20 min. This solution is then stirred at 35°C during 25 min., until complete conversion of nitroacetate is detected (HPLC control).
The reaction mixture is cooled down to 0°C and 5.812 g of $NaBH_3CN$ (92.4 mmol, 7.7 eq.) are added in five portions over a period of 1 hour 40 minutes. (pH=6).
The reaction mixture is quenched with 20 mL of water, and extracted with 100 mL of ethyl acetate. The organic phase is dried over $MgSO_4$, and concentrated in vacuum to yield 760 mg of crude product.
The aqueous phase is again extracted two times with 100 mL of ethyl acetate. The organic phase is dried over $MgSO_4$, and concentrated in vacuum to yield 113 mg of crude product.
The crude product is purified by column chromatography on silicagel (20 g) with heptane/ethyl acetate (3:1) to give in the pure fractions the desired alcohol **79** in mixture with the corresponding lactone **77**.

Determination of the diastereoisomeric ratio of the alcohol **79** by ^{1}H-NMR ($CDCl_3$, 400 MHz) shows the presence of 71% of the diastereoisomere A and 29% of the diastereoisomere B. Addition of trifluoracetic acid to a mixture of alcohol **79**-lactone **77** mixture leads to the formation of pure lactone **77**.

Spectroscopic data of methyl ester nitroalcohol 79:

79



A **or vice-versa** **B**

MW: 219.24 **MW: 219.24**

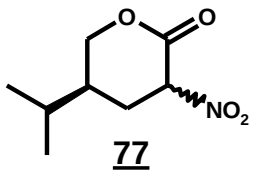
^{1}H-NMR: (400 MHz, $CDCl_3$) δ_H (ppm)
[0.90 - 0.97 (m, $CH_{3iPr\ Dia1}$), 0.97 - 1.05 (m, $CH_{3iPr\ Dia2}$)], 1.69 - 1.85 (m, 1H, CHiPr,), 2.08 - 2.18 (m, 1H, CH_2CHNO_2), 2.32 (t, J_1=7 Hz, 1H, CH_{iPr}) 2.38 - 2.52, (m, 1H, CH_2CHNO_2), [3.52 - 3.69 (m, CH_2OH), 3.71 - 3.83 (m, 1H, CH_2OH), 2H], [3.83 (s, $CH_{3ester\ dia1}$), 3.89 (s, $CH_{3ester\ dia2}$), 3H], [5.46 (t, J=7 Hz, $CHNO_{2\ dia1}$) 5.64 (dd, J_1=11 Hz, J_2= 3 Hz, $CHNO_{2\ dia2}$), 1H]

IR: (FTIR-microscopy in transmission)
3422 (OH), 2962 (CH-aliphatic), 2879 (O-CH_3), 1754 (C=O ester), 1562 (NO_2 ν_{as}), 1371 (NO_2 ν_s), 1258 (C-O), 1015 (C-O)

MS: MH^+ = 220, $M+NH_4^+$ = 237

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm. t_r=3.4/3.6 min

Spectroscopic data of lactone derivative **77:**



77 **(S,R) or (S:S) or vice-versa**

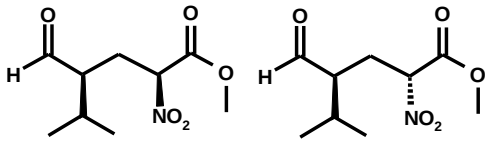
MW: 187.20

^{1}H-NMR: (400 MHz, $CDCl_3$) δ_H (ppm) (isomeric mixure 50:50 cis/trans)
0.66 - 1.03 (m, 6H, CH_{3iPr}), 1.51 - 1.72 (m, 1H, CH_{iPr}), 1.91 - 2.02 (m, 1H, CHiPr), 2.14 (td, J_1=12 Hz, J_2=10 Hz, 0.5H, CH_2-CH-NO_2), 2.32 - 2.45 (m, 1H, CH_2-CH-NO_2), 2.62 (dd, J_1=7 Hz, J_2=5 Hz, 0.5H, CH_2-CH-NO_2), 4.13 - 4.33 (m, 1H, CH_2-O), 4.33 - 4.41 (m, 0.5H, CH_2-O) 4.45 (ddd, J_1=11 Hz, J_2=5 Hz, J_3=1 Hz, 0.5H, CH_2-O), 5.98 (dd, 0.5H, CH-NO_{2cis}), 6.04 (t, J_1=9 Hz, 0.5H, CH-NO_{2trans})

IR: (FTIR-microscopy in transmission)
2964, 2930 (C-H aliphatic), 1757 (C=O lactone), 1565 (NO_2 ν_{as}), 1373($C(CH_3)_2$), 1347 (NO_2 ν_s), 1265 (C-O), 1015 (C-O)

MS: MH^+ = 188, $M+NH_4^+$ = 205
MH^- = 186

Spectroscopic data of nitro-aldehyde 20:



A or vice-versa **B**

20

MW: 217.22

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ_H (ppm) *mixture of two diastereoisomers*
0.94 - 1.07 (m, 6H, CH_{3iPr}), 2.19 - 2.34 (m, 3H) 2.40 - 2.62 (m, 1H, CH_2CHNO_2), [3.84 (s, $CH_{3ester\ dia1}$), 3.86 (s, $CH_{3ester\ dia2}$), 3H], [5.22 (dd, J_1=9Hz, J_2=5Hz, $CHNO_{2\ dia1}$), 5.25 - 5.32 (m, $CHNO_{2\ dia2}$), 1H], 9.70 (d, *J*=6Hz, 1H, HC=O)

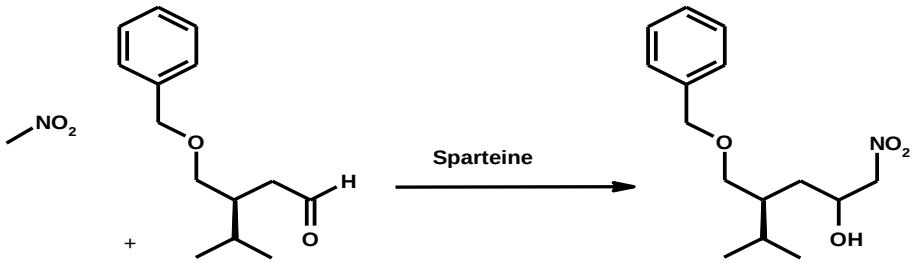
MS: MH^+= 218, $M+NH_4^+$= 235

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220 nm. t_r=4.8 min

I.7. Synthesis of Aliskiren: Pathway C

(S)-4-benzyloxymethyl-5-methyl-1-nitro-hexan-2-ol 87

Methode 1



27 MW: 61.04 + **28** MW: 220.31 → **87** (S,R):(S,S) MW: 281.35

443.2 mg of compound **28** (2.0 mmol, 1.0 eq.) are diluted at room temperature in 163.2 mg of nitromethane **27** (2.7 mmol, 1.3 eq.). 182.7 mg of sparteine (19.7 mmol, 0.78 eq.) are then added at room temperature. The reaction mixture is heated to 30°C and is stirred overnight (15 hours). After cooling to room temperature, the reaction mixture is diluted in 10 mL of ethyl acetate. The resulting organic layer is extracted three times with 10 mL of demineralized water, and the coresponding aqueous phase is extracted with 10 ml of ethyl acetate. The organic phase is dried over $MgSO_4$ and concentrated in vacuum to yield 339.0 mg of crude product **87** as a yellow liquid.

The crude material is purified by column chromatography on silicagel (0.040-0.063 nm) (50g) with heptane:ethyl acetate (4:1) to give in the pure fractions 254 mg (45%) of nitroaldol compound **87** as an isomeric mixture (*syn/anti* 60:40)

^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) (mixture of diastereoisomer ≈ 60/40)
0.82-0.91 (m, 6H, CH_{3iPr}), 1.28-1.44 (m, 2H, CH_2-CHOH), 1.63 - 1.66 (m, 0.4H, CH-$CH_{iPr,\ Dia2}$) 1.66 - 1.70 (m, 0.6H, CH-$CH_{iPr\ Dia1}$), 1.76 - 1.85 (m, 1H, CH-CH_{iPr}), 3.33-3.43 (m, 2H, CH_2-O), 4.13-4.23 (m, 1H, CHOH), 4.20 - 4.36 (m, 1H, $HCHNO_2$), 4.40-4.51 (m, 2H, CH_{2Benz}), 4.66 (dd, J_1=12 Hz, J_2=3 Hz, 0.6H, $HCHNO_{2\ Dia1}$), 4.73 (dd, 0.4H, $HCHNO_{2\ Dia2}$), 5.32 (m, 1H, OH), 7.25 - 7.43 (m, 5H, H_{arom})

IR: (FTIR-microscopy in transmission)
3399 (OH), 3089-3064 (CHaromatic), 2960-2931-2874 (C-Haliphatic), 1555 (NO_2 ν_{ass}), 1372 (NO_2 δ_s, $CH_3\delta$), 1090-1073 (C-O), 740-700 ($phenyl_{monosubs}$)

MS: (ES^+); MH^+= 282
(ES^-); MH^-= 280

HPLC method: reverse phase, inertsil ODS3 C18 4.6 mu 22 cm , AcN / H_2O + 0.01% $NH_4H_2PO_4$, gradient: from 55% to 97% AcN, 40°C, λ=220nm, tr = 7.2 min

Rf (hexan/ethyl acetate 4:1) = 0.11

Methode 2

18.3 mg of the (R,R) ligand (0.05 mmol, 0.05 eq.) are dissolved at 22°C in 0.5 mL of acetonitrile. 9.3 mg of copper (II) acetate monohydrate (0.05 mmol, 0.05 eq.) are then added at 22°C. After 31 min, a solution of 220.1 mg of aldehyde **28** (1.0 mmol, 1.0 eq.) in 0.5 mL of acetonitrile and 83.7 mg of nitromethane **27** (1.4 mmol, 1.4 eq.) are added at 22°C to the green reaction mixture. The reaction mixture is heated to 30°C and is stirred over night (14 hours 30 min).
The isomeric (*syn/anti*) ratio measured on CHIRALCEL OD-H (20°C, 93:7 hexane/isopropanol, isocratic, 1.5 mL/min) is 2% of the isomer 1 (t_R=7.7 min) and 98% of the isomer 2 (t_R=15.3 min).

Methode 3

18.4 mg of the (S,S) ligand (0.05 mmol, 0.05 eq.) are dissolved at 22°C in 0.5 mL of acetonitrile. 9.3 mg of copper (II) acetate monohydrate (0.05 mmol, 0.05 eq.) are then added at 22°C. After 31 min, a solution of 220.6 mg of aldehyde **28** (1.0 mmol, 1.0 eq.) in 0.5 mL of acetonitrile and 82.9 mg of nitromethane **27** (1.4 mmol, 1.4 eq.) are added at 22°C to the green reaction mixture. The reaction mixture is heated to 30°C and is stirred over night (14 hours 30 min).
The isomeric (*syn/anti*) ratio measured on CHIRALCEL OD-H (20°C, 93:7 hexane/isopropanol, isocratic, 1.5 mL/min) is 98% of the isomer 1 (t_R=7.8 min) and 2% of the isomer 2 (t_R=14.2 min).

Methode 4

36.4 mg of the (R,R) ligand (0.1 mmol, 0.1 eq.) are dissolved at 22°C in 1.0 mL of THF and 19.9 mg of copper (I) iodide (0.1 mmol, 0.1 eq) are added. After 16 min, 9 µL of diisopropyl ethyl amine (0.05 mmol, 0.5 eq) are added and the mixture is allowed to stir at 22°C for 15 min. 220.5 mg of aldehyde **28** (1.0 mmol, 1.0 eq) and 84.5 mg of nitromethane **27** (1.4 mmol, 1.4 eq.) are added at 22°C to the green reaction mixture. The reaction mixture is heated to 35°C and is stirred over night (14 hours 30 min).

The isomeric (*syn/anti*) ratio measured CHIRALCEL OD-H (20°C, 93:7 hexane/isopropanol, isocratic, 1.5 mL/min) is 2% of the isomer 1 (t_R=7.8 min) and 98% of the isomer 2 (t_R=14.9 min).

Methode 5

47.3 mg of the (R,R) ligand (0.1 mmol, 0.1 eq.) are dissolved at 22°C in 1.0 mL of THF and 19.5 mg of copper (I) iodide (0.1 mmol, 0.1 eq) are added. After 20 min, 9 µL of diisopropyl ethyl amine (0.05 mmol, 0.5 eq) are added and the mixture is allowed to stir at 22°C for 10 min. A solution of 219.3 mg of aldehyde **28** (1.0 mmol, 1.0 eq) in 0.5 mL of THF and 83.5 mg of nitromethane **27** (1.4 mmol, 1.4 eq.) are added at 22°C to the green reaction mixture. The reaction mixture is heated to 35°C and is stirred over 2.5 days. The reaction mixture is cooled down to room temperature and concentrated in vacuum. The residue is diluted in 10 mL of ethyl acetate, and the resulting organic layer is extracted once with 10 mL of brine and twice with 10 mL of demineralized water yielding 226 mg of the β-hydroxy nitro compound **87** as an isomeric mixture.

The isomeric (*syn/anti*) ratio measured on CHIRALCEL OD-H (20°C, 93:7 hexane/isopropanol, isocratic, 1.5 mL/min) is 1% of the isomer 1 (t_R=7.7 min) and 99% of the isomer 2 (t_R=15.3 min).

The crude material can be purified by column chromatography on silicagel (0.040-0.063 nm) (30g) with heptane:ethyl acetate (4:1) to give in the purest fractions 112 mg (41%) of nitroaldol compound **87** as an isomeric mixture (syn/anti 99:1).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm)
0.84 (dd, J_1= 17 Hz, J_2= 7 Hz, 6H, CH_{3iPr}), 1.29-1.39 (m,2H, CH_2-CHOH), 1.64 - 1.74 (m, 1H, CH-CH_{iPr}), 1.73 - 1.85 (m, 1H, CH-CH_{iPr}), 3.40 (d, J=5 Hz, 2H, CH_2-O), 4.12 - 4.22 (m, 1H, CHOH), 4.32 (dd, J_1=12 Hz, J_2= 9 Hz, 1H, HCHNO$_2$), 4.46 (m, 2H, CH_{2Benz}), 4.65 (dd, J_1=12 Hz, J_2=3 Hz, 1H, HCHNO$_2$),5.28 (bs, 1H, OH), 7.14 - 7.40 (m, 5H, H_{arom})

Methode 6

1.001 g of the (R,R) ligand (2.7 mmol, 0.05 eq.) are dissolved at 22°C in 10 mL of ethanol. 495.1 mg of copper (II) acetate (2.7 mmol, 0.05 eq.) are then added at 22°C. After 30 min, 11.86 g of aldehyde **28** (53.8 mmol, 1.0 eq.) and 16.40 g of nitromethane **27** (267.1 mmol, 4.9 eq.) are added at room temperature to the green suspension. The reaction mixture is heated to 35°C and is stirred overnight (18 hours 45 min). The reaction mixture is cooled down to room temperature and concentrated in vacuum. The yellow residue is diluted in 50 mL of ethyl acetate, and the resulting organic layer is extracted with 50 mL of brine and 20 mL of demineralized water yielding to the precipitation of a brown solid and the formation of three phases. The ethyl acetate phase is extracted with 50 mL of demineralized water and four times with 200 mL of brine. The second organic phase (in which **87** is the major compound) is extracted with 100 mL of brine. And after addition of 100 mL of methylene chloride, the organic layer is extracted two times with 100 mL, 400 mL and 500 mL of brine. Both organic phases are dried over $MgSO_4$ and concentrated in vacuum to yield 5.17 g and 5.82 g of crude product **87** as isomeric mixtures (*syn/anti* 98:2).

The isomeric ratio of the crude material is measured on CHIRALCEL OD-H (20°C, 93:7 hexane/isopropanol, isocratic, 1.5 mL/min), is 2% of the isomer 1 (t_R=7.9 min) and 98% of the isomer 2 (t_R=15.3 min).

A part of the crude material (5.167 g) is purified by column chromatography on silicagel (0.040-0.063 nm) (200g) with heptane:ethyl acetate (5:1) to give in the pure fractions 3.095 g (57%) of nitroaldol compound **87** as a diastereoisomeric mixture (*syn/anti* 98:2).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm)
0.83 (dd, J_1= 17 Hz, J_2= 2 Hz, 6H, CH_{3iPr}), 1.25-1.39 (m, 2H, CH_2-CHOH), 1.61 - 1.73 (m, 1H, CH-CH_{iPr}), 1.73 - 1.94 (m, 1H, CH-CH_{iPr}), 3.39 (d, J=5 Hz, 2H, CH_2-O), 4.18 (m, 1H, CHOH), 4.26 - 4.38 (m, 1H, $HCHNO_2$), 4.45 (d, J= 5Hz, 2H, CH_{2Benz}) 4.65 (dd, J_1=12 Hz, J_2=3 Hz, 1H, $HCHNO_2$), 5.30 (m, 1H, OH), 7.15 - 7.47 (m, 5H, H_{arom})

^{13}C NMR (101 MHz, DMSO-d_6) δ_C (ppm)
18.84 (CH_{3iPr}), 19.92 (CH_{3iPr}), 28.49 (CH_{iPr}), 32.40 (CH_2-CHOH), 39.20 (CH-CH_{iPr}), 66.59 (CHOH), 70.45 (O-CH_2-CH-iPr), 72.16 (CH_{2Benz}), 82.10 (CH_2NO_2), 127.39 (CH_{arom}) 128.25 (CH_{arom}) 138.69 (C_{arom})

IR: (FTIR-microscopy in transmission)
3418 (OH), 3064-3032 (CHaromatic), 2959-2878 (C-Haliphatic), 1556 (NO_2 ν_{ass}), 1373 (NO_2 δ_s, $CH_3\delta$), 1089-1073-1028 (C-O), 740-700 ($phenyl_{monosubs}$)

MS: (ES^+); MH^+= 282
(ES^-); MH^-= 280

HRMS($C_{15}H_{24}O_4N$, 0.14 (ppm)/MH^+): $[M+N]^+$= 282.16995, calcul. 282.16999, $C_{15}H_{24}O_4N$

[(2S,4S)-2-isopropyl-4-(1-methoxy-1-methyl-ethoxy)-5-nitro-pentyloxymethyl]-benzene 81

(S,S)-87
MW: 281.35

(S,S)-81
MW: 353.46

1.07 g of compound **87** (3.8 mmol, 1.0 eq.) is dissolved at 22°C (room temperature) in 20 mL of 2-methoxy propene (72.1 mmol, 55.0 eq.) and 24.1 mg of polymer bound pyridinium toluene-4-sulfonate (3.5 mmol/ g, 0.08 mmol, 0.02 eq.) are added to the solution. The reaction mixture is heated to 36°C and is stirred overnight. The reaction mixture is cooled down to room temperature and the polymer is filtered off and washed with 10 mL of ethyl acetate. The organic layer is concentrated in vacuum to yield 1.31 g of protected compound **81** (97%).

The crude material is purified by column chromatography on silicagel (0.040-0.063 nm) (40g) with heptane:ethyl acetate (5:1) to give in the pure fractions 1.05 g (78%) of compound **81**.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm)
0.84 (t, J= 6Hz, 6H, CH_{3iPr}), 1.23 (s, 6H, CH_{3MIP}), 1.34 - 1.49 (m, 1H, HCH-CHOH), 1.51 - 1.66 (m, 2H, HCH-CHOH, CH-CH_{iPr}), 1.73 - 1.87 (m, 1H, CH_{iPr}), 3.09 (s, 3H, OCH_3), 3.32 - 3.44 (m, 2H, CH_2-O), 4.32 -

4.40 (m, 1H, C<u>H</u>OH), 4.45 (s, 2H, CH_{2Benz}), 4.49 - 4.59 (dd, J_1=12 Hz, J_2=4 Hz, 1H, HC<u>H</u>NO_2), 4.60 - 4.69 (dd, J_1=13 Hz, J_2=6 Hz, 1H, <u>H</u>CHNO_2), 7.18 - 7.48 (m, 5H, H_{arom})

<u>^{13}C NMR</u> (101 MHz, DMSO-d_6) δ_C (ppm)
19.01 (CH_{3iPr}), 19.29 (CH_{3iPr}), 24.59 (CH_{3MIP}), 24.69 (CH_{3MIP}), 28.27 (<u>C</u>H-CH_{iPr}), 32.23 (<u>C</u>H_2-CH-OMIP), 39.61 (CH_{iPr}), 48.86 (OCH_{3MIP}), 67.83 (<u>C</u>H-OMIP), 70.89 (CH_2-0), 72.18 (CH_{2Benz}), 80.02 (CH_2NO_2), 100.80 (C_{MIP}), 127.34 (CH_{arom}), 127.46 (CH_{arom}), 128.19 (CH_{arom}), 138.55 (C_{arom})

<u>IR</u>: (FTIR-microscopy in transmission)
3064-3089 (CHaromatic), 2959-2874(C-Haliphatic), 1555 (NO_2 ν_{ass}), 1383 (NO_2 δ_s, $CH_3\delta$), 1073-1049 (C-O), 738-699 ($phenyl_{monosubs}$)

<u>MS</u>: (ES^+); M+Na^+= 376, m/z (-0CH_3)= 322, m/z (-MIP)= 282

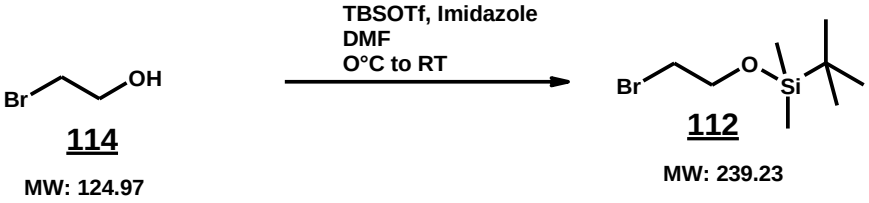
<u>HRMS</u> (0.14 ppm/MH_4+): M+NH_4] += 312.21694, C17H30O4N 380.24315

<u>HPLC method</u>: CHIRALCEL OD-H, 93:7 Hex/iPrOH, 1.0 mL/min, 20°C, t_R= 34 min

Rf (heptan/ethyl acetate 5:1, NEt_3) = 0.12

II. EXPERIMENTAL PART OF CHAPTER 3

2-Bromo- 1 -tert-butvldimethylsilyloxy-ethane 112
CAS Number: 86864-60-0
J. Vader, H. Sengers, A. De Groot, *Tetrahedron* **1989**, 45(7), 2131-42



14.15 mL of *tert*-butyldimethylsilyl trifluoromethanesulfonate (61.6 mmol, 1.0 eq.) and 10.0 mL of bromoethanol **114** (61.6 mmol, 1.0 eq.) are added dropwise at 0°C to a solution of 5.44 g of imidazole (80.1 mmol, 1.0 eq.) in 40 mL of dimethylformamide over a period of 20 min. The reaction mixture is allowed to warm up to room temperature (21°C) and stirred overnight. 4.2 mL *tert*-Butyldimethylsilyl trifluoromethanesulfonate (18.4 mmol, 0.3 eq.) are added and the reaction mixture is allowed to stirr over 25 hours until completion of the reaction. The reaction mixture is diluted in 120 mL of ethyl acetate, and extracted with 120 mL of brine. Both phases are separated and the organic layer is washed again with 80 mL of brine. The combined aqueous phase is extracted with 120 ml of ethyl acetate. The combined organic phases are dried over Na_2SO_4 and concentred in vacuum to yield 10.235 g of crude material **112** (69%).
5.52 g of crude material are purified by column chromatography on silicagel (0.040-0.063 nm) with hexane:ethyl acetate (10:1) to give in the pure fractions 1.68 g of (2-bromo-ethoxy)-tert-butyl-dimethyl-silane **112** (30%) and 1.60 g of **114**.

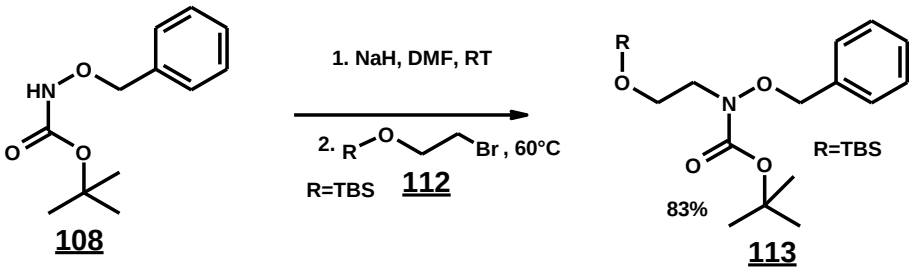
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm)
0.10 (s, 3H, CH_{3TBDMS}), 0.91 (s, 9H, $CH_{3tBu,\ TBDMS}$), 3.41 (t, *J*=6.5 Hz, 2H, CH_2-0), 3.90 (t, *J*=6.5 Hz, 2H, CH_2-Br)

IR: (FTIR-microscopy in transmission)
2999-2821 (C-Haliph.), 1398 -1348 ($(CH_3)_{3\delta}$), 1257 ($(CH_3)Si-(CH_3)_{2\delta}$), 1153-1068 (Si-O-C), 839 (Si-C)

(GC) MS: $[M-C_4H_9]^+$ = 181, 182

Rf (heptan:ethyl acetate 10 :1) = 0.39

2-[(phenylmethoxy)(*tert*-butylsilyloxy) amino]- *tert*-butyldimethylsilyloxy-ethane 113



1.11 g of *tert*-Butyl *N*-(benzyloxy)carbamate **108** (4.3 mmol, 1.0 eq.) is dissolved at room temperature in 22 mL of dry dimethylformamide. 228 mg of NaH (ca 50% dispersion in mineral oil) (4.7 mmol, 1.1 eq.) are added portionwise and the reaction mixture is allowed to stir over a period of 20 min. 1.05 g of 2-bromo-1-tert-butyldimethylsilyloxy-ethane **112** is added dropewise over a period of 15 min. The reaction mixture is warmed to 60°C and allowed to stir at 60°C over 2 hours. The reaction mixture is cooled down to room temperature, poured into 50 mL of demineralized water and extracted thrice with 60 mL of tert-butyl-mehyl ether. The combined organic layers are dried over Na_2SO_4, and concentred in vacuum to yield 1.36 g of **113** (83%).

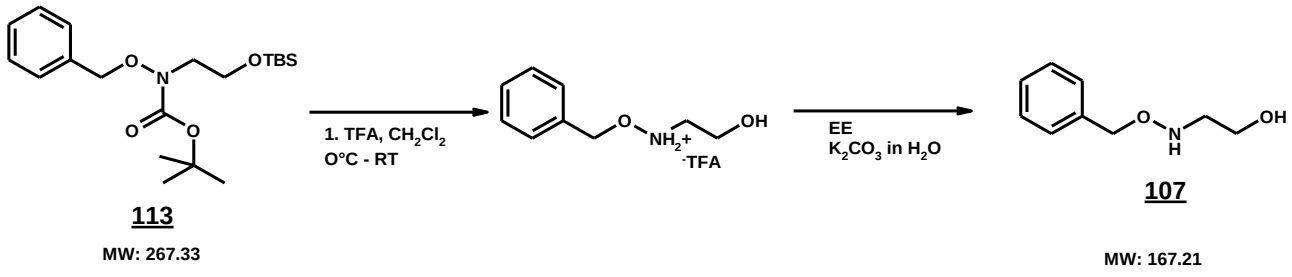
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm)
0.07 (s, 3H, CH_{3TBDMS}), 0.90 (s, 9H, $CH_{3tBu,\ TBDMS}$), 1.51 (s, 9H, CH_{3BOC}), 3.56 (t, *J*=6.5 Hz, 2H, CH_2-N), 3.75 (t, *J*=6.5 Hz, 2H, CH_2-O), 4.86 (s, 2H, $CH_{2Benz.}$), 7.38 (m, 5H, $CH_{Arom.}$)

IR: (FTIR-microscopy in transmission)
3120-3001 (CHarom.), 3006-2802 (CHaliph.), 1707(C-O_{BOC}), 1608 (Phenyl), 1589 (Phenyl), 1498 (Phenyl), 1456 (Phenyl), 1408-1342 (C-N_{BOC}, $(CH_3)_{3\delta}$), 1252 ((CH_3)Si-$(CH_3)_{2\delta}$), 1173 (C-O_{BOC}), 1157-1068 (C-O, N-O,Si-O), 837 (Si-C), 748 (Phenyl$_{\delta mono}$), 698 (Phenyl$_{\delta mono}$)

MS: $[M-H]^+$ = 382

HRMS ($C_{20}H_{36}NO_4SiNa$, 0.5 ppm/M-Na+): [M-Na]+= 404.22295, *calculated* 404.22276, $C_{20}H_{36}NO_4SiNa$

2-[(phenylmethoxy)amino]-ethanol 107
CAS Number: 16115-60-9
E. Fleckenstein, E. Heinrich, R. Mohr, **1974** DE -2230392



485.2 mg of 2-[(phenylmethoxy)(tert-butylsilyloxy) amino]- tert-butyldimethylsilyloxy-ethane **113** (1.81 mmol, 1.0 eq.) are dissolved at room temperature in 15 mL of dry dichloromethane. The reaction mixture is cooled down to 0°C and 10 mL of trifluoroacetic acid (12.9 mmol, 7.1 eq.) are

added dropwise over a period of 15 min. After being stireed at 0°C over a period of one hour, the reaction mixture is warmed to room temperature, and diluted in 20 mL of dichloromethane. 20 mL of demineralized water are slowly added to the solution. Both layers are separated, and the organic phase is extracted again twice with 60 mL of water. An aqueous solution of potassium carbonate (20% m/m) is added to the resulting aqueous phase until pH 8. The resulting solution is washed three times with 40 mL of ethyl acetate. Both organic phases are dried over Na_2SO_4, and concentred in vacuum to yield 646 mg of crude material. The crude material is diluted in 50 mL of ethyl acetate and 80 mL of a saturated solution of potassium carbonate are added to the solution until pH 9. The biphasic reaction mixture is stirred vigorously at room tempature over 30 min and both phases are separated. The aqueous phase is extracted with twice with 20 mL of ethyl acetate. The combined organic phases are dried over Na_2SO_4, and concentred in vacuum to yield 292.1 mg of 2-[(phenylmethoxy)amino]-ethanol **107** as a colorless oil.

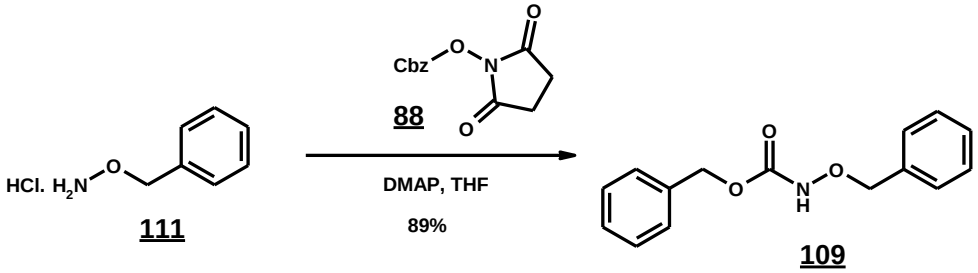
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm)
3.07 (m, 2H, CH_2-N), 3.73 (m, 2H, CH_2-O), 4.73 (s, 2H, CH_{2Benz}), 7.35 (m, 5H, CH_{arom})

IR: (FTIR-microscopy in transmission)
3995-3109 (OH, NH) 3107-2995 (CHarom.), 2970-2785 (CHaliph.), 1604 (Phenyl), 1587 (Phenyl), 1496 (Phenyl), 1454 (Phenyl), 1119-930 (C.O, N-O), 746 ($CH_{\delta mono}$), 698 ($Phenyl_{\delta mono}$)

(LC) MS: $[M-H]^+$ = 168

HRMS ($C_9H_{14}NO_2$, 0.4 ppm/M-H+): [M-H] += 168.10184, *calculated* 168.10191, $C_9H_{14}NO_2$

***N*-carbobenzoxy-*O*-benzylhydroxylamine 109**
CAS Number: 15255-86-4
T. Kolasa, M. J. Miller, *Journal of Organic Chemistry* **1987**, 52(22), 4978-84



10.00 g of *O*-benzylhydroxylamine hydrochloride **111** (62.6 mmol, 1.0 eq.) are dissolved at room temperature in 150 mL of dry tetrahydrofuran and a solution of 784.1 mg of DMAP (6.4 mmol, 0.1 eq.) and 15.60 g of *N*-(benzyloxycarbonyloxy) succinimide **88** (62.6 mmol, 1.0 eq.) in 100 mL of dry THF is added dropwise. The reaction mixture is warmed to 70°C and allowed to stir at reflux overnight. The reaction mixture is cooled down to room temperature and concentred (2/3) in vacuum. The resulting solution is diluted with 60 mL of ethyl acetate and washed twice with 20 mL of demineralized water. The organic layer is dried over Na_2SO_4, and concentrated in vacuum to yield 15.132 g of a white solid. The residue is recrystallized from ethyl acetate/hexane (1:2 v/v) to give 14.33 g of **109** as a white solid (89% yield).

^{1}H NMR (600 MHz, DMSO-d^6) δ_H (ppm)
4.76 (s, 2H, CH_{2Benz}), 5.06 (s, 2H, $CH_{2,Z}$), 7.23-7.37 (m, 5H, CH_{arom})

^{13}C NMR (150 MHz, DMSO-d^6) δ_C (ppm)
65.8 ($CH_{2,Z}$), 77.3 (CH_{2Benz}), 127.8, 128.0, 128.1, 128.2, 128.4, 128.5, 128.5, 128.7, 128.9 (CH_{arom}), 135.9 (C_{arom}), 136.4 (C_{arom}), 156.7 (C=O)

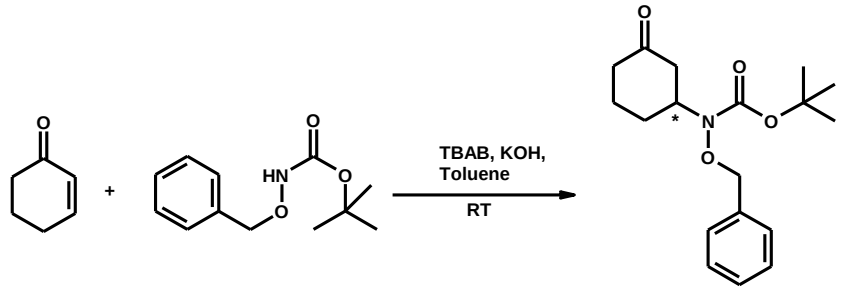
IR: (FTIR-microscopy in transmission)
3288 (NH), 3091-3036 (CHarom.), 2938-2879 (CHaliph.), 1715 (C=O), 1489 (Phenyl), 1455 (Phenyl), 1275 (C.O), 1125 (C.O), 744 ($CH_{\delta mono}$), 698 ($Phenyl_{\delta mono}$)

MS: $[M-H]^-$ = 256, $[M-H]^+$ = 258

HRMS ($C_9H_{14}NO_2$, 0.4 ppm/M-H+): [M-H] += 168.10184, *calculated* 168.10191, $C_9H_{14}NO_2$

Rf(hexane/ethyl acetate 1:1): 0.57

carbamic acid, *N*-(3-oxocyclohexyl)-N-(phenylmethoxy)-, 1,1-dimethylethyl ester 115
CAS Number: 1033064-95-7
J. Lee, M-H Kim, S.-S. Jew, H.-G. Park, B.-S. Jeong, *Chemical Communications* **2008**, 16, 1932-1934

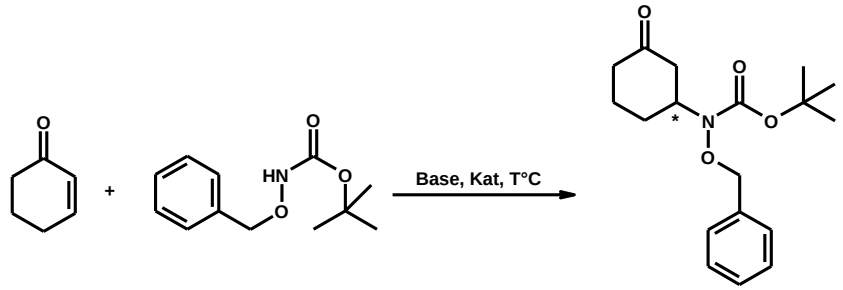


93 MW: 96.13 + **108** MW: 223.27 → **115** MW: 319.40

329.4 mg of tetrabutylammonium bromide (1.0 mmol, 0.1 eq.) are added at room temperature to a solution of 4.47 g of *tert*-butyl *N*-(benzyloxy)carbamate **108** (20.0 mmol, 2.0 eq.) in 40 mL of toluene, followed by the dropwise addition of a solution of 481 mg of KOH (12.0 mmol, 1.2 eq.) in 481 µL water. 935.3 µL of cyclohexenone **93** (10.0 mmol, 1.0 eq.) are added dropwise to the viscous solution, the reaction mixture turning into a brown suspension during the addition. The reaction mixture is stirred at room temperature over a period of 50 min and is in 80 mL of ethyl acetate diluted. The organic phase is washed twice with 80 mL of brine, while the resulting aqueous phase is extracted twice with 80 mL of ethyl acetate. The organic layer is dried over Na_2SO_4, and concentrated in vacuum to yield 4.549 g of crude material containing *tert*-butyl N-(benzyloxy)carbamate **108** and the Michael adduct **115**.
The crude material is purified by column chromatography on silicagel (0.040-0.063 nm) (100 g) with cyclohexane:ethyl acetate (9:1) to give in the pure fractions 0.642 g of **115** (20%) and 1.825 g of the starting material **108** in mixture with **115**.

Data are confirmed by iterature data
^{1}H NMR (400 MHz, $CDCl_3$-d) δ_H (ppm)
1.61 - 1.71, 1.89 - 2.13 (m, 4H, $CH_2CH_2CH_{cyclohex.,}$ $CH_{2,\beta C=O}$), 2.17 - 2.30 (m, 1H, $HCH_{,\alpha C=O}$), 2.32-2.36 (m, 1H, $HCH_{,\alpha C=O}$), 2.53 (dd, J_1=14 Hz, J_2= 2 Hz, 1H, $HCH_{,\alpha' C=O}$), 2.70 (t, J=12 Hz, 1H, $HCH_{,\alpha' C=O}$), 4.15 - 4.28 (m, 1H, CH-N), 4.85 (s, 2H, $CH_{2,CbZ}$), 7.33 - 7.45 (m, 5H, CH_{arom})

carbamic acid, N-(3-oxocyclohexyl)-N-(phenylmethoxy)-, 1,1-dimethylethyl ester 115
CAS Number: 1033064-95-7



93 MW: 96.13 **108** MW: 223.27 **115** MW: 319.40

To 101.4 µL of cyclohexenone **93** (1.07 mmol, 1.0 eq.) in 4 mL chloroform are added at room temperature 22.3 mg of (R)-5-pyrrolidin-2-yltetrazole (0.16 mmol, 0.16 eq.), 374.6 mg of **108** (1.61 mmol,1.5 eq.) and 114.6 µL of morpholine (1.07 mmol, 1.0 eq.). The reaction mixture is stirred at room temperature over two days and is diluted in 15 mL of ethyl acetate. The organic phase is extracted twice with 10 mL of an saturated aqeous solution of citric acid, and once with 10 mL of demineralized water. The organic layer is dried over $MgSO_4$, and concentrated in vacuum to yield 108.3 mg of crude material.

Chiral HPLC measurement of the crude material on CHIRALCEL OD-H (hexan/iPrOH/MeOH 97:2:1, 1.5 mL/min, 25°C, λ=215 nm) revealed the presence of two enantiomers with a ratio of 36 % at 5.3 min and 64% at 5.9 min

The crude material are purified by column chromatography on silicagel (0.040-0.063 nm) (100 g) with cyclohexane:ethyl acetate (9:1) to give in the pure fractions 63 mg of **115** (19%).

Chiral HPLC measurement on CHIRALCEL OD-H (hexan/iPrOH/MeOH 97:2:1, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of two enantiomers with a ratio of 36% at 5.2 min and 64% at 5.9 min.

Spectroscopic data of **115** are confirmed by the literature data

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ_H (ppm)
1.60 - 1.71, 1.89 - 2.13 (m, 4H, $CH_2CH_2CH_{,cyclohex.}$, $CH_{2,\ \beta C=O}$), 2.17 - 2.30 (m, 1H, $HCH_{,\ \alpha C=O}$), 2.32-2.36 (m, 1H, $HCH_{,\ \alpha C=O}$), 2.52 (dd, J_1=14 Hz, J_2= 2 Hz, 1H, $HCH_{,\alpha' C=O}$), 2.70 (t, *J*=12 Hz, 1H, $HCH_{,\ \alpha' C=O}$), 4.15 - 4.28 (m, 1H, CH-N), 4.84 (s, 2H, $CH_{2,Bz}$), 7.33 - 7.46 (m, 5H, $CH_{arom.}$)

^{13}C NMR (151 MHz, DMSO-d^6) δ_C (ppm)
21.51 ($CH_{2,cyclohex.}$), 27.55 ($CH_{2,cyclohex}$), 27.93 ($CH_{3,Boc}$), 39.94 (O=C-$CH_{2,cyclohex.}$), 44.32 (CH-$CH_{2,cyclohex.}$), 57.64 ($CH_{,cyclohex.}$), 77.95 (CH_{2Bz}), 81.23 (C_{Boc}), 128.40-129.43 ($CH_{arom.}$), 135.32($C_{arom.}$), 155.88 ($C=O_{Boc}$), 208.47 ($C=_{,cyclohex.}$)

LCMS: $[MH-H]^+$=320.3, $[M+NH4]^+$=337.3

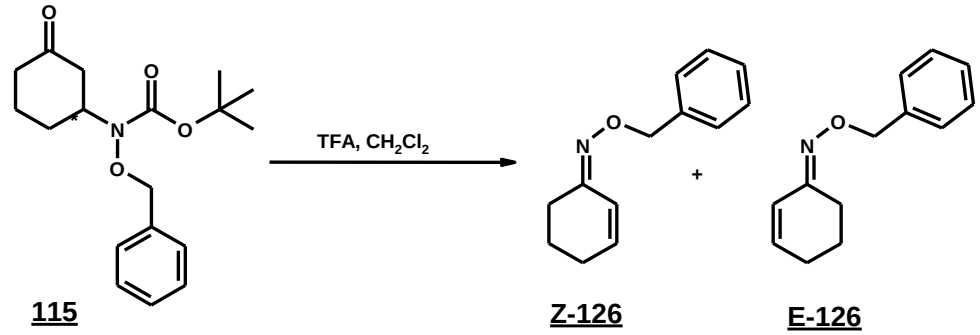
HRMS ($C_{18}H_{25}NO_4Na$, 0.6 ppm/M-Na+): [M+Na] += 342.16736, *calculated* 342.16758, $C_{18}H_{25}NO_4Na$

benzyl-cyclohex-2-en-(E/Z)-ylidene-oxonium 126

CAS Number: 1059652-35-5 (Z)

CAS Number: 1059651-58-9 (E)

M. Ueda, H. Miyabe, H. Shimizu, H. Sugino, O. Miyata, T. Naito, Takeaki, *Angew. Ch. Int. Ed.* **2008**, 47(30), 5600-5604



115
MW: 319.40

Z-126
MW: 201.27

E-126
MW: 201.27

154.1 mg of **115** (0.48 mmol, 1.0 eq.) are diluted in 3 mL of dry dichloromethane at 0°C and 105.7 µL of trifluoro acetic acid (1.38 mmol, 2.8 eq.) are added to the solution. The reaction mixture is stirred at room temperature over two hours and is concentrated in vacuum to yield 65.6 mg of crude material.

Column chromatography on silicagel (0.040-0.063 nm) (30 g) with cyclohexane:ethyl acetate (6:1) yield in the pure fractions 53.2 mg of benzyl-cyclohex-2-en-(E/Z)-ylidene-oxonium (55%) (**Z-126** and **E-126)**.

E-126

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ_H (ppm) E isomer

1.66 (q, *J*=6 Hz, 2H, $CH_{2\beta}C$=N), 2.03 - 2.13 (m, 2H, $CH_{2\delta}C$=N), 2.54 (t, *J*=6 Hz, 2H, $CH_{2\alpha}C$=N), 5.04 (s, 2H, CH_{2Benz}), 6.06 (dt, J_1=10 Hz, J_2=1Hz, 1H, N=C-C<u>H</u>=CH), 6.15 (dt, 1H, J_1=10 Hz, J_2=5 Hz,1H, N=C-CH=C<u>H</u>), 7.19 - 7.38 (m, 5H, Harom.)

Z-126

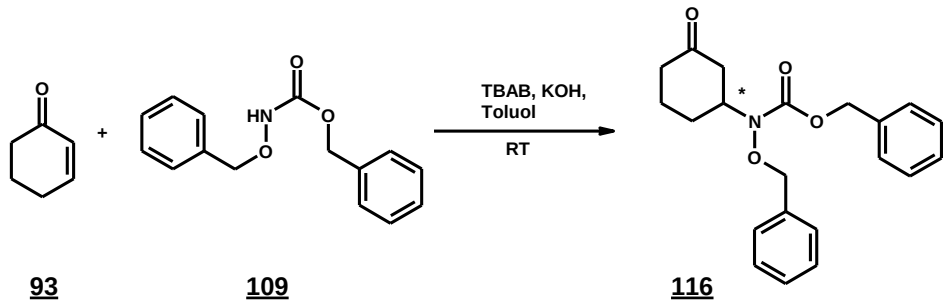
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ_H (ppm) Z isomer

1.73 - 1.81 (q., *J*=6Hz, 2H, $CH_{2\beta}C$=N), 2.12 - 2.20 (m, 2H, $CH_{2\delta}C$=N), 2.32 (t, *J*=6 Hz, 2H, $CH_{2\alpha}C$=N), 5.02 (s, 2H, CH_{2Benz}), 6.23 (dt, J_1=10Hz, J_2=4 Hz, 1H, N=C-C<u>H</u>=CH), 6.72 (dt, J_1=10 Hz, J_2=1 Hz,1H, N=C-CH=C<u>H</u>), 7.19 - 7.38 (m, 5H, Harom.)

MS: $[M-H]^+$ = 202, mixture of two isomers

Rf(hexane/ethyl acetate 1:1): 0.21

carbamic acid, N-(3-oxocyclohexyl)- N-(phenylmethoxy)-, phenylmethyl ester as racemic mixture 116

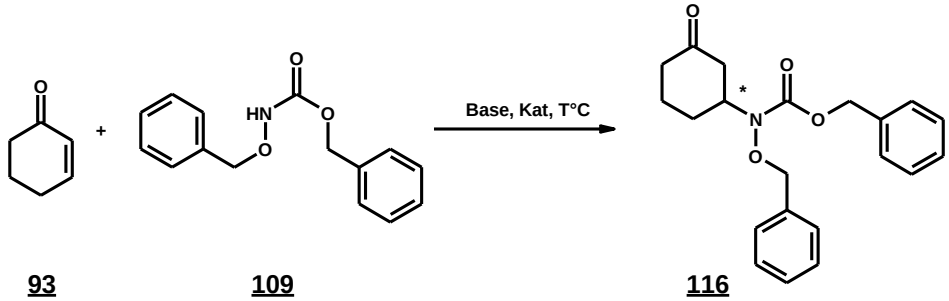


93 MW: 96.13 **109** MW: 257.29 **116** MW: 353.42

103.5 mg of tetrabutylammonium bromide (0.31 mmol, 0.1 eq.) are added at room temperature to a solution of 772.0 mg of *N*-carbobenzoxy-*O*-benzylhydroxylamine **109** (3.0 mmol,0.9 eq.) in 12 mL of toluene, followed by the dropwise addition of a solution of 154.5 mg of KOH (1.28 mmol, 1.2 eq.) in 154.5 µL water. 301.24 µL of cyclohexenone **93** (3.12 mmol, 1.0 eq.) are added dropwise to the viscous solution, the reaction mixture turning into a brown suspension during the addition. The reaction mixture is stirred at room temperature over a period of 6 hours and is diluted in 40 mL of ethyl acetate. The organic phase is washed three times with 100 mL of brine, while the resulting aqueous phase is extracted twice with 80 mL of ethyl acetate. The organic layer is washed twice with 100 mL of an aqueous solution of citric acid (20%, pH 6) and is dried over Na_2SO_4, and concentrated in vacuum to yield 0.920 g of crude material containing **109** and **116**.
The crude material is purified by column chromatography on silicagel (0.040-0.063 nm) (30 g) with cyclohexane:ethyl acetate (6:1) to give in the pure fractions 0.821 g of **116** (77%).

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ_H (ppm)
1.51 – 1.68, 1.91 - 2.11 (m, 4H, $CH_2CH_2CH_{cyclohex.,}CH_{2,\ \beta C=O}$), 2.18 - 2.29 (m, 1H, $HCH_{,\ \alpha C=O}$), 2.33-2.38 (m, 1H, $HCH_{,\ \alpha C=O}$), 2.52-2.56 (m, 1H, $HCH_{,\alpha' C=O}$), 2.71 (dd, J_1=14 Hz, J_2=11 Hz, 1H, $HCH_{,\ \alpha' C=O}$), 4.25 - 4.35 (m, 1H, CH-N), 4.87 (s, 2H, $CH_{2,CbZ}$), 5.20 - 5.29 (m, 2H, CH_{2Benz}), 7.34-7.42 (m, 10H, CH_{arom})

carbamic acid, N-(3-oxocyclohexyl)- N-(phenylmethoxy)-, phenylmethyl ester 116



93 MW: 96.13 **109** MW: 257.29 **116** MW: 353.42

To 301.2 µL of cyclohexenone **93** (3.00 mmol, 3.0 eq.) are added at room temperature, 22.4 mg of (R)-5-pyrrolidin-2-yltetrazole (0.16 mmol, 0.16 eq.), 260.1 mg of the amine **109** (1.00 mmol,1.0 eq.) and 97.6 µL of morpholine (1.0 mmol, 1.0 eq.). The reaction mixture is stirred at room temperature over fours days and is diluted in 10 mL of ethyl acetate. The organic phase is extracted twice with 10 mL of an saturated aqueous solution of citric acid, and once with 10 mL of demineralized water. The organic layer is dried over $MgSO_4$, and concentrated in vacuum to yield 104.2 mg of crude material.
The crude material is purified by column chromatography on silicagel (0.040-0.063 nm) (12 g) with hexane:ethyl acetate (4:1) to give in the pure fractions 41.4 mg of **116** (12%).

Chiral HPLC measurement on CHIRALPAK AD-H (hexan/iPrOH/MeOH 90:7.5:2.5, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of two enantiomers with a ratio of 63.5 % at 11.8 min and 36.5% at 13.3 min.

^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ_H (ppm)
1.31 – 1.65, 1.82- 2.20 (m, 4H, $CH_2CH_2CH_{cyclohex.,}CH_{2,\ \beta C=O}$), 2.28 - 2.36 (m, 1H, $HCH_{,\ \alpha C=O}$), 2.34-2.45 (m, 1H, $HCH_{,\ \alpha C=O}$), 2.50-2.58 (m, 1H, $HCH_{,\alpha' C=O}$), 2.71 (dd, J_1=14 Hz, J_2=11 Hz, 1H, $HCH_{,\ \alpha' C=O}$), 4.25 - 4.34 (m, 1H, CH-N), 4.87 (s, 2H, $CH_{2,CbZ}$), 5.21 - 5.28 (m, 2H, CH_{2Benz}), 7.31-7.42 (m, 10H, CH_{arom})

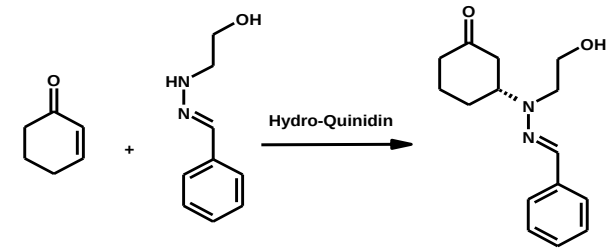
^{13}C NMR (125 MHz, DMSO-d^6) δ_C (ppm)
21.5 ($CH_{2,\ \beta C=O}$), 40.4 ($CH_{2,\ \alpha C=O}$), 44.3 ($CH_{2,\ \alpha' C=O}$), 58.0 (CH-N), 67.7 ($CH_{2,CbZ}$), 78.6 (CH_{2Benz}), 127.8, 128.0, 128.1, 128.2, 128.3, 129.0 (CH_{arom}), 134.4 (C_{arom}), 135.3 (C_{arom}), 156.74 ($C{=}O_{CbZ}$), 208.3 (C=O)

IR: (FTIR-microscopy in transmission)
3090-3033 (CHarom.), 2953-2883 (CHaliph.), 1713 (C=O), 1587, 1498, 1455 (Phenyl), 1392 (C-N), 1298, 1259,1220 (C.O),1029-1114 (N-O, C.O), 752 ($CH_{\delta mono}$), 699 ($Phenyl_{\delta mono}$)

MS: $[M-H]^+$ = 354

HRMS ($C_{21}H_{24}O_4N$, 0.5 ppm/M-H+): [M-H] += 354.17018, *calculated* 354.16999, $C_{21}H_{24}O_4N$

3-{N-(2-hydroxy-ethyl)-N'-[1-phenyl-meth-(E)-ylidene]-hydrazino}-cyclohexanone 119



93 MW: 96.13 **110** MW: 164.21 **119** MW: 260.34

To a solution of 660.5 mg of hydroquinidine (2.0 mmol, 0.19 eq.) in 20 mL toluene are added 1.6913 mg of **110** (10.3 mmol, 1.0 eq.) and dropwise 2 mL of cyclohexenone **93** (20.6 mmol, 2.0 eq.). The reaction mixture is stirred at room temperature over 3 days, and is concentred in vacuum to yield 3.852 g of an orange oil **119**.

Table 12: general procedure

To 110.4 µL of cyclohexenone **93** (1.04 mmol, 1.0 eq.) in 4 mL of chloroform are added at room temperature the selected catalyst (0.15 mmol, 0.15 eq.), 260.1 mg of **108** (1.00 mmol,1.0 eq.) and 97.6 µL of morpholine (1.0 mmol, 1.0 eq.). The reaction mixture is stirred at room temperature.
Chiral HPLC measurement on CHIRALPAK AD-H (hexan/iPrOH/MeOH 90:7.5:2.5, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two enantiomers at 3.6 min and 4.3 min.
Chiral HPLC measurement on CHIRALCEL OD-H (hexan/iPrOH/MeOH 97:2:1, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two enantiomers at 5.2 min and 5.9 min.

Table 13: general procedure

To 301.2 µL of cyclohexenone **93** (3.0 mmol, 1.0 eq.) in 4 mL of chloroform are added 20.8 mg of catalyst (0.15 mmol, 0.15 eq.), **108** (1.00 mmol,1.0 eq.) and 97.6 µL of morpholine (1.0 mmol, 1.0 eq.). The reaction mixture is stirred at the selected temperature.
Chiral HPLC measurement on CHIRALPAK AD-H (hexan/iPrOH/MeOH 90:7.5:2.5, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two enantiomers at 3.6 min and 4.3 min.
Chiral HPLC measurement on CHIRALCEL OD-H (hexan/iPrOH/MeOH 97:2:1, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two enantiomers at 5.2 min and 5.9 min.

Table 14: general procedure

To 110.4 µL of cyclohexenone **93** (1.04 mmol, 1.0 eq.) in 4 mL of chloroform are added the selected catalyst (0.15 mmol, 0.15 eq.), 260.1 mg of **108** (1.00 mmol,1.0 eq.) and 97.6 µL of morpholine (1.0 mmol, 1.0 eq.). The reaction mixture is stirred at the selected temperature.
Chiral HPLC measurement on CHIRALPAK AD-H (hexan/iPrOH/MeOH 90:7.5:2.5, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two enantiomers at 3.6 min and 4.3 min.
Chiral HPLC measurement on CHIRALCEL OD-H (hexan/iPrOH/MeOH 97:2:1, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two enantiomers at 5.2 min and 5.9 min.

Table 15: general procedure

To 110.4 µL of cyclohexenone **93** (1.04 mmol, 1.0 eq.) in 4 mL of chloroform are added the selected catalyst (0.15 mmol, 0.15 eq.), 260.1 mg of **108** (1.00 mmol,1.0 eq.) and the selected base additive (1.0 mmol, 1.0 eq.) The reaction mixture is stirred at the selected temperature.
Chiral HPLC measurement on CHIRALPAK AD-H (hexan/iPrOH/MeOH 90:7.5:2.5, 1.5 mL/min, 25°C, λ=215 nm) revealed the presence of the two enantiomers at 3.6 min and 4.3 min.
Chiral HPLC measurement on CHIRALCEL OD-H (hexan/iPrOH/MeOH 97:2:1, 1.5 mL/min, 25°C, λ=215 nm) revealed the presence of the two enantiomers at 5.2 min and 5.9 min.

Table 16: general procedure

To 110.4 µL of cyclohexenone **93** (1.04 mmol, 1.0 eq.) in 4 mL of chloroform are added the selected catalyst (0.15 mmol, 0.15 eq.), 260.1 mg of **108** (1.00 mmol,1.0 eq.) and the selected base additive. The reaction mixture is stirred at the selected temperature.
Chiral HPLC measurement on CHIRALPAK AD-H (hexan/iPrOH/MeOH 90:7.5:2.5, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two enantiomers at 3.6 min and 4.3 min.
Chiral HPLC measurement on CHIRALCEL OD-H (hexan/iPrOH/MeOH 97:2:1, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two enantiomers at 5.2 min and 5.9 min.

Table 17: general procedures

To 110.4 µL of cyclohexenone **93** (1.04 mmol, 1.0 eq.) in 4 mL of chloroform are added the selected catalyst (0.15 mmol, 0.15 eq.), 530.1 mg of **109** (1.50 mmol,1.5 eq.) and of the selected base additive. The reaction mixture is stirred at the selected temperature.
Chiral HPLC measurement on CHIRALPAK AD-H (hexan/iPrOH/MeOH 90:7.5:2.5, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two enantiomers at 11.6 min and 13.1 min.

To 110.4 µL of cyclohexenone **93** (1.04 mmol, 1.0 eq.) in 4 mL of chloroform are added 20.8 mg of catalyst (0.15 mmol, 0.15 eq.), 353.4 mg of **109** (1.00 mmol,1.0 eq.) and the selected base additive. The reaction mixture is stirred at the selected temperature.

Chiral HPLC measurement on CHIRALPAK AD-H (hexan/iPrOH/MeOH 90:7.5:2.5, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two enantiomers at 11.6 min and 13.1 min.

To 301.2 µL of cyclohexenone **93** (3.0 mmol, 1.0 eq.) are added 20.8 mg of catalyst (0.15 mmol, 0.15 eq.), 353.4 mg of **109** (1.00 mmol,1.0 eq.) and the selected base additive. The reaction mixture is stirred at the selected temperature.
Chiral HPLC measurement on CHIRALPAK AD-H (hexan/iPrOH/MeOH 90:7.5:2.5, 1.5 mL/min, 25°C, λ=215 nm) revealed the presence of the two enantiomers at 11.6 min and 13.1 min.

Table 18: general procedure

To 602.4 µL of cyclohexenone **93** (6.0 mmol, 3.0 eq.) in 8 mL chloroform are added at room temperature 41.6 mg of catalyst (0.30 mmol, 0.15 eq.), 103.8 µL of aziridine **102** (2.00 mmol, 1.0 eq.) and 97.6 µL of morpholine (1.0 mmol, 1.0 eq.). The reaction mixture is stirred at the selected temperature.
Chiral HPLC measurement on CHIRALPAK AD-H (hexan/iPrOH/MeOH 90:7.5:2.5, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two enantiomers at 6.0 min and 6.6 min.

Table 19,20: general procedure:

To a solution of 200.1 mg of **95** (0.9 mmol, 1.0 eq.) in 4 mL of the selected solvent, are added the selected additive, 11.4 mg of L-proline (0,04 mmol, 0.05 eq.) and one equivalent of the base additive.
Chiral HPLC measurement on CHIRALPAK AD-H (hexan/iPrOH/MeOH 90:7.5:2.5, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two diastereoisomers at 7.9 min and 10.2 min.

Table 21: general procedure

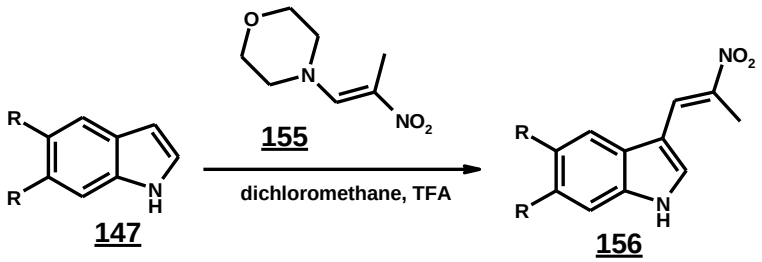
To a solution of 200.1 mg of **95** (0.9 mmol, 1.0 eq.) in 4 mL of the selected solvent, are added the selected additive, 0.1 mmol of the catalyst and 1.0 mmol of the base additive.
Chiral HPLC measurement on CHIRALPAK AD-H (hexan/iPrOH/MeOH 90:7.5:2.5, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two diastereoisomers at 7.9 min and 10.2 min.

Table 22: general procedure

To a solution of 200.1 mg of **96** (0.9 mmol, 1.0 eq.) in 4 mL of DMSO, are added 33.2 mg of TBAI (0.1 mmol, 0.1 eq.), 22.8 mg of L-proline (0.09 mmol, 1.0 eq.) and 129.3 mg of Hünig base (1.0 mmol, 1.0 eq.).
Chiral HPLC measurement on CHIRALPAK AD-H (hexan/iPrOH/MeOH 90:7.5:2.5, 1.5 mL/min, 25°C, λ=215 nm) reveals the presence of the two diastereoisomers at 7.9 min and 10.2 min.

III. EXPERIMENTAL PART OF CHAPTER 4

3-((E)-2-nitro-propenyl)-1H-indoles 156b-d

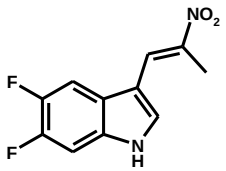


To a solution of 1 equivalent of **155** in dichloromethane (360µL/mmol) are added at 0°C under a Ar atmosphere trifluoroacetic acid (500 µL/mmol) and 1 equivalent of the selected indole **147** (5.0 mmol, 1 eq.). The orange reaction mixture is stirred in a argon atmosphere for 20 min, turning into a black suspension. The precipitate is filtered off, washed with 10 mL of cold dichloromethane and dried in vacuum to yield an orange solid (75%). The resulting mother layer is concentrated in vacuum and trifluoroacetic acid (100 µL/mmol) is added. The black reaction mixture ist stirred overnight turning into a black suspension. The precipitate is filtered off, washed with cold dichloromethane and dried in vacuum to yield again an orange product **156**, which is dried in vacuum.

5,6-difluoro-3-((E)-2-nitro-propenyl)-1H-indole 156b

CAS Number: 1235587-40-2

B.K.S. Yeung, B. Zou,M. Rottmann,S.B. Lakshminarayana , S. H. , S.Y. Leong, J. Tan , J. Wong, S. Keller-Maerki, C. Fischli, A. Goh, E.K. Schmitt, P. Krastel , E. Francotte ,K. Kuhen ,D. Plouffe , K. Henson,T. Wagner , E.A. Winzeler, F. Petersen,R. Brun, V. Dartois, T. T. Diagana, T.H. Keller *J. Med. Chem.* **2010**, 53(14), 5155-64



156b

MW: 238.20

Yield: 87%

^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm)

2.47 (s, 3H. CH_3), 7.46 - 7.57 (dd, J_1=7 Hz, $J_{2=}$ 4 Hz, 1H, CHarom), 7.93 - 8.03 (dd, J_1=8 Hz, $J_{2=}$ 4 Hz, 1H, CHarom), 8.05 (s, 1H, C=CH-NH), 8.40 (s, 1H, H_{vin}), 12.31 (bs, 1H, NH)

IR: (FTIR-microscopy in transmission)

3258 (NH), 3074 (CHarom.), 1631 (C=C), 1276 (NO_2)

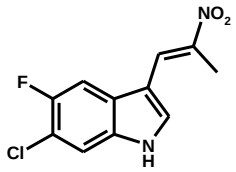
MS: MH^- = 237.2

HRMS ($C_{11}H_7O_2N_2F_2$, 0.6 ppm/M-H-): $[M-H]^-$= 237.04795, *calculated* 237.04811, $C_{11}H_7O_2N_2F_2$

Crystal data (100 °K, 1.54178 Å)

Empirical formula	C11 H10 F2 N2 O2
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.400(3) Å α= 97.89(2)°
	b = 8.195(3) Å β= 90.67(3)°
	c = 16.610(7) Å γ = 96.33(2)°
Volume	991.3(7) Å3
Z	4
Density (calculated)	1.610 g/cm3
Absorption coefficient	1.189 mm-1
F(000)	496
Crystal size	0.12 x 0.09 x 0.02 mm3
Theta range for data collection	2.69 to 66.66°
Index ranges	-8<=h<=8, -9<=k<=9, 0<=l<=19
Reflections collected	3785
Independent reflections	3785 [R(int) = 0.0000]
Completeness to theta = 66.66°	97.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9766 and 0.8705
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	3785 / 0 / 310
Goodness-of-fit on F2	1.000
Final R indices [I>2sigma(I)]	R1 = 0.0481, wR2 = 0.1436
R indices (all data)	R1 = 0.0614, wR2 = 0.1584
Largest diff. peak and hole	0.357 and -0.264 e.Å-3

6-chloro-5-fluoro-3-((E)-2-nitro-propenyl)-1H-indole 156c
CAS Number: 1193314-74-7
B.K.S. Yeung, B. Zou,M. Rottmann,S.B. Lakshminarayana , S. H. , S.Y. Leong, J. Tan , J. Wong, S. Keller-Maerki, C. Fischli, A. Goh, E.K. Schmitt, P. Krastel , E. Francotte ,K. Kuhen ,D. Plouffe , K. Henson,T. Wagner , E.A. Winzeler, F. Petersen,R. Brun, V. Dartois, T. T. Diagana, T.H. Keller *J. Med. Chem.* **2010**, 53(14), 5155-64



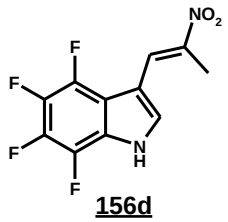
156c
MW: 254.65

Yield: 82%
^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm)
2.47 (s, 3H. CH_3), 7.64 - 7.70 (dd, J_1=7 Hz, $J_{2=}$ 6 Hz, 1H, CHarom), 7.94 - 8.00 (dd, J_1=10 Hz, 1H, CHarom), 8.08 (s, 1H, C=CH-NH), 8.39 (s, 1H, H_{vin}), 12.32 (bs, 1H, NH)

IR: (FTIR-microscopy in transmission)
3405(NH), 3059 (CHarom.), 1634 (C=C), 1278 (NO_2)

MS: MH^- = 253.1

4,5,6,7-tetrafluoro-3-((Z)-2-nitro-propenyl)-1H-indole 156d



156d
MW: 274.18

Yield: 76%

^{1}H NMR (500 MHz, DMSO-d_6) δ_H (ppm)
2.44 (s, 3H. CH_3), 8.11 (s, 1H, C=CH-NH), 8.31 (s, 1H, H_{vin}), 13.24 (bs, 1H, NH)

IR: (FTIR-microscopy in transmission)
3246 (NH), 3156 (CHarom.), 1637 (C=C), 1268 (NO_2)

MS: MH^- = 273.1

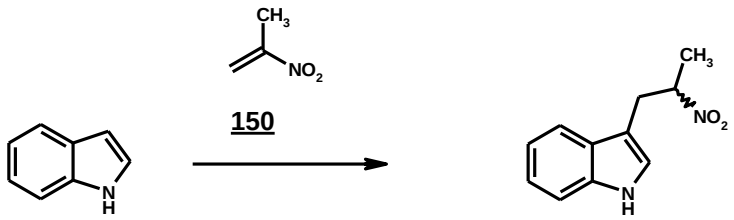
HRMS($C_{11}H_5O_2N_2F_4$, 0.7 ppm/MH^-): $[MH]^-$ = 273.02905, calculated 273. 02926 $C_{11}H_5O_2N_2F_4$

Crystal data (100 °K, 1.54178 Å)

Empirical formula	C11 H6 F4 N2 O2	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 4.9310(10) Å	α= 90°
	b = 17.465(3) Å	β= 100.766(10)°
	c = 12.378(2) Å	γ = 90°
Volume	1047.2(3) Å3	
Z	4	
Density (calculated)	1.739 g/cm3	
Absorption coefficient	1.504 mm-1	
F(000)	552	
Crystal size	0.15 x 0.06 x 0.05 mm3	
Theta range for data collection	4.43 to 66.52°	
Index ranges	-5<=h<=5, -20<=k<=20, -14<=l<=13	
Reflections collected	9075	
Independent reflections	1840 [R(int) = 0.0297]	
Completeness to theta = 66.52°	99.6 %	
Max. and min. transmission	0.9286 and 0.8058	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters 1	840 / 0 / 173	
Goodness-of-fit on F2	1.044	
Final R indices [I>2sigma(I)]	R1 = 0.0299, wR2 = 0.0772	
R indices (all data)	R1 = 0.0314, wR2 = 0.0786	
Largest diff. peak and hole	0.207 and -0.227 e.Å-3	

3-(2-nitro-propyl)-1H-indole <u>148a</u>

General procedure, racemic route



To 13.5 mL of a solution of 1.1 mmol of 2-nitropropene **<u>150</u>** in 15 mL toluene (1.0 mmol, 1.0 eq.) are added at room temperature 117.1 mg of indole **<u>147a</u>** (1.0 mmol, 1.0 eq.). The reaction mixture is stirred at 40°C over 20 hours turning into a black solution.
HLPC analysis on reverse phase ODS3 C18 (using a mixture of acetonitrile and demineralized water buffered with 0.01% of $NH_4H_2PO_4$ and a gradient of 55% to 97% acetonitrile in 15 min at 40°C) revals the presence of the signal corresponding to the 3-(2-Nitro-propyl)-1H-indole **<u>148a</u>** at 6.4 min.

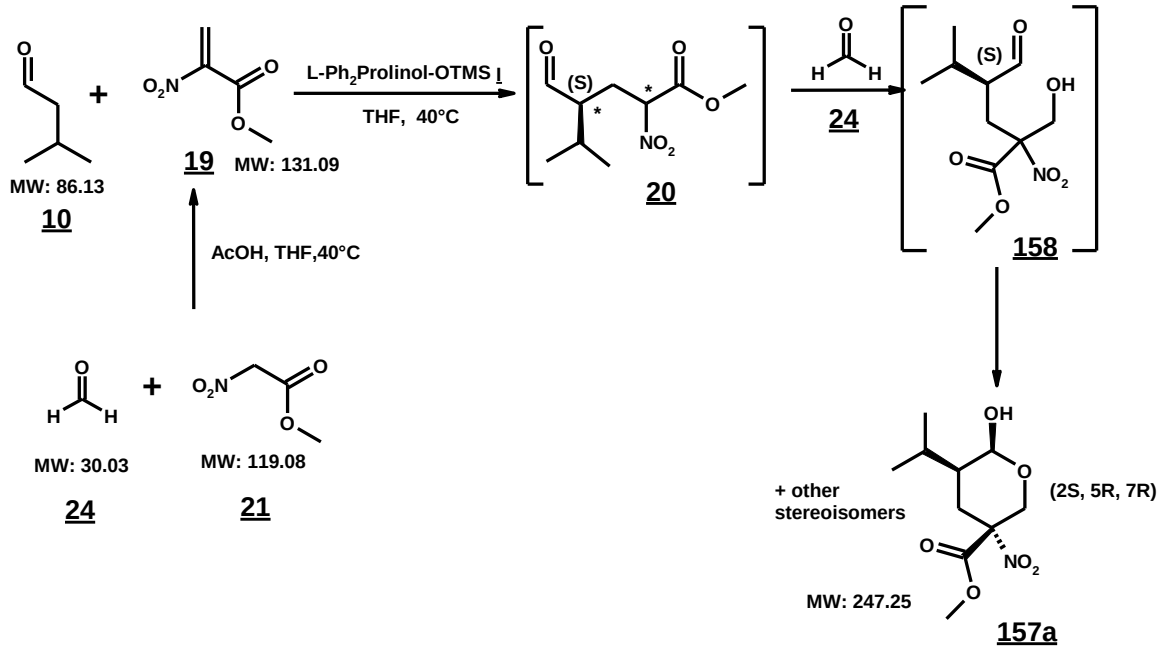
General procedure, asymmetric route

To 20 mL of a solution of 1.1 mmol of 2-nitropropene **<u>150</u>** in 15 mL toluene (1.0 mmol, 1.0 eq.) are added at room temperature 117.1 mg of indole **<u>147a</u>** (1.0 mmol, 1.0 eq.) and 0.10 equivalent of the selected catalyst.The reaction mixture is stirred at room temperature over 3 days turning into a black solution.

HLPC analysis on reverse phase ODS3 C18 (using a mixture of acetonitrile and demineralized water buffered with 0.01% of $NH_4H_2PO_4$ and a gradient of 55% to 97% acetonitrile in 15 min at 40°C) revals the presence of the signal corresponding to the 3-(2-nitro-propyl)-1H-indole **148a** at 6.4 min.

IV. EXPERIMENTAL PART OF CHAPTER 5

(3R,5S,6S)-6-hydroxy-5-isopropyl-3-nitro-tetrahydro-pyran-3-carboxylic acid methyl ester 157a

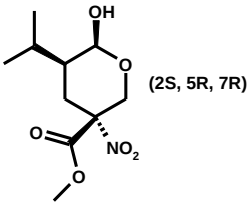


65.2 mg of (S)-diphenyl-prolinol-O-TMS-ether **I** (0.2 mmol, 0.10 eq.) are dissolved at room temperature in 6 mL of THF. 324.2 µL of isovaleraldehyde **10** (3.0 mmol, 1.5 eq.) and 540 mg of acetic acid (8.9 mmol, 4.5 eq.) are added to the mixture at room temperature. The mixture is then warmed to 35°C. A solution of 237.5 mg of methyl nitroacetate **21** (1.99 mmol, 1.0 eq.) in 3 mL of THF and a solution of 165.2 mg of aqueous formaldehyde **24** (~37% in water) (2.0 mmol, 1.0 eq.) in 3 mL of THF are added simultaneously at 35°C over a period of 30 min. After 30 min (the formation of the Michael intermediate is controlled by HPLC and proved by NMR spectroscopy (^{1}H NMR, 400 MHz, $CDCl_3$-d^6). 237.5 mg of aqueous formaldehyde (~37% in water) (2.9 mmol, 1.4 eq.) in 3 mL of THF are added dropwise at 35°C. The reaction mixture is allowed to stir over 7 hours at 35 °C and 5 mL of an aqueous solution of NaOH (2M) are added. The reaction mixture is allowed to stir overnight (~17h).
The reaction mixture is cooled down to room temperature and diluted with 10 mL of dichloromethane. 10 mL of water are added and the organic and aqueous phases are separated. The aqueous layer is extracted with 5 mL of dichloromethane. The combined organic phases are dried over $MgSO_4$, and concentrated in vacuum to yield 226.9 mg of **157** as a yellow oil, and as an isomeric mixture (LC-MS analysis shows the presence four diastereoisomers with a ratio of 61:26:13(P1:P2/P3:P4)).

The crude product is purified by column chromatography on silicagel (50 g) with hexane/ethyl acetate (3:1) to give in the pure fractions:

- 41.3 mg of lactol as a yellow oil, as an isomeric mixture of two diastereomers, 8%
- 52.7 mg of lactol as a yellow oil, as an isomeric mixture of diastereomers, 11%
- 108.0 mg of **157a** as white crystals, 22%

Spectroscopic data of (3R,5S,6S) 157a



157a

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ_H (ppm)
0.92 - 1.02 (m, 6H, CH_{3iPr}), 1.37 - 1.63 (m, 2H, CH-iPr, CH_{iPr}), 2.10 - 2.26 (m, 1H, CH_2 CH-iPr), 2.74 - 2.87 (m, 2H, CH_2 CH-iPr), 2.43 (bs, OH), 3.78 (s, 3H, OCH_3), 4.43 - 4.48 (m, 2H, CH_2O), 5.25 (d, *J*=3 Hz, 1H, CH-OH)

^{13}C NMR (150.0 MHz, dmso-d^6) δ_C (ppm)
19.80 (CH_{3iPr}), 27.72 (CH_2CH-iPr), 28.42 (CH-iPr), 41.44 (CH_{iPr}), 54.02 (OCH_3), 59.22 (CH_2), 91.42 (C-NO_2), 97.15 (CH_2O), 165.19 (C=O)

IR: (FTIR-microscopy in transmission)
3380 (OH), 2975-2877 (CH-aliphatic), 1762 (C=Oν, ester), 1552 (NO_2 ν_{ass}), 1349 (NO_2 ν_s), 1251 (C-O)

MS: $[M+H]^+$ = 248.2 (isomer A)

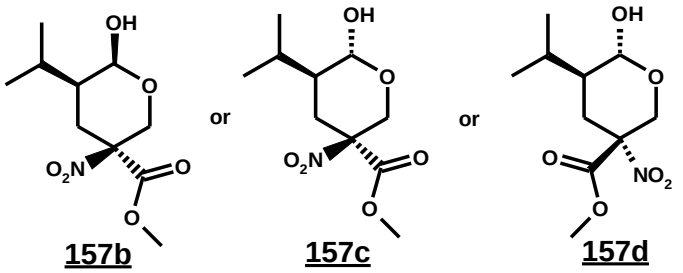
Rf (hexan/ethyl acetate, 3:1) =0.31

Crystal data (100°K, 1.54178 Å)

Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 5.842(2) Å	α= 90°
	b = 8.756(3) Å	β = 90°
	c = 24.449(7) Å	γ = 90°
Volume	1250.6(7) Å3	
Z	4	
Density (calculated)	1.313 g/cm3	
Absorption coefficient	0.930 mm-1	
F(000)	528	
Crystal size	0.34 x 0.16 x 0.10 mm3	
Theta range for data collection	3.62 to 68.13°	
Index ranges	-6<=h<=6, -10<=k<=10, -29<=l<=29	
Reflections collected	38166	
Independent reflections	2263 [R(int) = 0.0270]	
Completeness to theta = 68.13°	98.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9128 and 0.7428	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	2263 / 0 / 158	
Goodness-of-fit on F2	1.097	
Final R indices [I>2sigma(I)]	R1 = 0.0252, wR2 = 0.0673	
R indices (all data)	R1 = 0.0252, wR2 = 0.0673	

Absolute structure parameter 0.00(14)
Largest diff. peak and hole 0.211 and -0.171 e.Å-3

Spectroscopic data for the 157 as mixture of two of the diastereoisomers



157b **157c** **157d**

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ_H (ppm) (*isomeric mixture, dr 68:32)*
[0.88-0.92 (m, $CH_{3iPr\ isom\ B}$), 0.96-1.03 (m, $CH_{3iPr\ isom\ A}$), 6H], [1.49 - 1.75 (m), 1.92 - 2.08 (m), 1.97 - 2.17 (m), 2H, CH-iPr $_{isom\ A\ and\ isom\ B}$, $CH_{iPr\ isom\ A\ and\ isom\ B}$], [2.17 (t, *J*=12 Hz), 2.70 - 2.81 (m), CH_2 CH-iPr $_{isom\ A\ and\ isom\ B}$], [3.88 (s, $OCH_{3\ isom\ B)}$, 3.89 (s, $OCH_{3\ isom\ A}$), 3H], [4.16 (d, *J*=12 Hz, $CH_2O_{isom\ A}$), 4.29 - 4.37 (m, $CH_2O_{isom\ B}$), 4.39 - 4.47 (m, $CH_2O_{isom\ A}$), 4.54 (dd, J_1=12 Hz, J_2=12z, $CH_2O_{isom\ B}$, 2H], [4.80 (d, *J*=8 Hz, CH-$OH_{isom\ B}$), 5.22 (d, *J*=3 Hz, CH-$OH_{isom\ A}$), 1H]

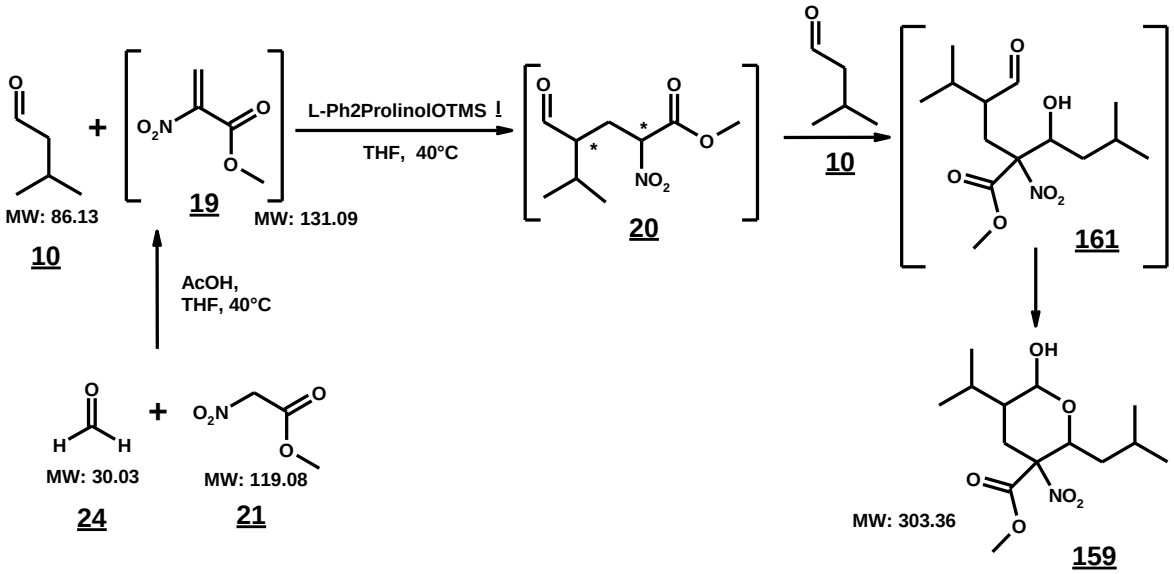
^{13}C NMR (150.0 MHz, dmso-d^6) δ_C (ppm) (*isomeric mixture, dr 68:32*
[16.57, 19.92, 20.18, 20.54] ($CH_{3iPr\ isom\ A\ and\ isom\ B}$), 28.54 ($CH_2$ CH-iPr $_{isom\ A\ and\ isom\ B}$), 29.97 (CH-iPr $_{isom\ A\ and\ isom\ B}$), 43.71 ($CH_{iPr\ isom\ A\ and\ isom\ B}$), 53.91 ($OCH_{3\ isom\ A\ and\ isom\ B}$), 59.09 ($CH_{2\ isom\ A}$), 64.63 ($CH_{2\ isom\ B}$), 89.49 (C-$NO_{2\ isom\ B}$), 90.24 (C-$NO_{2\ isom\ A}$), 91.69 ($CH_2O_{isom\ B}$), 96.86 (CH-$OH_{isom\ A}$), 165.19 (C=$O_{isom\ A\ and\ isom\ B}$)

IR: (FTIR-microscopy in transmission)
340 (OH), 2963, 2877 (C-H-aliphatic), 1765 (C=O, ν, ester), 1553 (NO_2 ν_{ass}), 1345 (NO_2, ν_s), 1242 (C-O)

MS: $[M+H]^+$ = 248.1, (isomer A)
$[M+H]^+$ = 248.1, (isomer B)

Rf (hexan/ethyl acetate, 3:1) =0.29

6-hydroxy-2-isobutyl-5-isopropyl-3-nitro-tetrahydro-pyran-3-carboxylic acid methyl ester 159



433.4 mg of (S)-diphenyl-prolinol-O-TMS-ether **I** (0.5 mmol, 0.15 eq.) are dissolved at room temperature in 16 mL of THF. 1.99 mL of isovaleraldehyde **10** (18.5 mmol, 5.0 eq.) and 1.108 g of acetic acid (18.4 mmol, 4.9 eq.) are added to the mixture at room temperature. The mixture was then warmed to 35°C. A solution of 433.4 mg of methyl nitroacetate **21** (2.6 mmol, 1.0 eq.) in 4 mL of THF and a solution of 300 mg of formaldehyde **24** (~37% in water) (3.7 mmol, 1.0 eq.) in 4 mL of THF are added simultaneously at 35°C over a period of 40 min. The reaction mixture is stirred over 8 days at 35°C.

The reaction mixture is cooled down to room temperature and diluted with 40 mL of ethyl acetate. 10 mL of water are added and the organic and aqueous phases are separated. The organic phase is then dried over $MgSO_4$, and concentrated in vacuum to yield 1.132 g of crude product **159** as an isomeric mixture of five diastereoisomers with a ratio of 29:9:42:10:10.

The crude product is purified by column chromatography on silicagel (120 g) with heptane/ethyl acetate (8:1) to give in the purest fractions 300 mg of **159** as a yellow oil (isomeric ratio: 17:26:45:12) (38% yields). Addition of a 8:1 solution (v/v) of hexan-ethyl acetate leads to the precipitation of a white solid (desired lactol as an isomeric mixture). The resulting oil can be triturated of a 1:1 solution (v/v) of hexan-diethyl ether to yield **159** with an isomeric ratio of 23:11:61:5.

Theses fractions are purified again by column chromatography on silicagel (50 g) with heptane/ethyl acetate (3:1) to give in the purest fractions 170 mg of the **159** as an isomeric mixture (isomeric ratio of 88:12), which can be recrystallised by addition of a 1:1 solution (v/v) of hexan-diethyl ether.

^{1}H NMR (600 MHz, DMSO-d_6) δ_H (ppm) (isomeric mixture dr 88:12)
0.80 - 0.95 (m, 12H, CH_{3iPr}), 1.39 - 1.46 (m, 1H, CH_2-CH_{iPr}), 1.53 - 1.65 (m, 2H, CH_2-$CH_{iPr'}$, CH-$CH_{iPr,}$), 1.65 - 1.77 (m, 1H, CH_{iPr}), 1.91 - 2.02 (m, 2H, $CH_{iPr'}$, CH_2-CH-iPr), 2.52 (m, 1H, CH_2-CH-iPr), 3.79 (s, 3H, OCH_3), 4.05 (d, J=9 Hz, 1H, CH-O), 4.65 (dd, J_1=9 Hz, J_2=7 Hz, 1H, CH-OH), 6.71 (d, J=7 Hz, 1H, OH)
isomer B: 4.57 (d, J=9 Hz, 0.12H, CH-O), 5.04 - 5.10 (m, 0.12H, CH-O), 6.69 (d, J=5 Hz, 0.12H, OH)

^{13}C NMR (150.0 MHz, dmso-d^6) δ_C (ppm)
16.36 (CH_{3iPr}), 20.49 (CH_{3iPr}, CH-iPr), 22.91 (CH-iPr), 25.33 (CH_2-CH-CH_{iPr}), 38.82 (CH_2-CH_{iPr}), 43.32 (CH-CH_{iPr}), 53.35 (OCH_3), 75.15 (CH-O), 91.06 (C-OH), 97.63 (C-NO_2), 159.51 (C=O)

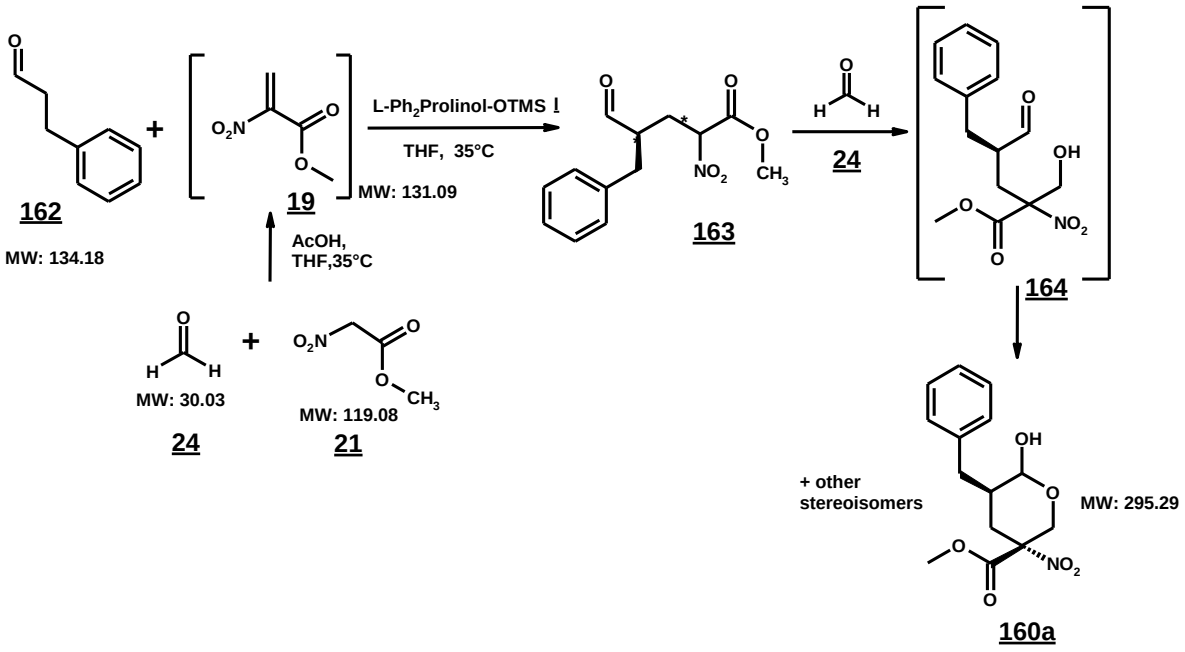
IR: (FTIR-microscopy in transmission)
3443 (OH), 2956-2933 (C-H-aliphatic), 1744 (C=O, ν, ester), 1559 (NO_2 ν_{ass}), 1342 (NO_2 ν_s), 1258 (C-O-ester)

MS: $[M+H^+]$ = 304.2 (isomer A in mixture with B)

HRMS($C_{14}H_{26}O_6N$, 0.5 ppm): $[MH-H_20]^+$= 286.16475, $C_{14}H_{24}O_5N$, calculated 286.16490
$[M+NH_4-H_20]^+$= 303.19145, $C_{14}H_{27}O_5N_2$, calculated 303.19145
$[M+NH_4]^+$= 321.20184, $C_{14}H_{29}O_6N_2$, calculated 321.20201

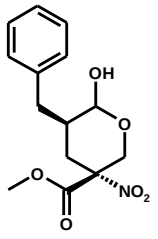
Rf (hexan/ethyl acetate, 3:1) =0.22

(3R,5R)-5-Benzyl-6-hydroxy-3-nitro-tetrahydro-pyran-3-carboxylic acid methyl ester 89a



162.8 mg of (S)-diphenyl-prolinol-O-TMS-ether **I** (10.5mmol, 0.1 eq.) are dissolved at room temperature in 10 mL of THF. 1.3 mL of acetic acid (20.6 mmol, 4.5 eq.) and 670.9 mg of hydrocinnamaldehyde **162** (5.0 mmol, 1.0 eq.) are added to the mixture at room temperature. The mixture was then warmed to 35°C. A solution of 595.6 mg of methyl nitroacetate **21** (5.0 mmol, 1.0 eq.) in 5 mL of THF and a solution of 405.7 mg of formaldehyde **24** (~37% in water) (5.0 mmol, 1.0 eq.) in 5 mL of THF are added simultaneously at 35°C for 20 min. This solution is then stirred at 35°C within 15 min and 811.6 mg of formaldehyde **24** (~37% in water) (10.0 mmol, 2.0 eq.) are added dropwise. The reaction mixture is stirred over night (~24h) at 35°C.
The reaction mixture is cooled down to room temperature and diluted with 40 mL of dichloromethane. 20 mL of an aqueous solution of NaOH (1M) are added and the both phases are separated. The organic phase is washed two times with 20 mL of water. The dichloromethane phase is then dried over $MgSO_4$, and concentrated in vacuum to yield 868.3 mg of crude product as an isomeric mixture of three diastereoisomers (isomeric ratio 62:38, P1/P2:P3).
The crude product is purified by column chromatography on silicagel (20 g) with hexane/ethyl acetate (5:1) to give in the pure fractions 452.3 mg of the lactol **160** (30%). **160a** is obtained with a yield of 8%.

Spectroscopic data of 160a



160a

MW: 295.29

^{1}H NMR: (500 MHz, dmso-d_6) δ_H (ppm) (*isomeric mixture, dr_{OH} 90:10, isomer A)*
1.86- 1.94 (m, 1H, CH-CH_{2Benz}), 2.17 (t, 1H, CH_2CNO_2), 2.32-2.42 (m, 2H, CH_2CNO_2, CH_{2benz}), 2.64 - 2.70 (m, 1H, CH_{2benz}), 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, $OCH_{3\ isom\ B}$), 4.25-4.40 (m, 2H, CH_2-O), 4.87 (t, *J*=3Hz, 1 H, CH-OH), 6.82 (dd, 1H, OH), 7.18 - 7.26 (m, 3H, CH_{arom}), 7.28 - 7.32 (m, 2H, CH_{arom})

^{13}C NMR: (101 MHz, dmso-d_6) δ_H (ppm)
28.82 (CH_2-C-NO_2), 36.74 (CH-CH_{2Benz}), 36.82 (CH_{2benz}), 53.89-53.92 (OCH_3), 59.27-59.51 (CH_2-O), 88.48 (NO_2-C-C=O), 90.95-91.49 (CH-OH), 126.10, (CH_{arom}), 128.64 (CH_{ar}) 129.12 (CH_{ar}) 139.16 (C_{ar}), 164.69 - 165.47 (C=O-ester)

IR: (FTIR-microscopy in transmission)
3375 (OH), 3031 (CHphenyl), 2953-2923 (C-Haliphatic), 1745 (C=Oν, ester), 1560 (NO_2 ν_{as}), 1585-1549 (phenyl ν), 1446-1434 (phenyl δ), 1355 (NO_2 ν_s), 1263-1143-1029 (C-O), 747 (C-$H_{monosubst}$ δ), 702 ($Phenyl_{monosubst}$ δ)

MS: $[M+NH_4]^+ = 313$, $[M+NH_4 -H_2O]^+ = 295$

Rf (hexan/ethyl acetate, 5:1)=0.18

Crystal data (100°K, 1.54178 Å)

Empirical formula	C14 H17 N O6	
Crystal system	Monoclinic	
Space group	P21	
Unit cell dimensions	a = 9.487(2) Å	α= 90°
	b = 6.3360(10) Å	β= 93.756(11)°
	c = 11.759(3) Å	γ = 90°
Volume	705.3(3) Å3	
Z	2	
Density (calculated)	1.390 g/cm3	
Absorption coefficient	0.926 mm-1	
F(000)	312	
Crystal size	0.15 x 0.14 x 0.07 mm3	
Theta range for data collection	3.77 to 68.25°	
Index ranges	-11<=h<=11, -7<=k<=7, -14<=l<=14	
Reflections collected	14405	
Independent reflections	2580 [R(int) = 0.0330]	
Completeness to theta = 68.25°	100.0 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.9380 and 0.8735
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2580 / 1 / 192
Goodness-of-fit on F2	1.091
Final R indices [I>2sigma(I)]	R1 = 0.0268, wR2 = 0.0668
R indices (all data)	R1 = 0.0281, wR2 = 0.0679
Absolute structure parameter	0.00(14)
Largest diff. peak and hole	0.156 and -0.155 e.Å-3

Spectroscopic data of the isomeric mixture 160

^{1}H NMR: (500 MHz, dmso-*d6*) δ_H (ppm) (*isomeric mixture, dr_{OH} 52:48)*
1.70- 1.80 (m, 1H, CH-$CH_{2Benz\ isomer\ A}$), 1.88-2.00 (m, 2.6H, CH-$CH_{2Benz\ isomere\ B}$, $CH_2CNO_{2\ isomer\ B}$), 2.14 (t, 2H, $CH_2CNO_{2\ isomer\ A}$), 2.32-2.37 (m, 3H, CH_2CNO_2, $CH_{2benz\ isomer\ A\ and\ isomer\ B}$), 2.63 - 2.68 (m, 2H, $CH_{2benz\ isomer\ A}$), 2.98-3.04 (m, 0.8H, $CH_{2benz\ isomer\ isomere\ B}$), 3.67 (s, 1.5H, $OCH_{3\ isomer\ B}$), 3.73 (s, 3H, $OCH_{3\ isomer\ A}$), 4.03-4.04 (m, 2H, $CH_2O_{isomer\ B}$), 4.25-4.40 (m, 2H, $CH_2O_{isomer\ A}$), 4.70 (t, *J*=3Hz, 1 H, CH-OH $_{isomer\ A\ and\ isomer\ B}$), 6.85 (dd, 1H, $OH_{isomer\ A}$), 6.97 (dd, 0.4H, $OH_{isomer\ B}$), 7.16 - 7.25 (m, 3H, CH_{arom}), 7.27 - 7.35 (m, 2H, CH_{arom})

^{13}C NMR: (101 MHz, dmso-d_6) δ_C (ppm)
28.81 (CH_2-C-NO_2), 36.71 (CH-CH_{2Benz}), 36.80 (CH_{2benz}), 54.00 (OCH_3), 59.4 (CH_2-O), 88.46 (NO_2-C-C=O), 90.93-91.46 (CH-OH), 126.08 (CH_{arom}), 128.31 (CH_{arom}) 128.80 (CH_{arom}), 138.81 (C_{ar})) 165.45 (C=Oester)

IR: (FTIR-microscopy in transmission)
3375 (OH), 3030 (CH-phenyl), 2954-2923 (C-Haliphatic), 1746 (C=Oν, ester), 1560 (NO_2 ,ν_{ass}), 1604-1495-1458 (Phenyl ν), 1446-1434 (Phenyl δ), 1354 (NO_2 ν_s), 1263-1019 (C-O), 747 (C-$H_{monosubst}$ δ), 702 ($Phenyl_{monosubst}$ δ)

MS: $[M+NH_4]^+$ = 313, $[M+NH_4^+ -H_2O]$ = 295 (isomer A)
$[M+NH_4]^+$ = 313, $[M+NH_4^+ -H_2O]$ = 295 (isomer B)

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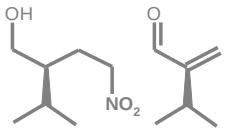
CHAPTER 2: ALISKIREN PRECURSORS



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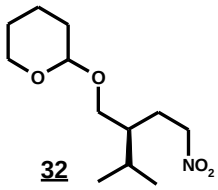

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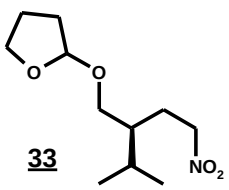

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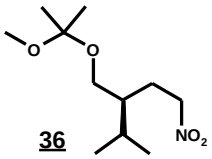

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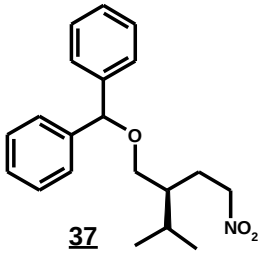

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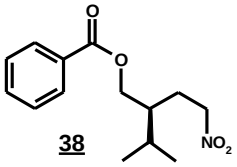

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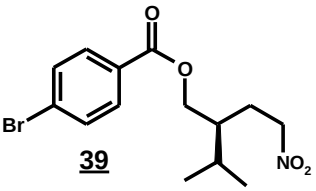

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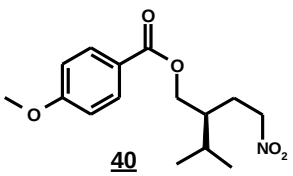

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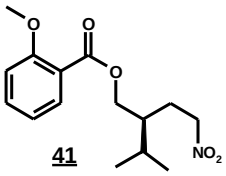

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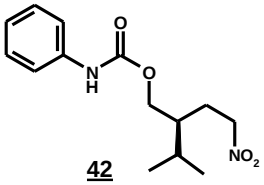

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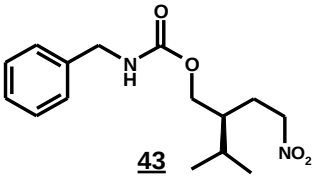

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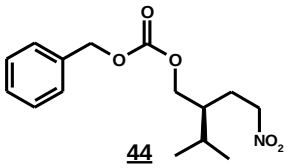

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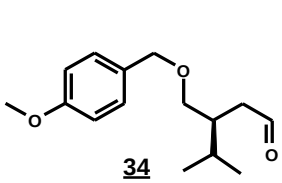

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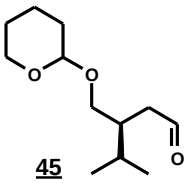

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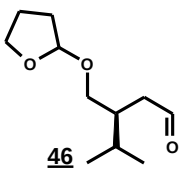

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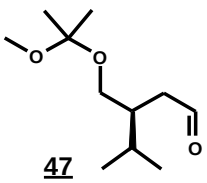

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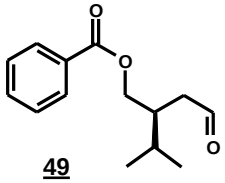

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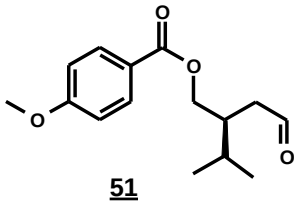

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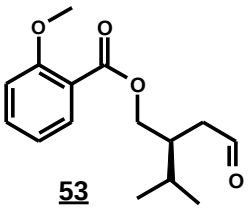

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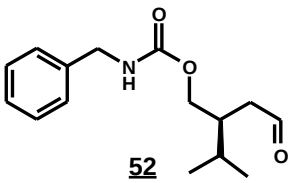

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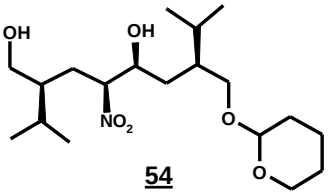

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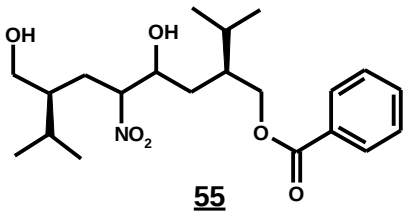

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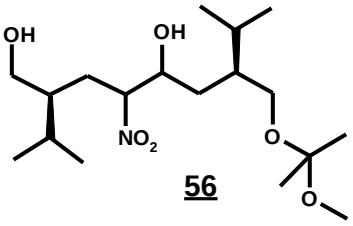

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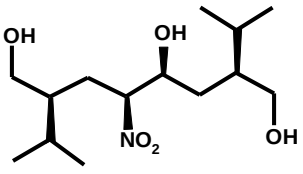

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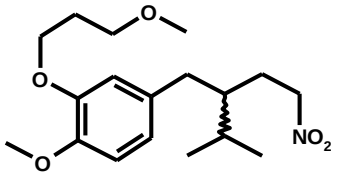

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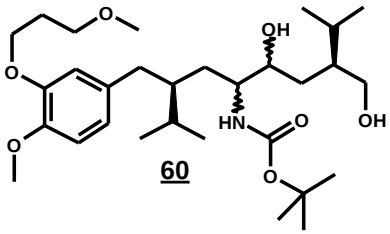

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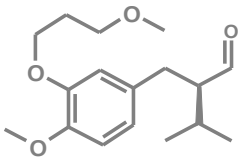

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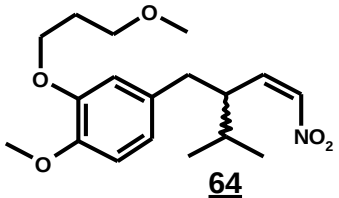

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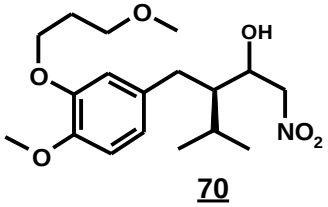

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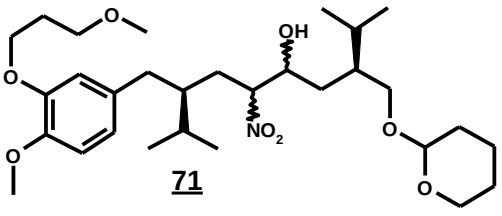

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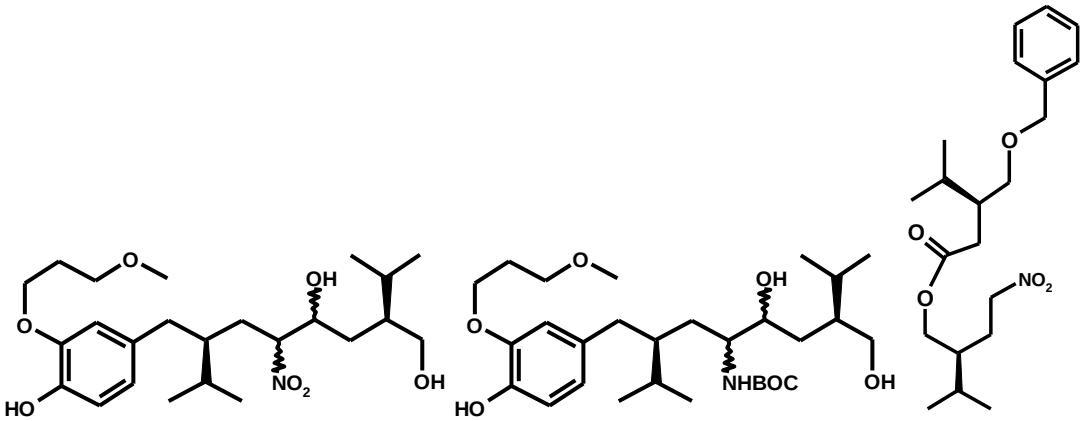

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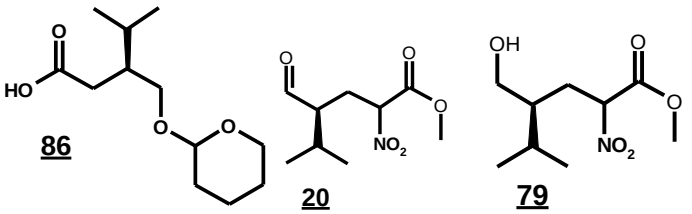

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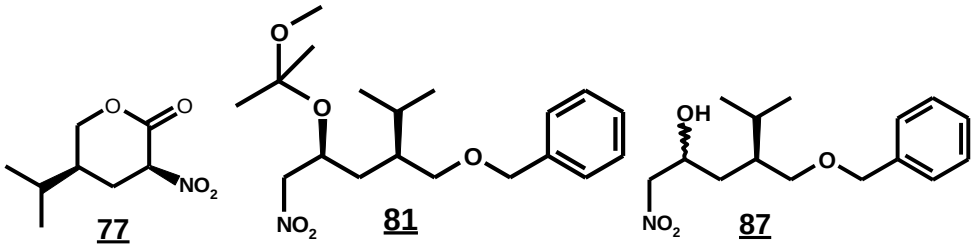

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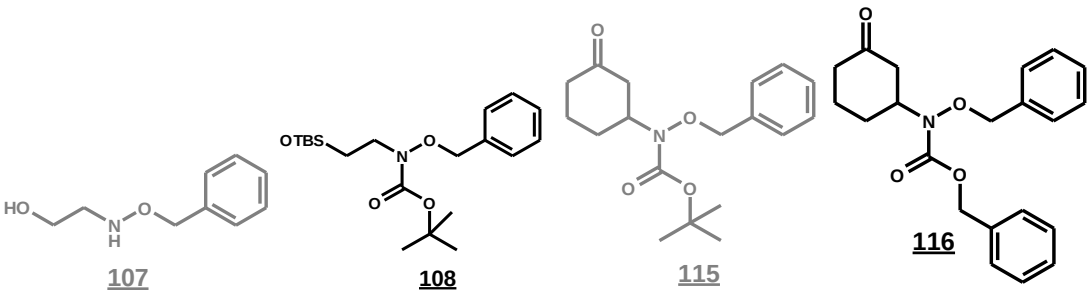
CHAPTER 3: AFQ056 PRECURSORS



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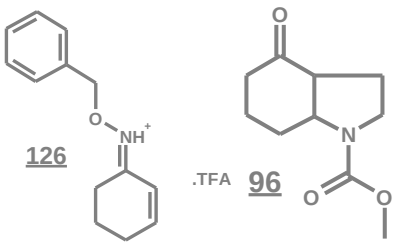

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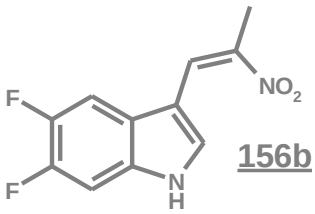
CHAPTER 4: KAE609 PRECURSORS



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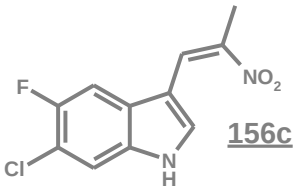

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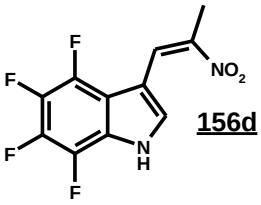

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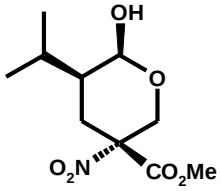
CHAPTER 5: MULTICOMPONENT DOMINO-REACTIONS



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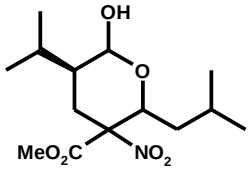

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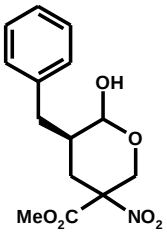

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