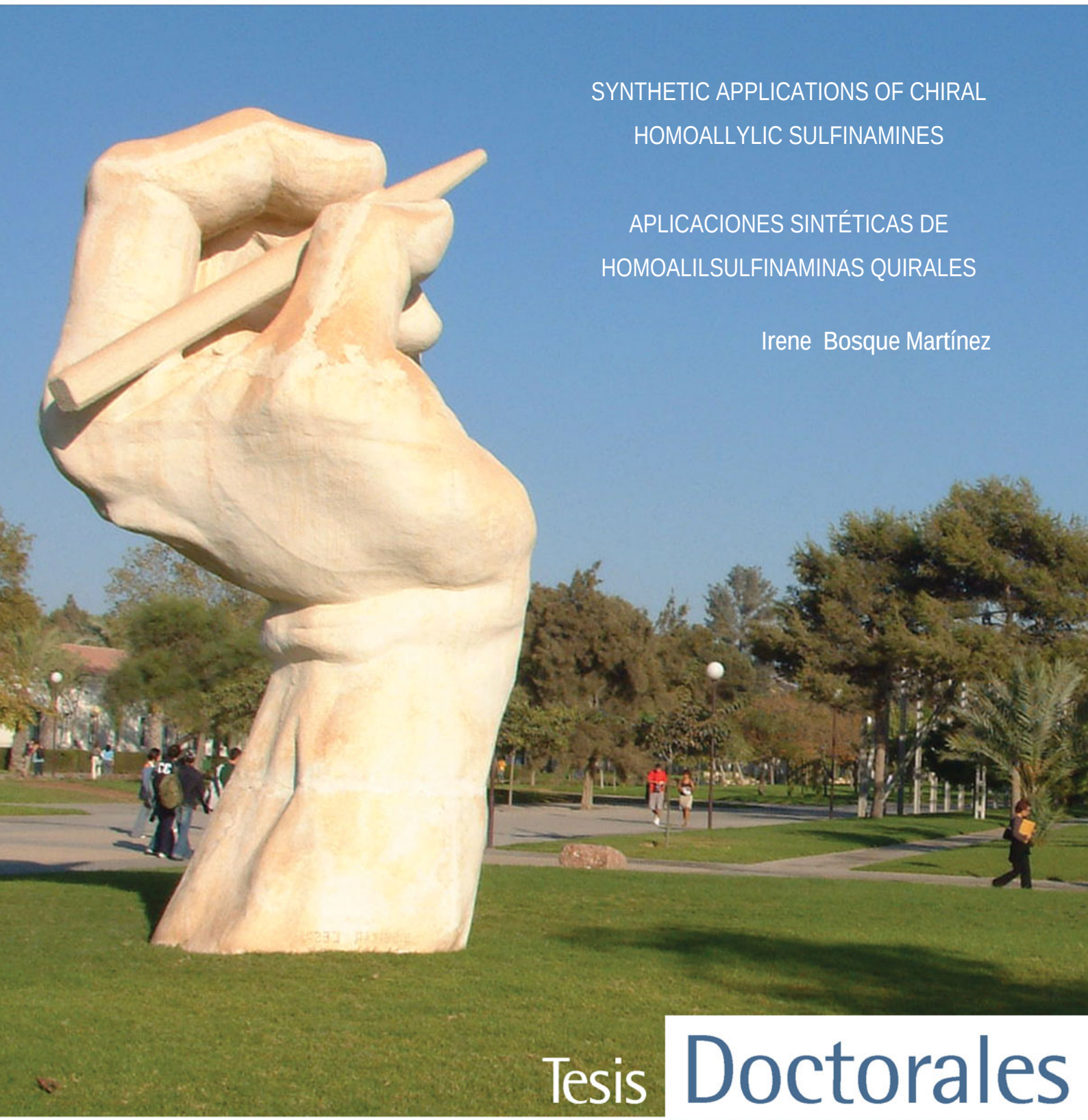
Universitat d'Alacant
Universidad de Alicante

SYNTHETIC APPLICATIONS OF CHIRAL HOMOALLYLIC SULFINAMINES

APLICACIONES SINTÉTICAS DE HOMOALILSULFINAMINAS QUIRALES

Irene Bosque Martínez



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SYNTHETIC APPLICATIONS OF CHIRAL HOMOALLYLIC SULFINAMINES

APLICACIONES SINTÉTICAS DE HOMOALILSULFINAMINAS QUIRALES

Memoria para optar al Título de Doctor Internacional por la Universidad de Alicante presentada por la Licenciada:

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Alicante, Febrero de 2014

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A mis padres, a mi hermano

y a Javi

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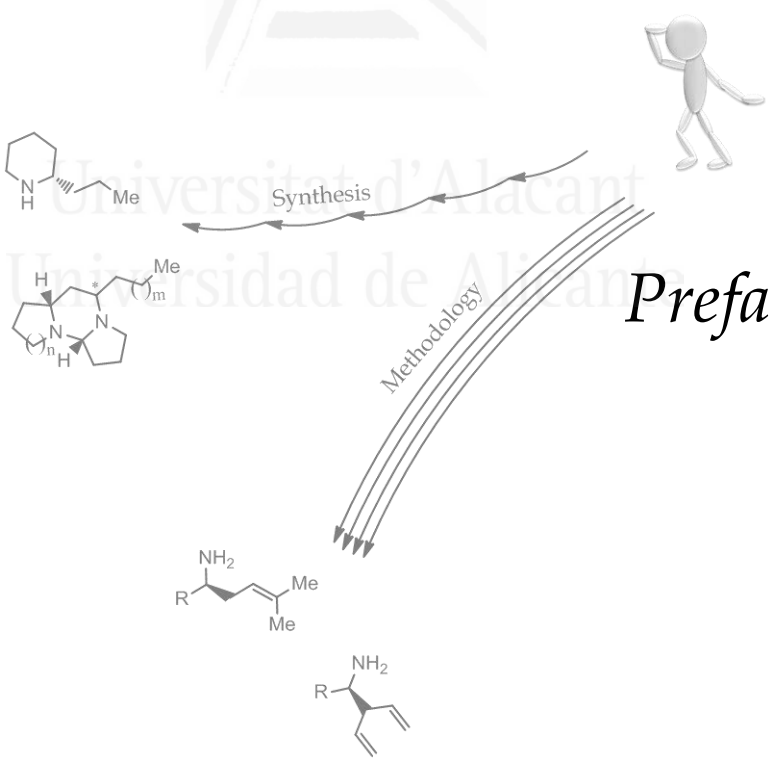


Preface

This Ph.D. dissertation describes the use of the indium-mediated aminoallylation protocol, developed in our research group, in the synthesis of enantioenriched homoallylamines which act as potent building blocks in the synthesis of several natural products. Diverse allyl bromide derivatives have been explored as well as their potential in synthetic applications.

This thesis contains an initial Bibliographic Background in which a summary of the most relevant synthetic approaches to chiral homoallylic amines and their use as building blocks is presented. A special attention has been pointed out in *t*-butylsulfinylamine and indium, which are key substrates of this thesis.

The content of the dissertation has been divided in four chapters. Each one contains a specific intoduction directly related with the content of the chapter, the objectives, a section for results and discussion and an experimental section. The chapters have been organized according to the chronological sequence in which they were completed. Literature references are included at the bottom of the page which mentiones it.

A Supplementary Information CD has been attached at the end of this book, which gathers the ^{1}H and ^{13}C NMR spectra for all compounds, GC-MS for tetraponerines (from Chapter II) and HPLC and selected GSP-GC traces for enantioenriched prepared compounds. Besides, optimized geometries and zero point energies, as well as thermodynamic data for all calculated structures of **T3** and **T4** by DFT (from Chapter II) have been included. The CD also contains the cystallographic data in CIF format for all crystal structures shown.

A brief summary of each chapter is given in the following paragraphs.

CHAPTER I: Enantioenriched 2-Allylpiperidine: A Very Useful Precursor in the Synthesis of Alkaloids. An efficient stereocontrolled preparation of (2*R*,R_s)-2-allyl-*N*-(*tert*-butylsulfinyl)piperidine and its enantiomer up to 4 g scale has been developed. Their potential as building blocks has been demostrated by the synthesis of some natural and unnatural compounds such as (+)-coniine, (-)-pelletierine or 5-*epi*-(+)-cermizine C.

CHAPTER II: Tetraponerines: A Singular Family of Alkaloids. The use of DFT calculations and the analysis of the reported biosynthetic assays for some tetraponerines led to the development of a divergent synthetic route to afford all natural tetraponerines, from **T1** to **T8**. The use of two consecutive indium-mediated aminoallylations, the predominant stereocontrol by the *tert*-

butylsulfinyl group in the second aminoallylation and the thermodynamic control of the aminal stereogenic center, made possible the synthesis of the eight mentioned tetraponerines in a high enantiomeric purity. Bolhmann Bands in the IR spectra of all synthesized tetraponerines were identified and analyzed.

CHAPTER III: A General Procedure to Afford Enantioenriched Linear Homoprenylamines. The well known 2-azonia-Cope rearrangement has been used for the synthesis of enantioenriched linear homoallylamines with good yields and enantioselectivities. A chiral molecule, synthesized by using the indium-mediated aminoallylation protocol, has been used as chiral amino-prenyl transfer reagent to a variety of aldehydes, including aliphatic substrates. The synthesized homoprenylamines have been transformed by intramolecular hydroamination into the corresponding pyrrolidines, showing their utility as building blocks.

CHAPTER IV: Pentadienylation of Carbonyl Compounds. The indium-mediated amino-pentadienylation of carbonyl compounds was examined using 2,4-prentadienyl bromide and *tert*-butylsulfinylamine. The methodology allowed the preparation of the desired compounds with high regioselective γ-addition in all cases. Notably, the protocol accommodates not only aldehydes but also ketones with good regio- and diastereoselectivity. Some applications of these homoallylic amines have been developed, being of special interest the synthesis of enantiopure 2,2,3-trisubstituted pyrrolidines.

These studies have been financially supported by the *Ministerio de Ciencia e Innovación* (CTQ2011-24165). I also thank the *Generalitat Valenciana* for a predoctoral fellowship (ACIF/2011/159).

Abbreviations

aq	aqueous
Ar	Aromatic group
atm	Atmosphere
9-BBN	9-Borabicyclo[3.3.1]nonane
Boc	*tert*-Butoxicarbonyl
cat	Catalyst
Cbz	Benzyloxicarbonyl
COSY	Correlation spectroscopy
CSA	Camphorsulfonic acid
DCE	Dichloroethane
DMI	1,3-Dimethyl-2-imidazolidinone
dr	Diasteromeric ratio
ee	Enantiomeric excess
equiv	Equivalents
DABCO	1,4-Diazabicyclo[2.2.2]octane
DEPT	Distortionless Enhancement by Polarization Transfer
DFT	Density functional theory
DIBAL-H	Diisobutylaluminium hydride
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
d	Doublet
EDC	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide
ESI	ElectroSpray Ionization
GC	Gas Chromatography
IR	Infrared
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence spectroscopy
KHMDS	Potassium bis(trimethylsilyl)amide

m-CPBA	*meta*-Chloroperbenzoic acid
mp	Melting point
nOe	Nuclear Overhauser effect
MS	Molecular sieves *or* Mass spectroscopy
OTf	Triflate
PG	Protecting group
PhMe	Toluene
p-TS	*p*-Tolensulfinyl
py	pyridine
q	Quartet
ref	Reference
(*R*)-MPA	(*R*)-methoxyphenylacetic acid
s	Singulet
t	Time
t	Triplet
$t_{R.}$	Retention time
t-BS	*tert*-Butylsulfinyl
T	Temperature
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
Tol	Toluene
TS	Transition state
^{1}H-NMR	Proton nuclear magnetic resonance
^{13}C-RMN	Proton nuclear magnetic resonance
δ_H	Nuclear magnetic resonance shifting

Bibliographic Background

1. CHIRAL HOMOALLYLIC AMINES: IMPORTANT BUILDING BLOCKS OF BIOACTIVE COMPOUNDS.

The presence of nitrogen atoms in small molecules leads to desirable medicinal properties, including improved solubility under physiological conditions, favorable polar surfaces, and hydrogen-bonding interactions with amino acid residues. Not surprisingly, a vast majority of pharmaceutical drugs approved by the U.S. Food and Drug Administration (FDA) are nitrogenated compounds. Chiral amines represent an important class of bioactive small nitrogenated molecules with important effects on the discovery of new drugs.

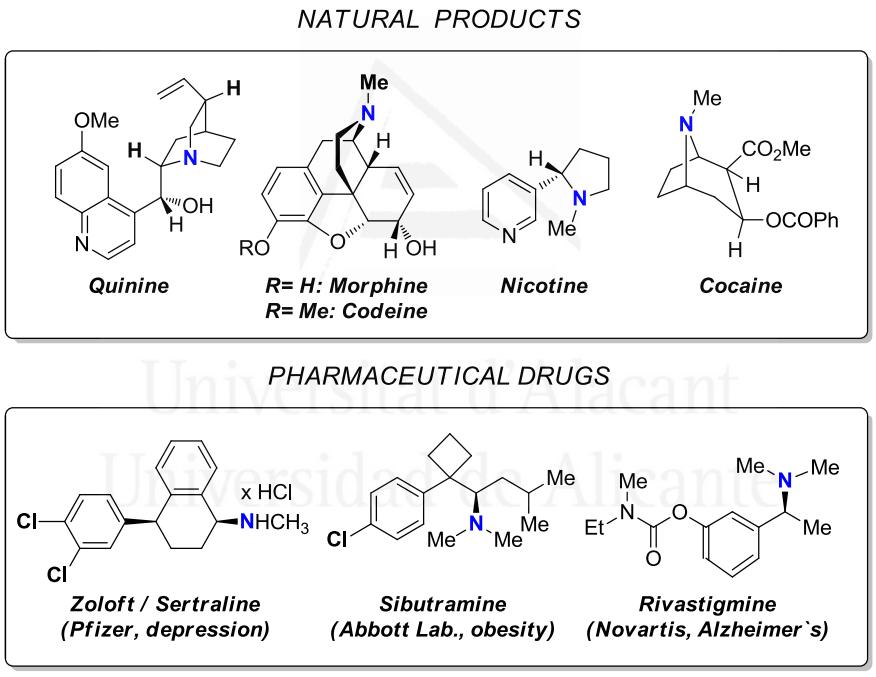
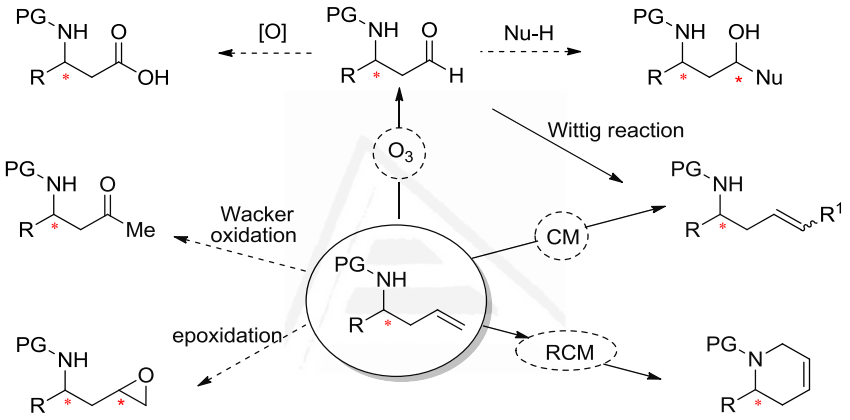


Figure I

From this group, amines with a stereogenic carbon center adjacent to the nitrogen atom constitute an important subclass of powerful pharmacophores in drugs derived from natural or synthetic sources.[1] A few examples of medicinally relevant α-chiral amines are given in **Figure I**.

[1] Nugent, T. C. *In Chiral Amine Synthesis: Methods, Developments and Applications*; Wiley-VCH; Weinheim **2010**.

The discovery of many bioactive molecules depends on the development of general and reliable methods to prepare α-chiral amines and this reason is behind the effort that several synthetic groups have invested in this field. In this context, α-chiral homoallylic amines represent very valuable building blocks of more complex molecules. The versatility of these compounds resides on the possibility of the allyl moiety to participate in a number of synthetically useful transformations as well as on the diverse functionalities that can be introduced on the nitrogen atom.

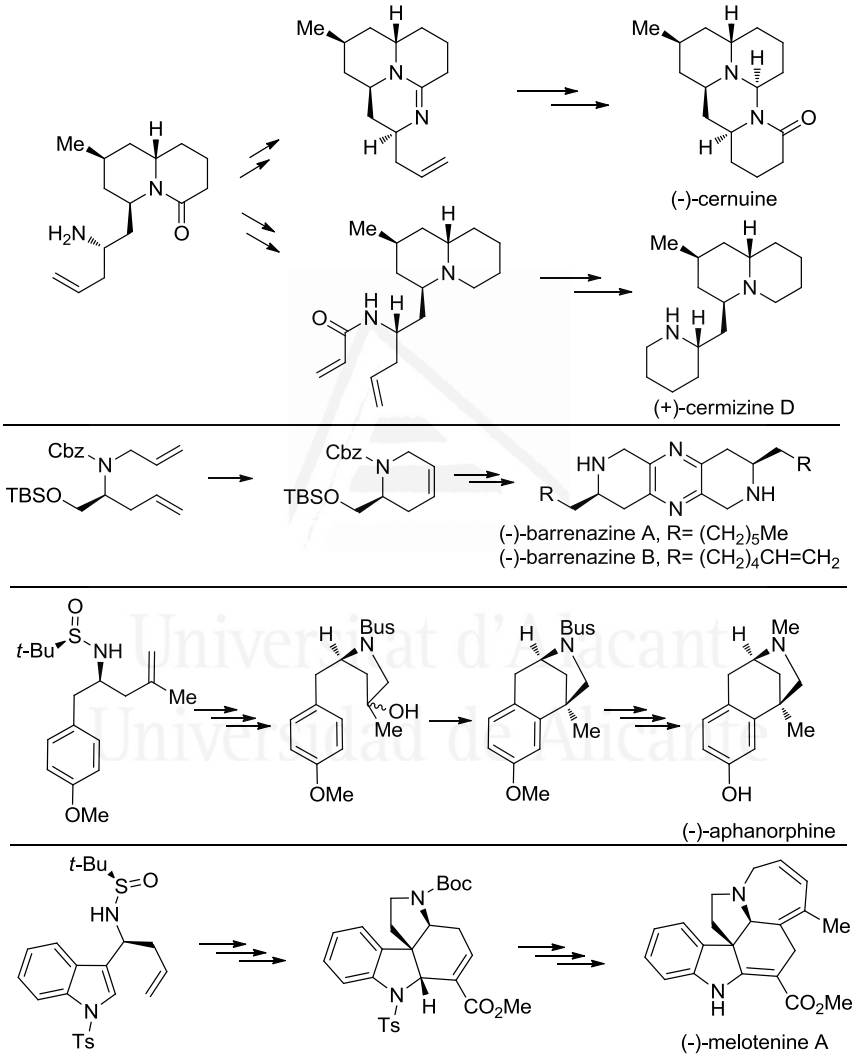


Scheme I

Among a wide range of transformations of the chiral homoallylic amines, the oxidative cleavage of the double bond by ozonolysis or other methods can give access to the corresponding aldehydes, which could be easily converted in β-aminoacids or suffer the addition of different nucleophiles to prepare β-amino alcohols. Epoxidation or Wacker oxidation are another two examples of synthetic transformations that allow the straightforward preparation of β-amino ketones or β-amino epoxides, respectively, which also constitute very versatile building blocks. Moreover, the recent progresses achieved in the field of alkene metathesis[2] have greatly expanded the synthetic utility of chiral homoallylic amines (**Scheme I**).

[2] (a) Olszewski, T. K.; Bieniek, M.; Skowerski, K.; Grela, K. *Synlett* **2013**, *24*, 903. (b) McKinty, A. M.; Lund, C.; Stephan, D. W. *Organometallics* **2013**, *32*, 4730. (c) Grela, K.; Gulajski, L.; Skowerski, K., Edited by Dixneuf, P. H.; Cadierno, V. *Metal-Catalyzed Reactions in Water* **2013**, 291. For more information see: Grubbs, R. H. *Handbook of Metathesis*, Wiley-VCH: Weinheim **2003**.

To illustrate the usefulness of these compounds as intermediates of more complex molecules, several bioactive natural products have been prepared. Some recent examples are the (-)-cernuine, (+)-cermizine D,[3] (-)-barrenazines A and B,[4] (-) and (+)-aphanorphine[5] or (-)-melotenine A,[6] among others (**Scheme II**).

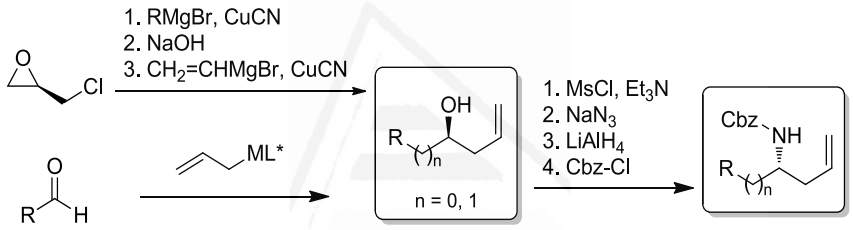


Scheme II

[3] Nishikawa, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 1987.
[4] Peña-López, M.; Martínez, M. M.; Sarandeses, L. A.; Sestelo, J. P. *Org. Lett.* **2010**, *12*, 852.
[5] Medjahdi, M.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem.* **2011**, 2230.
[6] Zhao, S.; Sirasani, G.; Vaddypallly, S.; Zdilla, M. J.; Andrade, R. B. *Angew. Chem. Int. Ed.* **2013**, *52*, 8309.

2. SYNTHETIC APPROACHES TO CHIRAL HOMOALLYLIC AMINES.

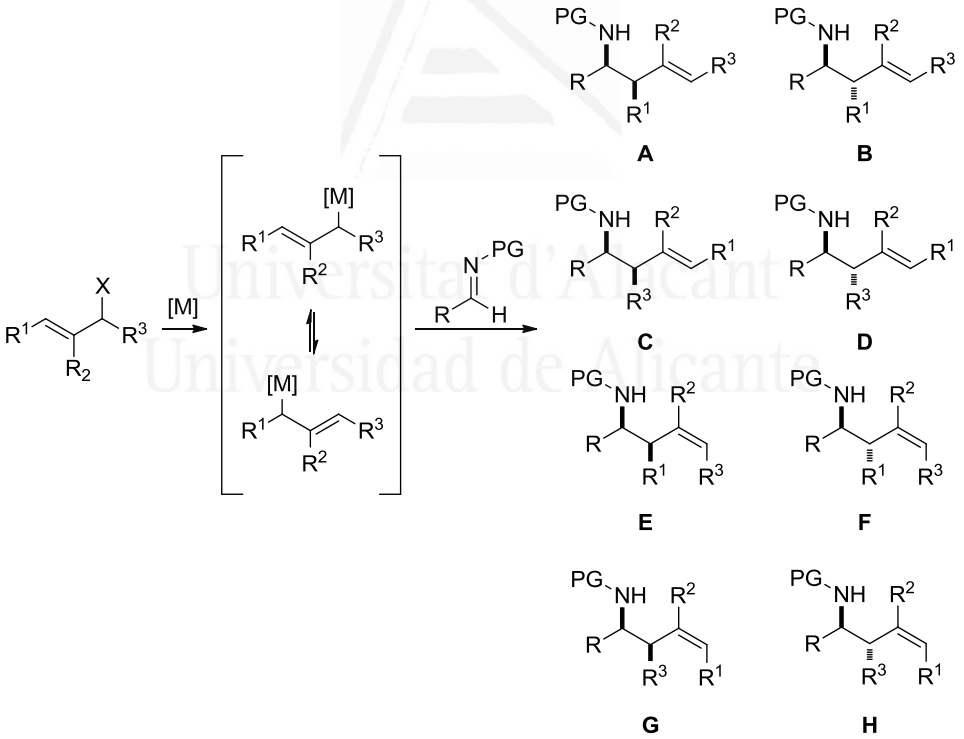
A reliable, robust and easy to scale protocol is highly desirable for the formation of chiral homoallylic amines when they are required as synthetic precursors. One of the commonly used strategies implies the preparation of an enantioenriched alcohol, which can easily be transformed into the corresponding amine *via* azide, formed by nucleophilic displacement of the corresponding mesilate or under Mitsunobu reaction conditions (DPPA/Ph_3P/DEAD) (**Scheme III**). Moreover, the protection of the free amine functionality is often accomplished to avoid complications during the synthetic transformations of this building block.



Scheme III

Obviously, shorter reaction sequences in the preparation of chiral homoallylic amines increase their utility as synthetic precursors. A more direct and successful approach is the stereoselective allylation of imines. However, the imines exhibit some intrinsic problems of reactivity as their poor electrophilicity compared to carbonyl compounds. Another common problem is encounter in aliphatic imines which can be deprotonated in their alpha positions to form the corresponding metaloenamine, preventing the desired nucleophilic addition of the allylic moiety onto the iminic carbon. For these reasons, an imine activation turns to a necessity for a successful reaction, and limits the use of allylic organometallic species to non-nucleophilic reagents when imines with alpha acidic protons are used as substrates.

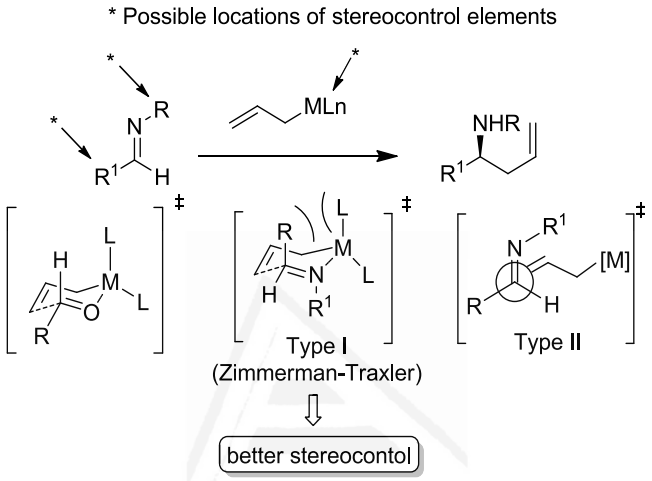
One of the biggest challenges in the imine allylation is the wide range of products that can be generated when substituted organometallic allyl reagents are used (**Scheme IV**).[7] In fact, 16 possible isomers could be formed from this apparently simple reaction as a consequence of four possible variables: enantioselectivity of the reaction (all showed compounds *vs* their enantiomers); regioselectivity derived from α- or γ-attack and/or the allylic isomerization of the organometallic allyl intermediate (A, B, E, F vs C, D, G, H); *E*/*Z* geometry of the double bond (A, B, C, D vs E, F, G, H); and relative configuration of both carbon stereocenters (A, C, E, G vs B, D, F, H). Moreover, some problems of chemoselectivity could arise if the organometallic species are not compatible with functional groups of the substrate. For all the above mentioned, in order to generate only one of the possible allylation products a careful election of reaction partners and conditions is needed.



Scheme IV

[7] Chen, M. Z.; McLaughlin, M.; Takahashi, M.; Tarselli, M. A.; Yang, D.; Unemura, S.; Micalizio, G. C. J. *Org. Chem.* **2010**, *75*, 8048.

On the other hand, one advantage of imines over carbonyl compounds, is the possibility of a stereocontrol element not only in the substrate, or in the reagent, but also in a chiral moiety attached to the nitrogen atom (**Scheme V**). This chiral auxiliary might also act as a protecting group after the formation of the desired homoallylic amine.



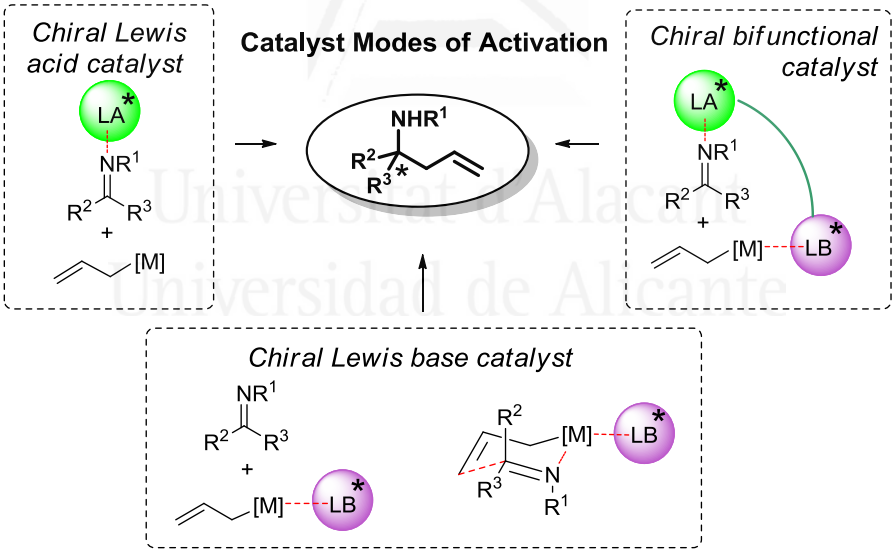
Scheme V

In general, a cyclic Zimmerman-Traxler transition state[8] (or Type I reactivity[9]) seems to reign in the addition of some organometallic species (Mg, Ti, B, In) to imines. However, an acyclic type II[10] reactivity seems to be more common with other allylic species (Si, Sn) which require a Lewis acid. It is interesting to remark that while in type I allylilation of aldehydes the R substituent is preferentially posed on the equatorial position of the cyclic transition state in order to minimize non-bonding steric interactions, a different scenario is observed for aldimines. In order to maintain their antiperiplanar configuration in the cyclic transition state, it is reported that (*E*)-aldimines prefer to place the R/R^1 groups in adjacent axial positions. Consequently it is also reported that the ligands attached to the metal play a more important role in type I allylation of aldimines, being a key aspect to achieve a good stereocontrol.[11]

[8] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
[9] This terminology was introduced in the carbonyl compounds allylation: Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655.
[10] For mechanistic issues: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
[11] First studies: Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Itoh, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778.

2.1. CATALYTIC ENANTIOSELECTIVE ALLYLATION OF IMINES: CHIRAL LEWIS ACID AND/OR LEWIS BASE ACTIVATION.

The catalysts used in enantioselective allylations can promote the reaction through different activation modes. In some cases Lewis acids with a chiral environment are used to activate the imine towards the nucleophilic attack. On the other hand, chiral Lewis bases can promote the allylation of imines with allyl metal reagents in a conceptually different way. Binding of the chiral ligand to the allylmetal specie enhance its nucleophilicity while further coordination of the metal by the imine increase the electrophilicity of the iminic carbon. Double activation could be also achieved by using chiral bifunctional catalysts. In this case, the simultaneous activation of both electrophilic and nucleophilic reaction partners occurs ideally through a cooperative action of different functionalities of the chiral ligand(s) (**Scheme VI**). A few representative examples will be illustrated in this section.[12]

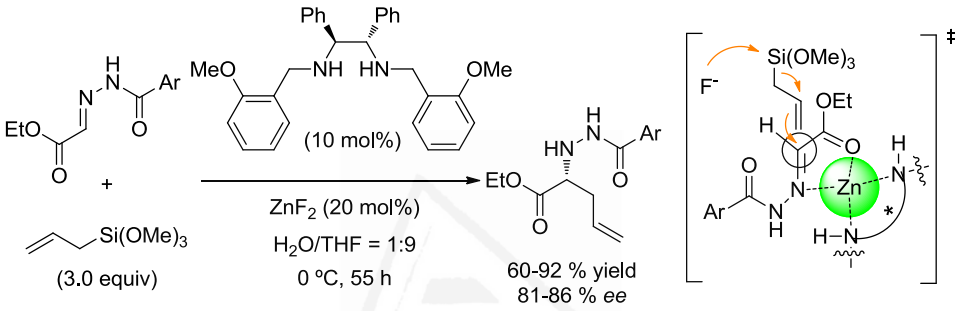


Scheme VI

The group of Kobayashi has recently described the addition of allyltrymethoxisilane to α-ethoxicarbonyl acylhydrazones by using substoichometric amounts of a chiral diamine and ZnF_2, achieving good

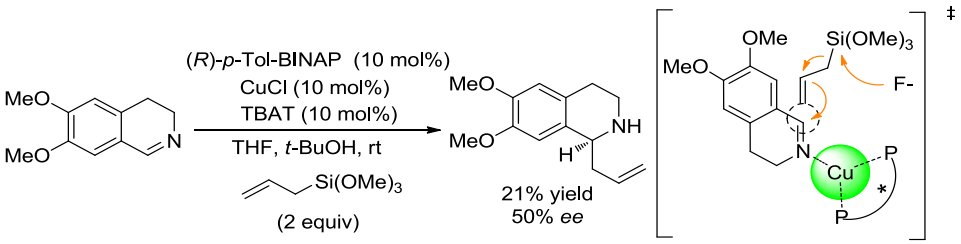
[12] For a more complete revision of this topic, see: Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774.

enantioselectivities in the presence of water (**Scheme VII**).[13] It is believed that in this case the Zn (II) is coordinated to the chiral diamine ligand and acts as a *Lewis acid activating the hydrazone* towards the addition of the allylsilane nucleophile. At the same time, the liberated fluoride anions attack the silicon atom enhancing the nucleophilicity of the allyl group *via* Lewis base activation. It seems that the methoxy group in the chiral diamine ligand plays an essential role for attaining high yields and stereoselectivities.



Scheme VII

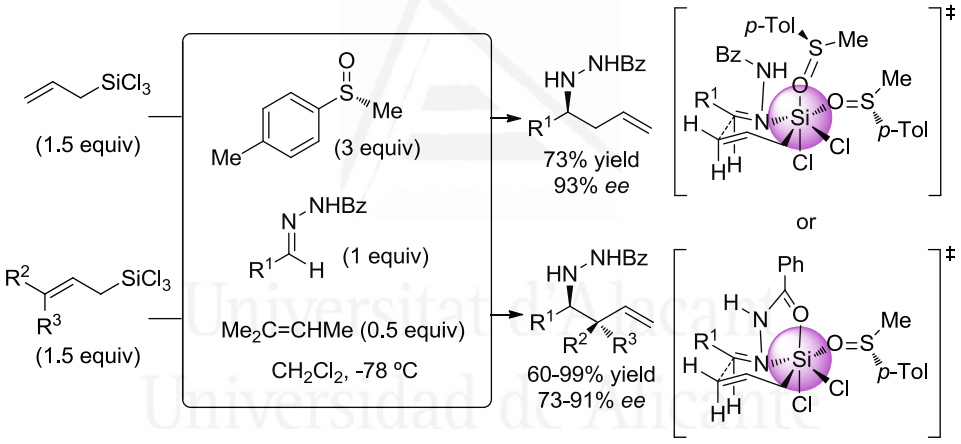
The first catalytic enantioselective allylation of a cyclic imine was reported by Itoh.[14] The best results were achieved with allyltrimethoxysilane in the presence of substoichometric amounts of a complex prepared from CuCl and (*R*)-*p*-Tol-BINAP (**Scheme VIII**). As in the example previously shown, it is proposed that liberated fluoride anions promote the addition of the allylsilane. However the bidentate chiral ligand is supposed to be bound to the copper metal which also is coordinated by the imine, exerting a crucial *Lewis acid activation*.



Scheme VIII

[13] Hamada, T.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2003**, 42, 3927 (*corrigenda*: *Angew. Chem., Int. Ed.* **2003**, *42*, 4565).
[14] Itoh, T.; Miyazaki, M.; Fukuoka, H.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1295.

Allyltrihalosilanes are typical reagents for the enantioselective allylation of carbonyl/imine derivative compounds promoted by Lewis base ligands.[15] It is proposed that the silicon atom is electrophilic enough to be coordinated by the chiral ligand and the electrophile, taking place the allyl transfer with efficient transfer of chirality. In this context the group of Kobayashi found that chiral aryl alkyl sulfoxides were effective in the enantioselective allylation of *N*-benzoylhydrazones with allyltrichlorosilane (**Scheme IX**). In order to obtain better enantioselectivities it was found that the use of 3 equivalents of the chiral Lewis base promoter was essential. After the work-up of the reaction this promoter was efficiently recovered (<90%). Interestingly, the addition of 2-methyl-2-butene as acid scavenger was also found important to suppress undesired racemization of the chiral sulfoxide.[16]



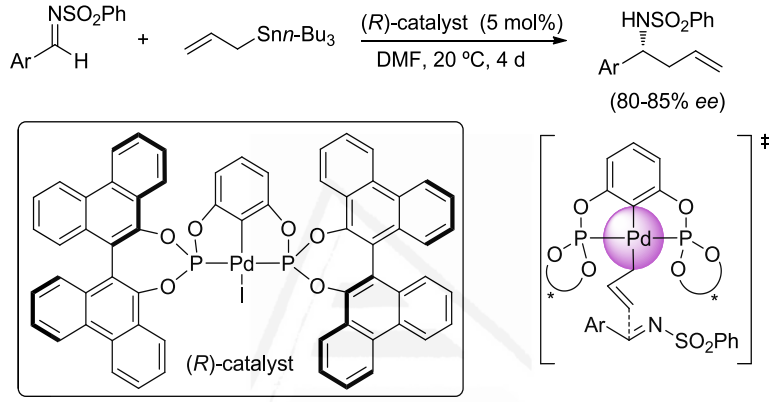
Scheme IX

Moreover, when crotyltrichlorosilanes were used, high stereospecificity and enantioselectivity of the reaction were observed (**Scheme IX**). Thus, (*Z*)-crotyltrichlorosilanes gave the *anti*-adducts whilst (*E*)-crotylchlorosilanes gave the *syn* products. This stereospecificity is in line with a cyclic chair-like transition state, but the authors did not mention whether one or two sulfoxide units are involved. After this work, many other chiral ligands have been used as *Lewis base promoters* in the addition of allyltrichlorosilanes to *N*-benzoylhydrazones, including BINAP-dioxides derivatives,[17] bridged bisulfoxides[18] and

[15] For pioneer contributions, see: (a) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161. (b) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620.
[16] Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610.
[17] Ogawa, C.; Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 6491.

sulfinamides.[19]

Pincer complexes of palladium have also been examined as catalysts for the enantioselective allylation of sulfonimines.[20] In this case the allylation reactions of aryl sulfonyl imines with allyltri-*n*-butyl stannane, conducted at 20 ºC in dry DMF, were accomplished in the presence of a chiral biphenanthrol palladium complex with good levels of enantioselection (**Scheme X**).



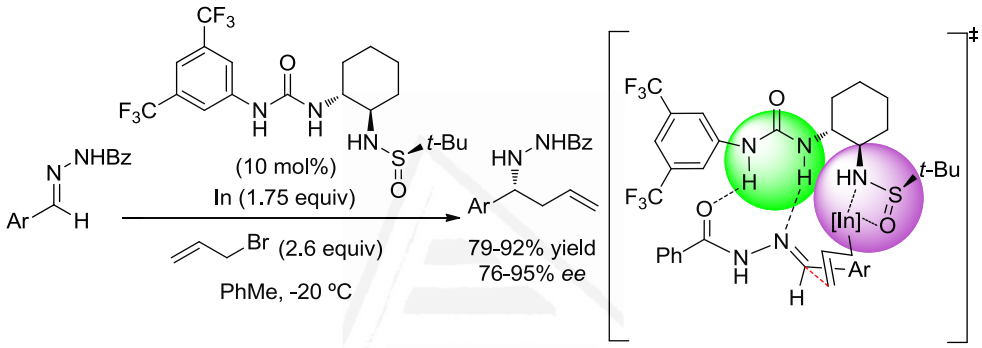
Scheme X

Based on previous DFT and experimental studies,[21] the authors suggest that the nitrogen atom of the sulfonylimine unit does not coordinate to palladium as the negative charge is efficiently delocalized towards the sulfonyl group. Therefore, the sulfonylimine substrate does not form a six-membered ring transition state with the allyl moiety and palladium, and the stereoselectivity is determined by steric interactions between the sulfonyl group and the chiral pincer ligand. This proposed mechanism suggests a *Lewis base activation* mode.

Examples of real chiral bifunctional catalysts promoting the allylation of imine derivatives are very scarce in the literature. To illustrate this mode of activation we have chosen an example reported by the group of Jacobsen in the addition of allylindium reagents to *N*-benzoylhydrazones. The authors examined this addition at –20 ºC with several ligands derived from a simple chiral diamine

[18] (a) García-Flores, F.; Flores-Michel, L. S.; Juaristi, E. *Tetrahedron Lett.* **2006**, *47*, 8235. (b) Fernández, I.; Valdivia, V.; Pernía Leal, M.; Khiar, N. *Org. Lett.* **2007**, *9*, 2215.
[19] Fernández, I.; Alcudia, A.; Gori, B.; Valdivia, V.; Recio, R.; García, M. V.; Khiar, N. *Org. Biomol. Chem.* **2010**, *8*, 4388.
[20] Aydin, J.; Kumar, K. S.; Sayah, M. J.; Wallner, O. A.; Szabo, K. J. *J. Org. Chem.* **2007**, *72*, 4689.
[21] Wallner, O. A.; Szabó, K. J. *Chem. Eur. J.* **2006**, *12*, 6976.

which incorporated an urea/thiourea moiety as hydrogen-bond donor and a Lewis base in close proximity to promote the addition of the allylindium specie through *dual activation*. The best result was achieved with a catalyst containing trifluoromethyl groups in the phenyl ring of the urea moiety, which improved its hydrogen-bond-donor capacity, and a chiral *tert*-butylsulfinamide functioning as a Lewis base (**Scheme XI**).[22] Aromatic and heteroaromatic substrates gave uniformly good yields and enantioselectivities whereas aliphatic *N*-benzoylhydrazones gave substantially lower enantioselection (<50% *ee*).



Scheme XI

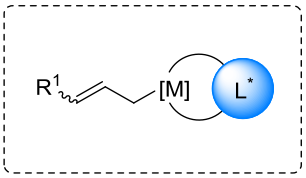
2.2. CHIRAL STOICHIOMETRIC REAGENTS IN THE ALLYLATION OF IMINE DERIVATIVES.

Despite the rapid evolution of catalytic methods in recent years, the use of stoichiometric reagents (including substrates and/or allylic organometallic partners) is still the favorite choice of organic chemists in the synthesis of chiral homoallylic amines as intermediates of natural products. This preference may be motivated by the highest predictability of the stereochemical result when stoichiometric reagents are used, or simply because in the construction of complex molecules the allylation step is sometimes performed over chiral substrates (chiral pool or advanced intermediates). In this section we will briefly comment some selected examples of this general strategy.[23]

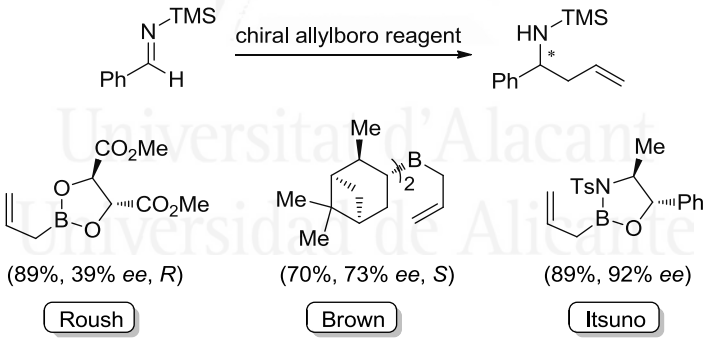
[22] Tan, K.; Jacobsen, E. N. *Angew. Chem. Int. Ed*. **2007**, *46*, 1315. The transition state shown here was not proposed by the authors and is purely speculative. We just wanted to illustrated the dual activation of this catalyst through possible "reasonable interactions".

[23] For a more exhaustive discussion of this topic, see: Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev*. **2013**, *113*, 5595.

2.2.1 Allylic Reagents Covalently Modified with a Chiral Moiety in the Metal Center.



One common strategy in the asymmetric allylation of imines implies the use of allylic reagents with stereogenic centers in the transferred hydrocarbon backbone; however this methodology limits the substitution pattern of the allylic moiety. A more general reagent control approach makes use of allylic organometallic reagents with the chiral information in non-transferred ligands bonded to the metal center. The first example of an enantioselective imine allylation was published by Itsuno's group[24] with the same chiral allylboranes that Roush and Brown had previously used in the allylation of carbonyl compounds. Further optimization studies performed by the same group showed that an allylborane modified with (-)-norephedrine ligand added to imines gave excellent yields and better enantioselectivities (**Scheme XII**).[25]

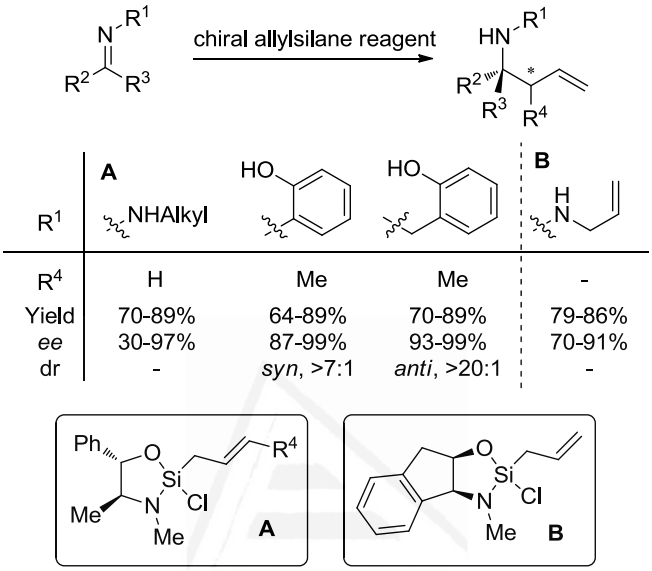


Scheme XII

The group of Leighton also examined derivatives of pseudoephedrine as chiral modifier of allyl silanes in the addition to different imines ranging from acetylhydrazones to *o*-aminophenol-derived aldimines. Good to excellent diastereo- and enantioselectivities were successfully achieved with the

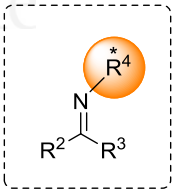
[24] Watanabe, K.; Ito, K.; Itsuno, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1531.
[25] Itsuno, S.; Watanabe, K.; Ito, K.; El-Shehawy, A. A.; Sarhan, A. A. *Angew. Chem. Int. Ed.* **1997**, *36*, 109.

pseudoephedrine-modified allylsilane,[26] as well as using allylchlorosilanes derived from (1*R*,2*S*)-1-amino-2-indanol (**Scheme XIII**).[27]



Scheme XIII

2.2.2. Substrate Stereocontrol with a Chiral Modifier Attached to the Nitrogen Atom.

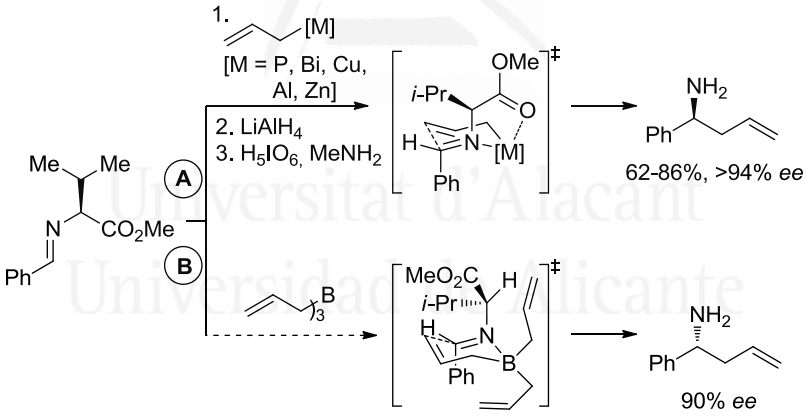


The stereochemistry in the addition of allylic organometallic reagents to imines can also be controlled by a chiral moiety attached to the nitrogen atom. Compared to the allylation of imines with a chiral hydrocarbon backbone, this approach can accommodate a wider range of substrates. Moreover, the chiral auxiliaries attached to the nitrogen atom can commonly be removed after the allylation process under mild conditions and sometimes can also be conveniently recycled.

Among all the chiral auxiliaries found in the literature with this purpose, natural aminoacid derivatives play a central role. This strategy is clearly exemplified in the addition of a wide range of organometallic allylic reagents (Pb, Bi, Cu, Al,

[26] (a) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686. (b) Rabbat, F. M. A.; Valdez, S. C.; Leighton, J. L. *Org. Lett.* **2006**, *8*, 6119. (c) Huber, J. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2007**, *129*, 14552. (d) Huber, J. D.; Perl, N. R.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 3037.
[27] Perl, N. R.; Leighton, J. L. *Org. Lett.* **2007**, *9*, 3699.

Zn) to (*S*)-methyl valinate derivatives, which take place with excellent diastereoselectivities (**Scheme XIV,A**).[28] The use of allyl lithium or allyl magnesium bromide reagents resulted in significantly lower yields due to a competitive addition to the ester moiety, obtaining the best yields with allyl zinc bromide. Importantly, removal of the chiral auxiliary was performed by reduction of the ester group followed by oxidative C=C bond cleavage. Moreover, the stereochemistry of the product was explained by using a cyclic chelation control model for the transition state. Interestingly, the use of triallylborane was also examined observing a complementary stereochemical pathway compared to the other organometallic reagents (**Scheme XIV,B**). This difference was related to the coordination of the boron atom by only the iminic nitrogen (chelation is not possible here) in the cyclic transition state. Rotation around the N-C bond of the chiral auxiliary results in a more stable conformation where the $A^{1,3}$ is minimized. This conformational turn in the transition state can explain the reversal in the stereochemical outcome.



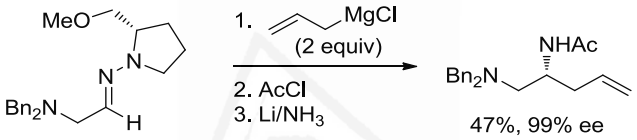
Scheme XIV

β-aminoalcohols derived from natural aminoacids constitute another prominent group of chiral auxiliaries due to its potential for chelation. A good stereocontrol could result if the metal of the allylic reagent is coordinated by the oxygen atom and the iminic nitrogen (chelation control). Enders' group pioneered the development of this synthetic strategy, studying the nucleophylic addition to

[28] Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766.

hydrazones derived from (*S*)-1-*A*mino-2-(*M*etoximethyl)*P*yrrolidine (*SAMP*) or its enantiomer (*RAMP*).[29]

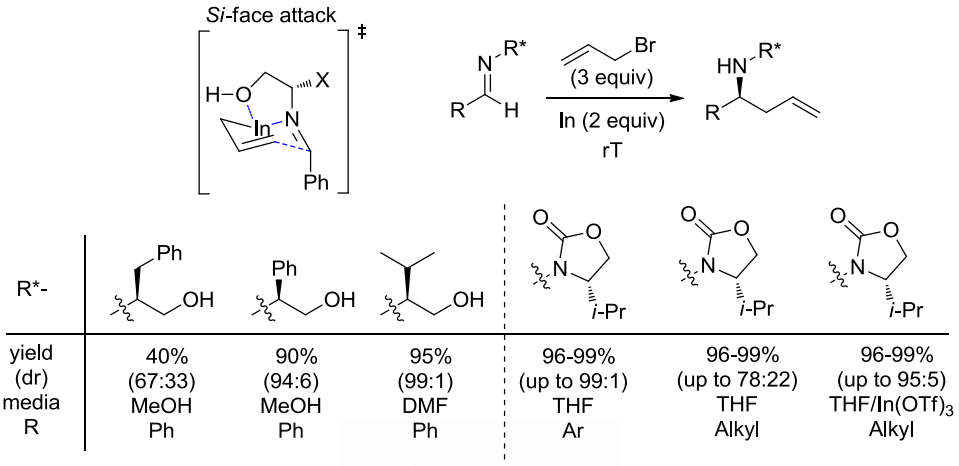
An example of the application of these auxiliaries to the formation of chiral homoallylamines would be the addition of allylmagnesium bromide to SAMP hydrazone derivative (**Scheme XV**).[30] In this case, the acylation and subsequent reduction of the hydrazine allows the synthesis of the correspondent protected diamine. The mechanism involves two equivalents of the organometallic reagent: one to form the chelate and the other to perform the correspondent addition. Similar additions have been examined over dihydrazones with a C_2 symmetry axis with excellent stereocontrol.[31]



Scheme XV

Indium-mediated allylation of imines bearing (*S*)-valinol-derived chiral auxiliaries were examined in DMF at 25 ºC, affording the corresponding products in good yields and diastereoselectivities.[32] Interestingly, similar results were obtained when (*S*)-phenylglicinol or (*S*)-benzylglicinol derivatives were used in alcoholic solvents (i.e. MeOH)[33] (**Scheme XVI**). Moreover, different structurally related hydrazones with a chiral oxazolidinone moiety have also shown excellent diastereoselection for aromatic substrates in THF.[34] In the case of aliphatic compounds, it was necessary the addition of a Lewis acid as $In(OTf)_3$ to attain good levels of diastereoselection (**Scheme XVI**, last example).

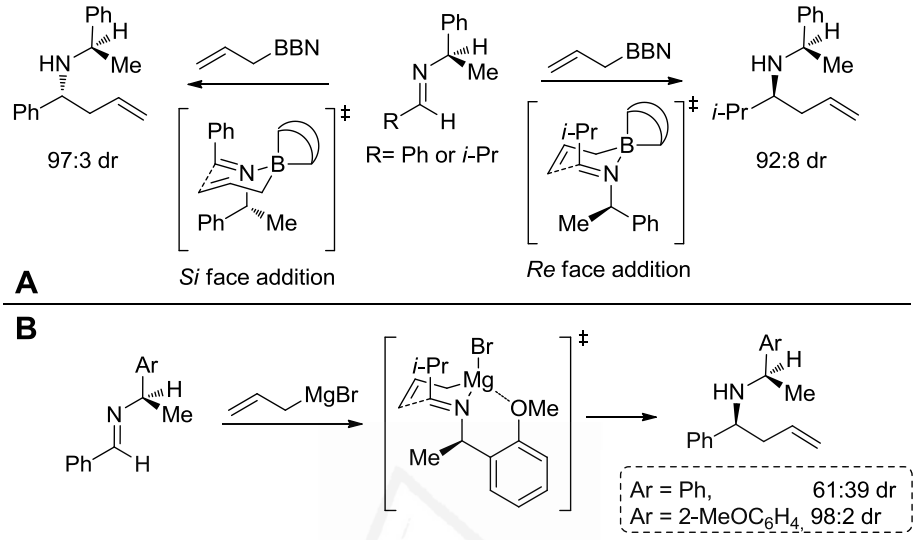
[29] Enders, D.; Shubert, H.; Nfibling, C. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1109.
[30] (a) Enders, D.; Schankat, J.; Klatt, M. *Synlett* **1994**, 795. (b) Enders, D.; Chelain, E.; Raabe, G. *Bull. Soc. Chim. Fr.* **1997**, *134*, 299.
[31] Enders, D.; Meiers, M. *Synthesis* **2002**, 2542.
[32] (a) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931. (b) Paquette, L. A.; Mitzel, T. M. *J. Org. Chem.* **1996**, *61*, 799.
[33] Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464.
[34] Cook, G. R.; Maity, B. C.; Kargbo, R. *Org. Lett.* **2004**, *6*, 1741.



Scheme XVI

Apart from chiral auxiliaries derived from natural α-aminoacids other stereocontrol elements attached to the iminic nitrogen have been examined, including simple chiral amine moieties. A seminal contribution in this area was the addition of 9-allyl-9-borabicyclo[3.3.1]nonane to *N*-(1-arylethyl)imines, reported by the group of Yamamoto.[11] Interestingly it was found that the reaction took place with high diasteroselection for both aromatic and aliphatic aldimines, but leading to opposite configurations for the new stereogenic carbon centers substrates (**Scheme XVII**, **A**). This switch in the sterochemical outcome was attributed to different reactive conformation of the aromatic imines compare to the aliphatic. From this result it was clear that locking the configuration of this type of chiral imines around the N-C* bond should have important consequences on the diastereoselectivity of the allylation. Having this in mind, the group of Hashimoto demonstrated that the addition of allyl magnesium bromide to chiral *N*-(1-arylethyl)imines was much more diastereoselective when the phenyl group of the auxiliary was replaced by an *o*-methoxyphenyl group[35] (**Scheme XVII**, **B**). The role of the methoxy group is to coordinate the magnesium, which makes the transition state more rigid with a consequently positive impact on the diastereoselection.

[35] Kohara, T.; Hashimoto, Y. *Tetrahedron* **1999**, *55*, 6453.



Scheme XVII

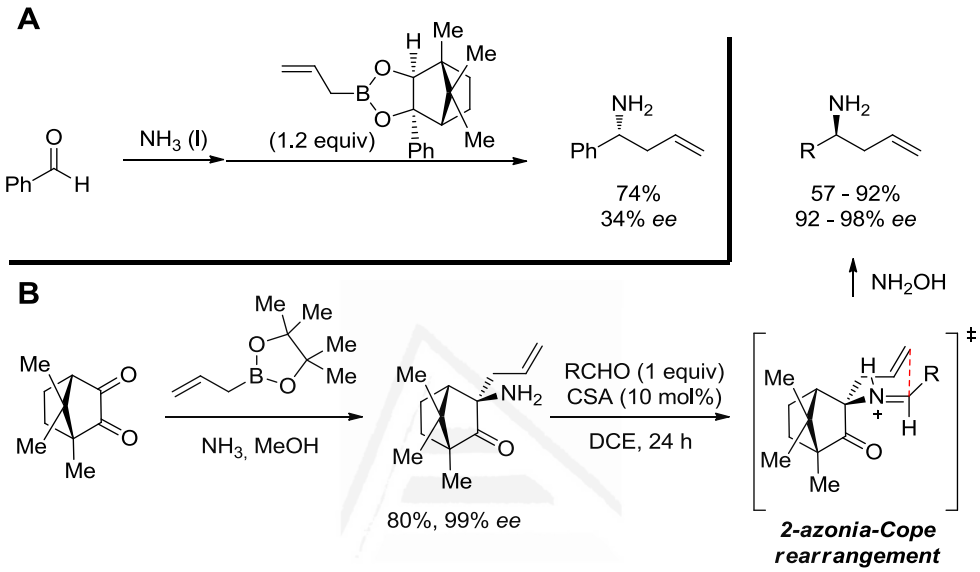
Chiral sulfinimines constitute another important group imines with a stereocontrol element attached to the nitrogen, but this group will be discussed in the next section.

2.3. α-AMINOALLYLATION OF ALDEHYDES

A more direct approach to prepare chiral homoallylic amines is an α-aminoallylation process of a carbonyl compound, in which the isolation of the imine is not required. In this context, Kobayashi studied the reaction of aldehydes with ammonia and chiral allyl boronate observing good chemoselectivity but modest enantioselectivity (**Scheme XVIII**, **A**). Continuing their efforts in this area, the same group prepared a chiral homoallylic amine in excellent enantioselectivity by α-aminoallylation of (*R*)-camphorquinone with allyl pinacolate and ammonia. More importantly, this compound served as a chiral template for the transfer aminoallylation to different aromatic and aliphatic aldehydes with excellent enantioselective approach.[36] It was found that the presence of substoichiometric amounts of CSA was crucial for the reaction, which is in accordance with the required formation of the iminiun that is involved in a 2-azonia-Cope rearrangement. It seems that the steric hindrance in

[36] Sigiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11038.

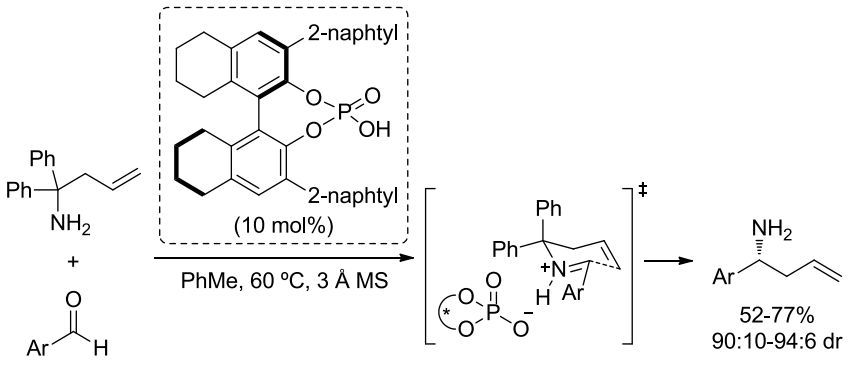
the chiral α-branched homoallylic iminium gets closer the reacting centers (Thorpe Ingold Effect) and also helps to shift the equilibrium to the desired linear products (**Scheme XVIII**, **B**).



Scheme XVIII

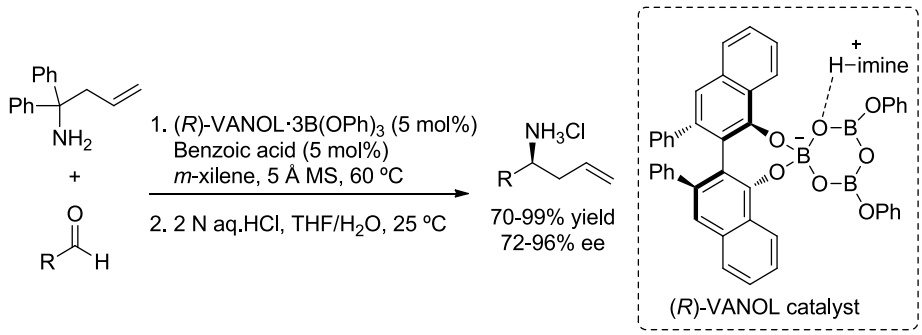
Using the same strategy, Rueping *et al*. designed a catalytic method where the achiral aminoallyl donor was activated by a chiral Brønsted acid. It is worth noting that the diphenyl amine moiety was crucial to electronically drive the reversible Cope rearrangement to the observed product. In this case, the chiral phosphate of the involved ion-pair should be responsible for the chiral induction (**Scheme XIX**).[37] The resulting enantioenriched homoallylamines were obtained in good yields and enantioselectivities, although the methodology was limited to the use of aromatic or α,β-unsaturated aldehydes.

[37] Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.*, **2008**, *47*, 10090.



Scheme XIX

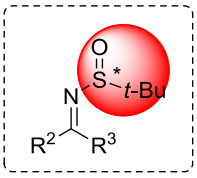
More recently, and directly related with these studies, the group of Wulff designed a strategy where chiral and non-chiral Brønsted acids cooperate to achieve a good chiral induction in the process (**Scheme XX**).[38] They found that the addition of benzoic acid to the VANOL boroxinate catalyst produced in the presence of the correspondent imine (chiral Brønsted acid catalyst) led to a significant enhacement in the enantioselection (synergetic effect between a chiral and a non-chiral Brønsted acid). Remarkably, when 4 Å MS were used to remove the water very poor conversion was observed, whereas 5 Å MS allowed completion of the reaction. The scope of the reaction was extended to imines derived from both, aromatic and aliphatic aldehydes, which led to the expected products in good yields and excellent enantioselectivities. Moreover, the protocol was amenable to work on gram scale.



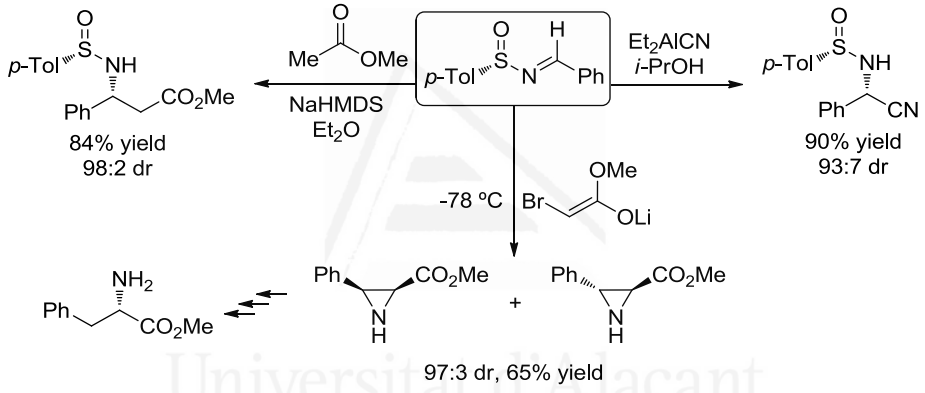
Scheme XX

[38] Wulff, W. D.; Ren,H. *J. Am. Chem. Soc.*, **2011**, *133*, 5656.

3. *t*-BS IMINES AS CHIRAL FRAMEWORK FOR IMINE ALLYLATION



In 1974, the group of Davis described the first synthesis of racemic *p*-tolensulfinylimines (*p*-TS imines).[39] From that moment, enantioselective preparations of these imines and their applications in organic synthesis were accomplished by many research groups.[40,41] The first studies about organometallic reagent additions to *p*-TS imines were also developed by Davis' group, showing the huge synthetic potential of this substrate (**Scheme XXI**).[42]

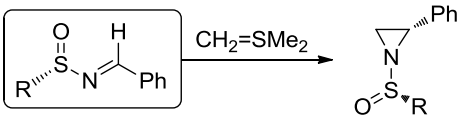


Scheme XXI

Thenceforth, this type of addition reaction has been widely used in the stereoselective syntheses α-chiral amines.[43] In this context, the groups of García Ruano and Fernandez demonstrated in 1996 that *tert*-butylsulfinylimines (*t*-BS imines) exerted better diastereocontrol than the parent *p*-TS imines in the aziridation reaction with sulfur ylides (**Scheme XXII**).[44] Inspired in this work, the group of Ellman discovered that Grignard reagents are added to *t*-BS imines with

[39] Davis, F. A.; Friedman, A. J.; Kluger, E. W. *J. Am. Chem. Soc.* **1974**, *96*, 5000.
[40] Annunzaita, R.; Cinquini, M.; Czzi, F. *J. Chem. Soc. Perkin Trans 1*, **1982**, 339.
[41] Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. S. *Tetrahedron Lett.* **1993**, *34*, 6229.
[42] (a) Davis, F. A.; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243. (b) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. *J. Org. Chem.* **1995**, *60*, 7037. (c) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y.-H. *J. Org. Chem.* **1996**, *61*, 440.
[43] Reviews: (a) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13. (b) Zhou, P.; Chen, B.-C.; Davis, F.A. *Tetrahedron* **2004**, *60*, 8003. (c) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.
[44] García Ruano, J. L.; Fernández, I.; del Prado Catalina, M.; Alcudia Cruz, A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407.

high diasteroselectivity.[45] After these seminal contributions, a plethora of nucleophiles have been examined in the 1,2-diasteroselective addition to *t*-BS imines which are nowadays one of the most common intermediates in the synthesis of α-chiral amines.[46]



R	Yield	dr
p-Tol	73%	60:40
t-Bu	70%	85:15

Scheme XXII

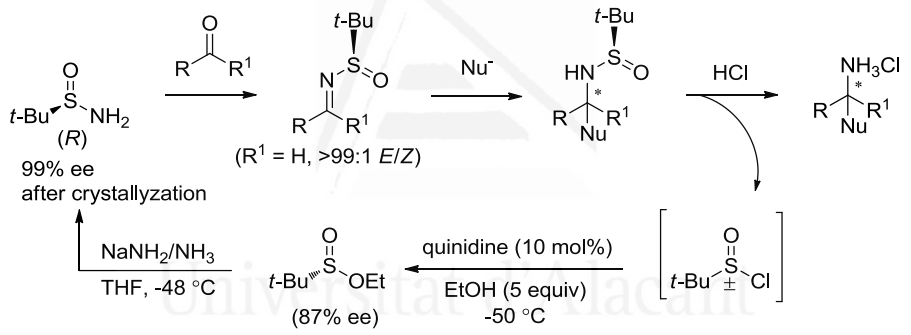
The studies performed by Ellman's group and others have shown that the biggest steric hindrance of the *tert*-butyl group, not only allows a more efficient stereocontrol, but improves the chemoselectivity in the nucleophilic addition to imines due to a lower electrophilic character of the sulfur atom in the sulfinyl group. The increase of the popularity of *t*-BS imines as precursors of α-chiral amines in the last 15 years is undoubtedly related to the advantages above mentioned and some others listed herein:[47]

- ✓ Both enantiomers of *tert*-butylsulfinamide can be prepared in large scale and are commercially available.
- ✓ A straightforward condensation of carbonyl compounds with *tert*-butylsulfinamide allows the preparation of *t*-BS imines.
- ✓ The *t*-BS group is electrophilic enough to minimize the undesired formation of the corresponding metaloenamine in the reaction with an organometallic reagent.
- ✓ The possibility of coordination of the *t*-BS group to a metal, through the oxygen/sulfur or nitrogen atom, enhances the diastereoselectivities in the 1,2-addition.

[45] Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc*. **1997**, *119*, 9913.
[46] For some reviews, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res*. **2002**, *35*, 984. (b) Ellman, J. A. *Pure and App Chem*. **2003**, *75*, 39. (c) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev*. **2009**, *38*, 1162. (d) Ellman, J. A.; Robak, M. T.; Herbage, M. A. *Chem. Rev*. **2010**, *110*, 3600.
[47] Over 250 related publications.

- ✓ The *t*-BS group serves as an amine protecting group and can be easily removed by treatment with MeOH/HCl at room temperature to obtain the products in essentially quantitative yields.

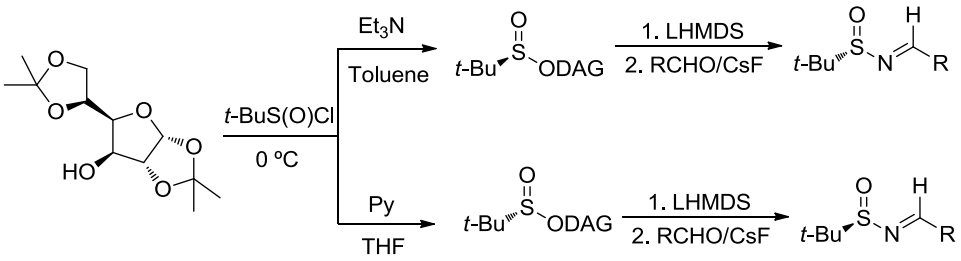
- ✓ Importantly, efficient procedures have been developed to recycle the chiral auxiliary. The group of Ellman has found that when the *t*-BS amine is deprotected with HCl in the absence of nucleophiles, racemic *t*-BS-Cl is produced. In the presence of substoichiometric amounts of quinidine, the reaction of this substrate with EtOH produces enantioenriched *t*-BS-OEt through a dynamic kinetic resolution process, which can be easily transformed in the desired enantiopure *t*-BS-NH_2 (**Scheme XXIII**).[48] An alternative resolution protocol has been disclosed by the group of Aggarwal where the chiral additive is *N*-methylephedrine.[49]



Scheme XXIII

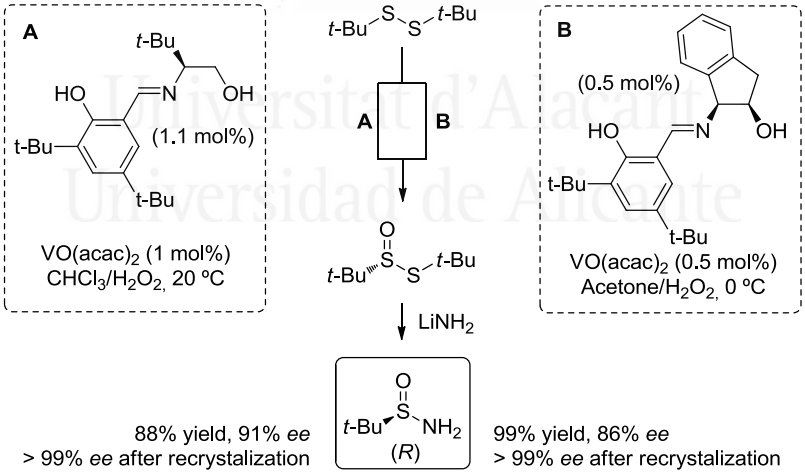
The first method described to prepare enantioenriched *t*-BS imines was based in Alcudia's studies on the dynamic kinetic resolution of racemic *t*-BS-Cl, using diacetone-D-glucose (DAG) as chiral inductor (**Scheme XXIV**). [50] The method allowed the preparation of a wide range of *t*-BS imines, although large scale was not possible (limited up to 1.4 mmol).[44]

[48] Wakayama, M.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 2646.
[49] Aggarwal, V. K.; Barbero, N.; McGarrigle, E. M.; Mickle, G.; Navas, R.; Suarez, J. R.; Unthank, M. G.; Yar, M. *Tetrahedron Lett.* **2009**, *50*, 3482.
[50] (a) Fernández, I; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789. (b) Khiar, N.; Fernández, I; Alcudia, F . *Tetrahedron Lett.* **1994**, *35*, 5719.



Scheme XXIV

A breakthrough advance in this area was the protocol developed by Ellman's group for the large scale synthesis of enantioenriched *tert*-butylsulfinamide.[51] The key step of the procedure is the enantioselective oxidation of *tert*-butyldisulfide, an oil waste product that serves as extremely cheap starting material. A vanadium catalyst (1 mol%) modified with (+)-*tert*-leucinol was initially used in a biphasic media of $CHCl_3/H_2O_2$ (**Scheme XXV**, **A**). Subsequent optimization studies showed that *cis*-1-amino-2-indanol ligands were more convenient since both enantiomers were readily accessible.



Scheme XXV

[51] For the full account after the previous communication in 1997, see: Cogan, D. A.; Liu, G., Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011.

Moreover, the introduction of homogeneous conditions (Acetone/H_2O_2) made the synthesis more robust and amenable to large scale.[52] The reaction of the thiosulfinate with $LiNH_2$ took place with total inversion of the sulfur configuration, giving a crystalline product which, after recrystallization from *n*-hexane, was obtained in >99% *ee* (**Scheme XXV**, **B**). Since this procedure was reported, both enantiomeric forms of the product can be prepared in 1 mole-scale and are also commercially available. The group of Senanayake has also developed an efficient methodology which allows the preparation of enantiopure *tert*-butylsulfinamide in multikilo-scale.[53]

The allylation of chiral *t*-BS imines has become in a very reliable method to obtain homoallylic α-chiral amines. The first successful example was the addition of allylmagnesium bromide to chiral *t*-BS ketimines, reported by the group of Ellman.[54] In this study, two example of methyl ketone derivatives were examined and the additions took place at – 78 ºC, obtaining excellent diastereoselectivities. In this model (**Scheme XXVIa**), coordination of the metal to the iminic nitrogen enhances the imine electrophylicity, whilst coordination to the sulfinyl oxygen atom determines the observed stereochemistry.

The first satisfying results in *t*-BS aldimines allylation were described by our research group employing allylindium reagents under Barbier conditions (**Scheme XXVIb**).[55] Under these reaction conditions, aldimines derived from aliphatic enolyzable aldehydes reacted with good stereoselectivity even at 60 ºC. It is worth mentioning that the low basicity of allylindium(III) reagents is crucial to the successful of this methodology with enolyzable substrates.[56] Recently our group has extended this method to ketoimines achieving good diastereoselectivities, even from *E*/*Z* mixture of ketoimines through a dynamic kinetic resolution.[57] Both, aldimines and ketimines, show the same chiral induction sense in the addition of allylmagnesium bromide and allylindium reagents, thus similar cyclic transition states have been proposed.

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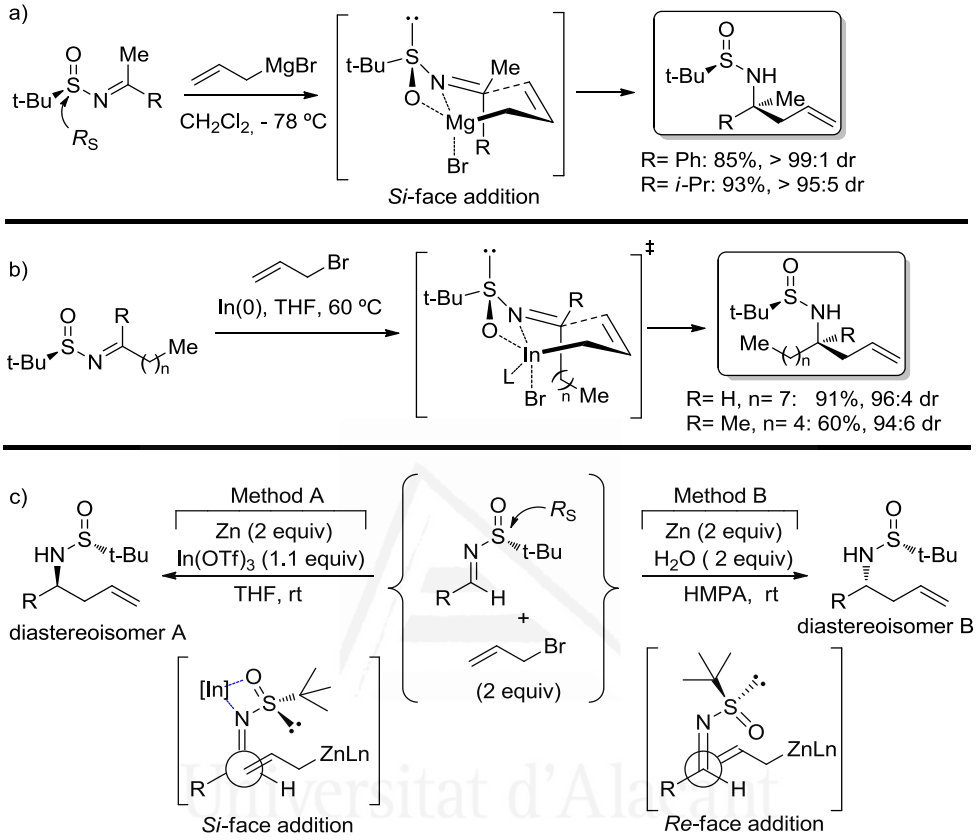
[52] (a) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317. (b) Weix, D. J.; Ellman, J. A.; Wang, X.; Curran, D. P. *Org. Synth.* **2005**, *82*, 157.
[53] (a) Han, Z.; Kishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880. (b) Han, Z.; Kishnamurthy, D.; Pflum, D.; Grover, P.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2002**, *4*, 4025. (c) Senanayake, C. H.; Kishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichimica Acta*, **2005**, *38*, 93.
[54] Cogan, D. A.; Liu, G.-C.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883.
[55] Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823.
[56] (a) Yasuda, M.; Haga, M.; Baba, A. *Eur. J. Org. Chem.* **2009**, 5513. (b) Yasuda, M.; Haga, M.; Nagaoka, Y.; Baba, A. *Eur. J. Org. Chem.* **2010**, 5359.
[57] Sirvent, J. A.; Foubelo, F.; Yus, M. *Chem. Commun.* **2012**, *48*, 2543.



Scheme XXVI

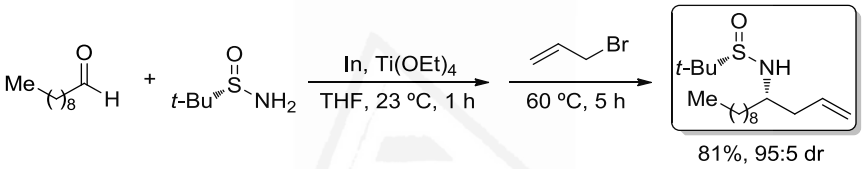
Efficient methods for the Zn-mediated allylation of *t*-BS aldimines have been also developed. One of these protocols make use of stoichiometric amounts of zinc and $In(OTf)_3$ in THF to obtain the diastereoisomer resulting from the *Si*-face addition to the (R_S)-sulfinimine in good selectivity for a wide range of aliphatic and aromatic substrates (**Scheme XXVIc**, **Method A**).[58] To explain this stereoselectivity the authors proposed an open transition state where the $In(OTf)_3$ chelates the sulfinyl group, locking an *s-trans*-like conformation for the sulfinylimine and facilitating the allyl attack over the sterically unblocked *Si*-face.

On the other hand, the opposite stereocontrol was achieved by using HMPA as solvent and H_2O as additive (**Scheme XXVIc**, **Method B**). Under these reaction conditions, the authors proposed that the sulfinimine adopts the more stable *s*-

[58] Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979.

cis-like conformation for the C=N-S=O unit,[59] guiding the attack of the allylzinc reagent over the least hindered *Re*-face. Similar stereochemical outcome was observed in the indium mediated allylation in aqueous NaBr solution,[60] or in the Zn-mediated addition using LiCl as additive in DMF.[61]

Our research group has recently optimized the In-mediated allylation process making possible the allylation of imines formed *in situ*, avoiding its isolation and purification. The protocol required the addition of a Lewis acid compatible with the *in situ* formed allylindium reagent, being $Ti(OEt)_4$ the best choice (**Scheme XXVII**).[62] Importantly, the same sense and degree of stereoinduction was achieved with this procedure compare with the two steps methodology.



Scheme XXVII

Although a broad range of aldehydes were tolerated with this one-pot protocol, the best results were obtained for aliphatic enolizable aldehydes, where other methods clearly fail to give good results. Formally this protocol represents an α-amino allylation of aldehydes, although homogeneus good results are obtained when the indium is added after initial formation of the aldimine over 1 h at room temperature. Due to its reliability and robustness, this protocol has being used by our group[63] and others[6,64] to prepare chiral homoallylic amines as building blocks of natural bioactive α-chiral amines. During this work, this methodology also plays a central role, as will be disclosed in the next chapters.

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[59] This *s-cis*-like conformation has been reported as the most stable for *t*-BS aldimines with an estimated rotational barrier of 9.9 kcal mol^{-1}, mainly as a result of a significant $n_N \rightarrow \sigma^*_{S=O}$ negative hyperconjugation interaction. For related crystal structures and theoretical calculations, see: (a) Bharatam, P. V.; Uppal, P.; Kaur, A.; Kaur, D. *J. Chem. Soc. Perkin Trans. 2* **2000**, 43. (b) Owens, T. D.; Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 3. (c) Ferreira, F.; Audouin, M.; Chemla, F. *Chem. Eur. J.* **2005**, *11*, 5269.

[60] Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1259.

[61] Liu, M.; Shen, A.; Sun, X.-W.; Deng, F.; Xu, M.-H.; Lin, G.-Q. *Chem. Commun.* **2010**, *46*, 8460.

[62] (a) González-Gómez, J. C.; Medjahdi, M.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2010**, *75*, 6308. (b) González-Gómez, J. C.; Foubelo, F.; Yus, M. *Org. Synth.* **2012**, *89*, 88.

[63] Medjahdi, M.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem.* **2011**, 2230.

[64] Andrade, R. B.; Sirasani, G. *Org. Lett.* **2011**, *13*, 4736.

4. ALLYLINDIUM REAGENTS: STRUCTURE AND REACTIVITY

As discuss before, allylation reaction has become a very powerful tool in organic synthesis to create enantioenriched homoallylic amines. From a large range of allylic organometallic reagents, the allylindium ones have emerged as an attractive alternative.[65] Some outstanding features of the organoindium reagents are: 1) stable in aqueous media and resistant to air, which makes its preparation and handling more simple and reliable because exclusion of moisture and/or air is not required; 2) exhibit good tolerance towards functional groups such as halide, nitro, nitrile, ester, hydroxyl groups among others; 3) Wurtz coupling or β-hydride elimination are common side reactions of other organometallic species that are minimized with these reagents; 4) indium metal and its reagents are nontoxic. *A drawback in the use of indium reagents is the increasingly price of the metal over the last decade, motivated by its applications in the field of material science.*[66]

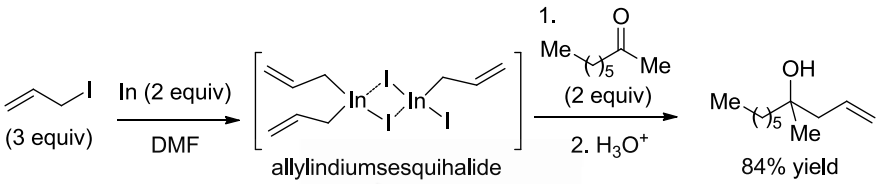
However, the potential of these innocuous reagents that can be manipulated in aqueous media and in open to air environments is still increasing in the context of modern Green Chemistry. The unique properties of allylindium species also include their low basicity, which minimize α-deprotonation of carbonyl compounds or imine derivatives, exhibiting better performance than their organomagnesium and organozinc counterparts with aliphatic enolizable substrates.

To the best of our knowledge, the first preparation of an organoindium compound dates back to 1934 when Dennis' group synthesized trimethylindium (Me_3In) *via* transmetalation of dimethylmercury with indium.[67] Organoindium compounds were also prepared by transmetalation of indium(III) halides with organoaluminium,[68] organolithium[69] and organomagnesium[70] reagents. But it was not until 1974 that Rieke and co-workers reported the first application of indium in organic synthesis.[71] In this seminal contribution indium(0) was prepared by reduction of indium(III)trichloride in the presence of potassium -

[65] Shen, Z.-L.; Wang, S.-Y.; Chok, Y.-K.; Xu, Y.-H.; Loh, T.-P. *Chem. Rev.* **2013**, *113*, 271.
[66] In the last decade the price has growth from 2 €/g (data from 1992) to 13 €/g (current price).
[67] Dennis, L. M.; Work, R. W.; Rochow, E. G. *J. Am. Chem. Soc.* **1934**, *56*, 1047.
[68] Eisch, J. J. *J. Am. Chem. Soc.* **1962**, *84*, 3605.
[69] Clark, H. C.; Pickard, A. L. *J. Organomet. Chem.* **1967**, *8*, 427.
[70] Viktorova, I. M.; Sheverdina, N. I.; Endovin, Yu. P.; Kocheshkov, K. A. *Bull. Acad. Sci. USSR Ser. Khim.* **1968**, 2288.
[71] (a) Chao, L.-C.; Rieke, R. D. *J. Organomet. Chem.* **1974**, 67, C64. (b) Chao, L.-C.; Rieke, R. D. *J. Org. Chem.* **1975**, *40*, 2253. (c) Rieke, R. D. *Acc. Chem. Res.* **1977**, *10*, 301.

indium Rieke from then on- and successfully applied in the Reformatsky reaction.

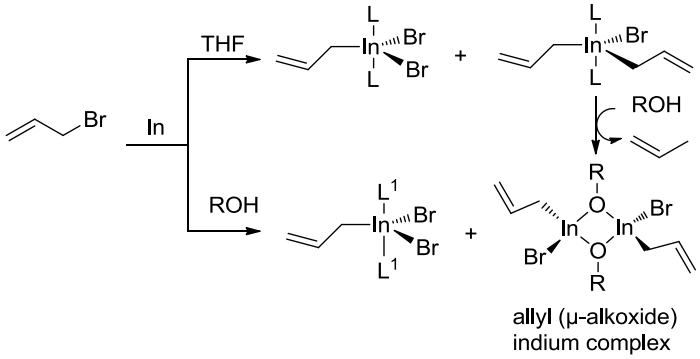
The first indium mediated allylation was reported in 1988, using commercially available indium and allyl iodide in DMF or THF.[72] This was the first time that the allylindium sesquihalide specie was proposed for the reagent formed *in-situ* by insertion of In(0) into an allyl halide (**Scheme XXVIII**).



Scheme XXVIII

Whilst the sesquihalide structure was well accepted for the allylindium reagent generated in organic solvents, Chan and Yan postulated an allylindium(I) specie when the reaction was conducted in aqueous media.[73] The real nature of allylindium species *in situ* generated has motivated a long debate with contradictory conclusions mostly based on ^{1}H-NMR studies.[74] However, it was not until very recently that the actual structures of allylindium species generated by different ways were unambiguously elucidated by X-ray crystallography.[56] By mixing allyl bromide with indium in THF, followed by complexation with pyridine ligands (L), suitable crystals for X-ray diffraction were obtained of a monoallylindium(III) bromide and the corresponding diallylindium specie. Importantly, it was found that when the two generated species were treated with an aldehyde, the diallyindium bromide was more reactive. Most significantly, it was also found that the allyl indium dibromide was stable in aqueous media, but the diallylindium(III) bromide reacts with water or alkoxides to form an allyl(μ-alkoxide)indium complex that was confirmed by X-ray crystallographic analysis (**Scheme XXIX**).

[72] Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831.
[73] Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228.
[74] (a) Preite, M. D.; Pérez-Carvajal, A. *Synlett* **200**6, 3337. (b) Law, M. C.; Cheung, T. W.; Wong, K.-Y.; Chang, T. H. *J. Org. Chem.* **2007**, *72*, 923.

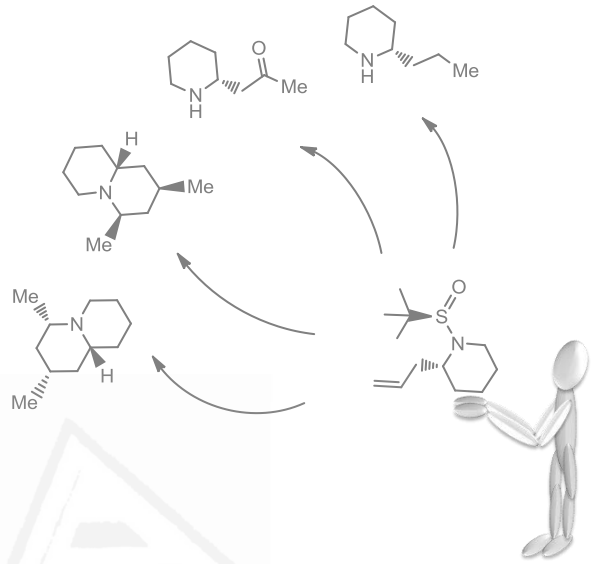


Scheme XXIX

An important parameter to take into account in reactions involving indium(0) is the size of indium metal, which considerably affects the outcome of the allylation reaction. For instance, Rieke indium exhibited higher reactivity than indium nanoparticules, but the reactivity of the latest was, at the same time, higher than powdered indium reactivity.[75] Even so, indium is less liable to form an oxide layer than other metals due to its resistance to moisture. In consequence, activation is not necessary although in some cases ultrasound or even the addition of an acid have been proved to help to the reaction process.[76]

[75] Li, J.; Zha, Z.; Sun, L.; Zhang, Y.; Wang, Z. *Chem. Lett*. **2006**, *35*, 498.

[76] (a) Loh, T.-P.; Cao, G.-Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1453. (b) Kim, D. Y.; Wiemer, D. F. *Tetrahedron Lett*. **2003**, *44*, 2803. (c) Ranu, B. C.; Das, A. *Tetrahedron Lett*. **2004**, *45*, 6875. (d) Suh, K. H.; Kim, D. Y. *Synth. Commun*. **2009**, *39*, 792.



Chapter I :

Enantioenriched 2-Allylpiperidine:

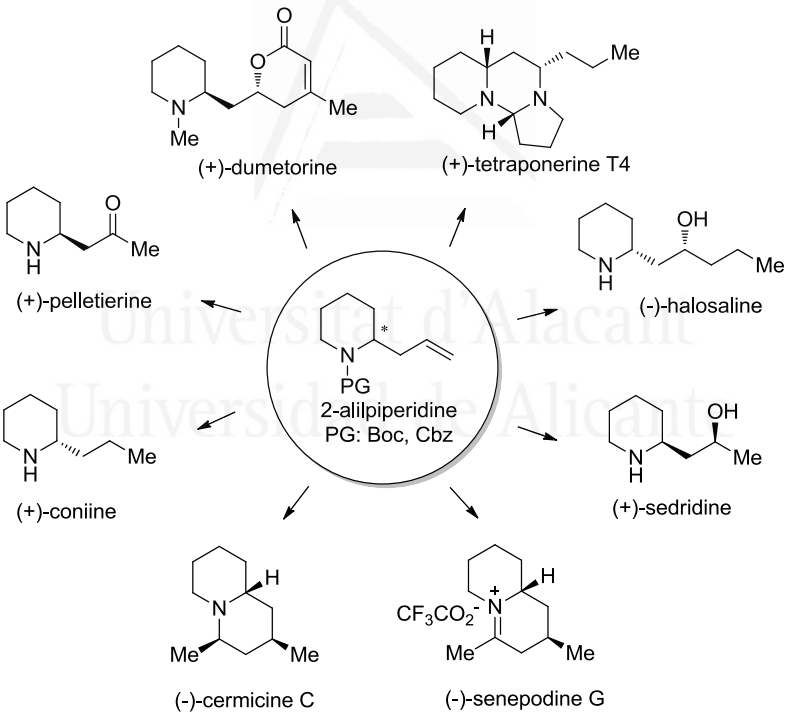
A Very Useful Precursor in the Synthesis of Alkaloids.

PART OF THE CONTENT OF THIS CHAPTER HAS BEEN PUBLISHED IN:

Bosque, I.; González-Gómez, J. C.; Foubelo, F.; Yus, M.
J. Org. Chem. **2012**, *77*, 780.

I.1. INTRODUCTION

Alkaloids are nitrogenated compounds involved in the secondary metabolism of some living organisms. Considering that their biosynthesis is catalyzed by enzymes, most of them are normally chiral compounds that can be easily recognized by biological receptors (enzymes mostly). Therefore, alkaloids usually exhibit a wide range of biological activities. It is worth saying that although these compounds can be isolated from their natural sources, a huge amount of the natural source is usually needed to get a few milligrams of the desired pure compound. In this context, the development of new methodologies for the efficient synthesis of these natural products is clearly justified as one of the permanent aims in organic synthesis research.

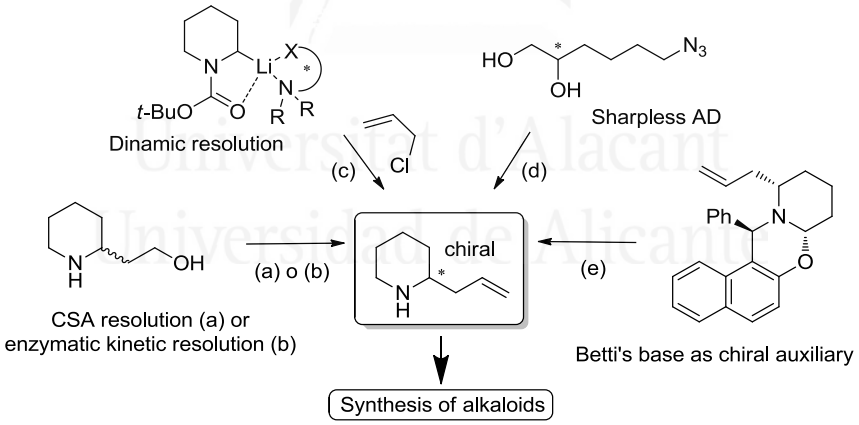


Scheme 1

As we have already discussed in the Bibliographic Background, our interest in chiral homoallylamines resides in their application as building blocks in organic synthesis. Among others, chiral 2-allylpiperidines constitute prominent examples that have been used as precursors of a wide variety of alkaloids. For instance,

straightforward synthetic manipulations of the allyl moiety have allowed access to coniine, pelletierine, sedredine or halosaline (**Scheme 1**).[77] At the same time, pelletierine itself has been recently proved to be a synthetic intermediate of a variety of natural products.[78] On the other hand, other alkaloids like dumetorine,[79] senepodine G, cermicine C[80] or tetraponerines, among others, are accesible by modifying the nitrogen environment.

Remarkably, 2-allylpiperidine alkaloid derivatives can exhibit both configurations (*R*/*S*) at the stereogenic carbon center adjacent to the nitrogen atom. This difference is presumably a result of their different biosynthetic origins.[81] This fact, together with the possibility to explore the biological activities of all possible stereoisomers derived from this moiety, have boosted the development of synthetic methodologies to access both enantiomeric forms of this moiety. The most common approaches to get 2-allylpiperidine have been summarized in **Scheme 2**.



Scheme 2

[77] (a) Takahaka, H.; Kubota, M.; Takahashi, S.; Momose, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3047 (b) Takahaka, H.; Kubota, M.; Ikota, N. *J. Org. Chem*. **1999**, *64*, 8594. (c) Coldman, I.; Leonoti, D. *J. Org. Chem*. **2010**, *75*, 4069. (d) Veerasamy, N.; Carlson, E. C.; Collett, N. D.; Saha, M.; Carter, R. G. *J. Org. Chem*. **2013**, *78*, 4779.

[78] Bhat, C.; Tilve, S. G. *Tetrahedron*, **2013**, *69*, 6129.

[79] Passarella, D.; Riva, S.; Grieco, G.; Cavallo, F.; Checa, B.; Arioli, F.; Riva, E.; Comi, D.; Danieli, B. *Tetrahedron: Asymmetry* **2009**, *20*, 192.

[80] Snider, B. B.; Grabowski, J. F. *J. Org. Chem*. **2007**, *72*, 1039.

[81] Torssell, K. B. G. Natural Product Chemistry; Swedish Pharmaceutical Press: Stockholm, **1997**, *8*, 349.

The first two approaches are resolutions of racemic 2-piperidinethanol through the use of enantiomerically pure camphosulfonic acid (a),[82] or enzymatic resolution (b).[83] The third one requires a dynamic resolution of *N*-*Boc*-2-lithiopiperidine followed by transmetalation and reaction with allyl chloride (c),[77c,84] whilst other route implies a Sharpless asymmetric dihydroxilation (AD) of 5-hexenylazide (d).[77a] All mentioned methods present certain limitations related to the maximum yield that can be obtained in classical resolutions (a, b: < 50%), or as a consequence of the long reaction sequence used (d). On the other hand, method (c) is elegant and efficient; however, makes use of expensive (sparteine–like ligands) and dangerous reagents (*sec*-BuLi) that limit the scale up of the process. Another practical approach recently described to obtain enantioenriched 2-allylpiperidine in gram-scale implies the use of the Betti's base as a chiral auxiliary (e).[85] Unfortunately, the preparation of this auxiliary in our hands was not as efficient as originally described by the authors. Despite all these efforts, it is still necessary the development of more efficient and safe synthetic alternatives to prepare both enantiomers of 2-allylpiperidine. The access to gram-quantities of these enantioenriched building blocks would allow to expand their applications in the synthesis of more complex molecules, including alkaloids.

The ready availability of both enantiomers of *tert*-butylsulfinamide in large-scale processes, the easy deprotection of the amine under acidic conditions, and practical procedures for recycling the chiral auxiliary have contributed to its widespread use in many practical asymmetric synthesis of amines.[86] Recently, an efficient asymmetric synthesis of 2-substituted pyrrolidines by addition of Grignard reagents to γ-chloro-*N*-*tert*-butylsulfinyl aldimines followed by base-mediated cyclization was reported.[87] We reasoned that the indium- mediated α-aminoallylation of 5-bromopentanal with (R_S)- or (S_S)-*tert*-butylsulfinamide could be implemented in a similar approach to enantioenriched 2-allylpiperidine derivatives. The non-toxic character of indium allylic reagents and their tolerance to the presence of water or air, make this α-aminoallylation protocol well suited to work in gram quantities.[62b]

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[82] Toy, M. S.; Price, C. C. *J. Am. Chem. Soc.* **1960**, *82*, 2613.
[83] Angoli, M.; Barilli, A.; Lesma, G.; Passarella, D.; Riva, S.; Silvani, A.; Danielli, B. *J. Org. Chem*. **2003**, *68*, 9525.
[84] Beng, T. K.; Gawley, R. E. *J. Am. Chem. Soc.* **2010**, *132*, 12216.
[85] Cheng, G.; Wang, X.; Su, D.; Liu, H.; Liu, F.; Hu, Y. *J. Org. Chem.* **2010**, *75*, 1911.
[86] These aspects were already discussed in the Bibliographic Background.
[87] Reddy, L. R.; Prashad, M. *Chem. Commun*. **2010**, *46*, 222.

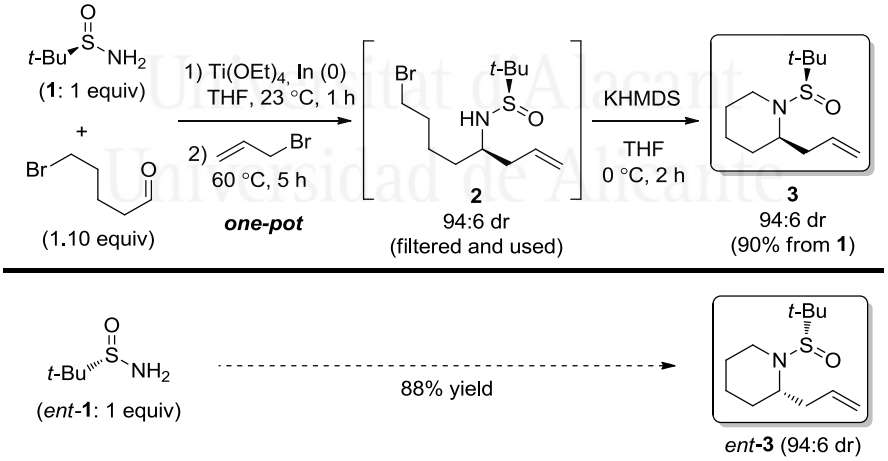
I.2. OBJECTIVES

We decided to study the indium-mediated α- aminoallylation of 5-bromopentanal with (R_S) or (S_S)-*tert*-butylsulfinamide aimed to prepared enantioenriched 2-allylpiperidine derivatives in gram-scale. The utility of these chiral intermediates will be examined through the synthesis of some alkaloids.

I.3. RESULTS AND DISCUSSION

Synthesis of 2-Allylpiperidine

The one-pot α-aminoallylation of 5-bromopentanal[88] with (R_s)-*tert*-butylsulfinamide and *in situ* generated allylindium reagent took place smoothly, obtaining the corresponding homoallylamine with good chemo- and diasteroselectivity (**Scheme 3**). Remarkably, side products derived from substitution or elimination processes on the primary alkyl bromide were hardly detected by ^{1}H-NMR of the crude reaction mixture.

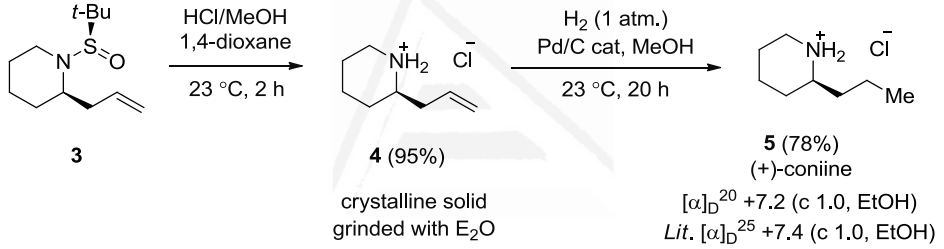


Scheme 3

This chemoselectivity highlights the potential of this protocol with diverse substituted aliphatic aldehydes, otherwise problematic with other organometallic reagents. The crude reaction mixture was filtered through Celite, and the

[88] 5-bromopentanal is commercially available, but its preparation was performed by reduction of ethyl 5-bromovaleronate with DIBAL-H: Nodes, W. J.; Nutt, D. R.; Chippindale, A. M.; Cobb, A. J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16016.

cyclization of the resulting product (94: 6 dr by ^{1}H-NMR) was examinated using different bases and reaction temperatures. Among other conditions explored, Et_3N/MeCN at 80 °C, KOH/THF-H_2O at 80 °C as well as KHMDS/ THF at 23 °C,[87] gave the desired product in poor yield and contaminated with undetermined side products. However, when KHMDS was used in THF at 0 °C, a clean conversion to the desired product was verified by TLC. After purification by column chromatography, the corresponding 2-allylpiperidine derivative **3** was isolated in a 90% global yield in a 4-gram scale. Importantly, *ent*-**3** was prepared with similar efficiency following the same methodology, but using (S_s)-*tert*-butylsulfinamide as starting material. Remarkably, only two synthetic operations and a few hours are needed to prepare each enantioenriched 2-allylpiperidine derivative.



Scheme 4

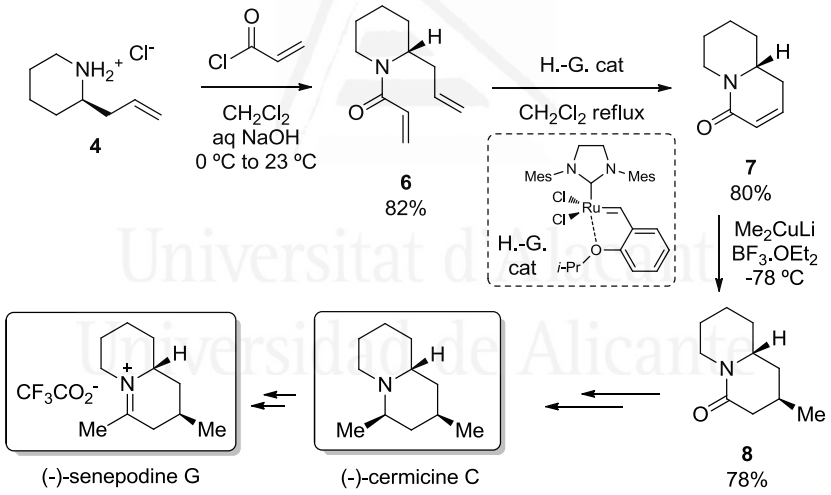
To assign the stereochemistry of 2-allylpiperidines **3** and *ent*-**3** we used our working model that implies a chair-like transition state and predicts the attack of the allylindium to the *si*-face of the (*R*s)-*t*-BS imine and to the *re*-face of the (*S*s)-*t*-BS imine (**Scheme XXVI**, Bibliographic Background). In order to verify this stereochemistry, the synthesis of (+)-coniine **5** -the major alkaloid extracted from hemlock which possess neurotoxic properties-[89] was accomplished (**Scheme 4**). Treatment of compound **3** with a solution of HCl in dioxane and MeOH led to the corresponding piperidinium salt **4** isolated as a crystalline solid in almost quantitative yield, after removing of all volatiles and grinding with Et_2O.[90] Catalytic hydrogenation of the double bond took place efficiently to finally obtain the coniine hydrochloride **5**. The spectroscopic data and optical rotation obtained were in full agreement with the data reported in the literature for (+)-coniine.[91] On the other hand, the observed absolute configuration fits with the

[89] Review: López, T. A.; Cid, M. S.; Bianchini, M. L.; *Toxicon* **1999**, *37*, 841.
[90] The enantioselectivity was not examined at this point, but we think that could be higher than the initial 94:6 er.
[91] For comparison of $[\alpha]_D$ and other physical and spectroscopic data: (a) see ref . 77a. (b) Amat M.; Llor, N.; Hidalgo, J.; Escolano, J.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919.

chiral induction predicted by our working model for the α-aminoallylation step, demonstrating the reliability of this process.

Synthesis of Some Related Alkaloides

Treatment of compound **4** with acryloyl chloride under aqueous basic conditions (Schotten Baumann conditions), followed by ring-closing metathesis with Hoveyda−Grubbs catalyst, allowed the efficient preparation of unsaturated lactam **7** (**Scheme 5**), the enantiomer of a key intermediate in the synthesis of lycopodium alkaloids.[92] The conjugate addition of Me_2CuLi to the least hindered convex face of compound **7** took place with excellent stereoselectivity to afford lactam **8**, following a protocol described by Snider in the first total synthesis of senepodine G and cermizine C.[80] This method represents a formal synthesis of the enantiomers of the above-mentioned quinolizidine alkaloids.[93,94]

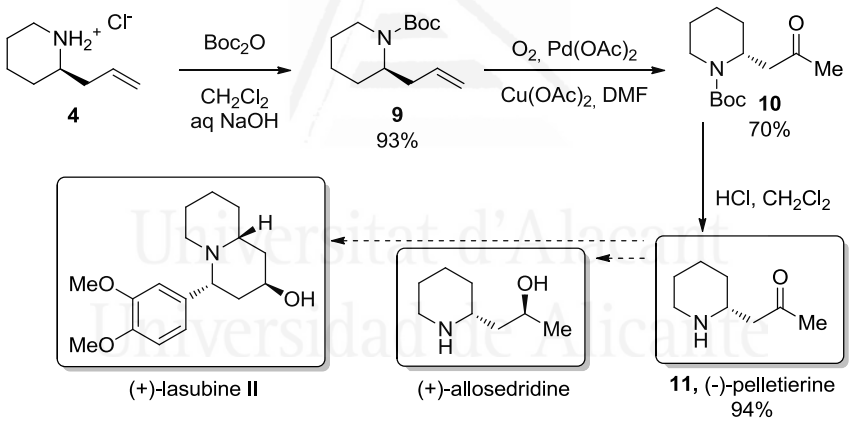


Scheme 5

Pelletierine has been recognized to play an important role in the biosynthesis of a number of alkaloids,[95] and consequently this molecule is potentially a key intermediate in the biomimetic synthesis of natural alkaloids.[78] However, the

[92] Amat, M.; Griera, R.; Fabregat, R.; Bosch, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1233.
[93] For the isolation and structural determination of senepodine G and cermizine C, see: Morita, H.; Hirasawa, Y.; Shinzato, T.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 7015.
[94] For other recent synthesis of these alkaloids, see: (a) Nishikawa, Y.; Kitajima, M.; Kogure, N.; Takayama, H. *Tetrahedron* **2009**, *65*, 1608. (b) See ref 85.
[95] For proposed biosynthetic pathway from pelletierine to Lycopodium alkaloids, see: Ma, X.; Gang, D. R. *Nat. Prod. Rep*. **2004**, *21*, 752.

application of pelletierine in synthesis is limited, probably because its asymmetric preparation in the required amounts to be used as building block is not straightforward. With this in mind we examined the Wacker oxidation of *N*-sulfinyl-protected piperidine **4** under different reaction conditions, but complex mixture of products was always obtained. Therefore we decided to use a protecting group more resistant to oxidative conditions and the *N*-Boc-protected piperidine **9** was prepared and submitted to Wacker oxidation conditions. In this case the expected methyl ketone was obtained with the right regioselectivity and after conventional acidic deprotection, the unnatural (*R*)-(−)-pelletierine **11** was obtained in good overall yield (**Scheme 6**). It is worth mentioning that stereoselective reduction of (*R*)-*N*-Boc-pelletierine **11** has been recently reported to obtain natural (+)-allosedridine.[96] In addition, only two synthetic steps were required to transform (*S*)-(+)-pelletierine into (−)-lasubine II by Cheng and coworkers.[85]

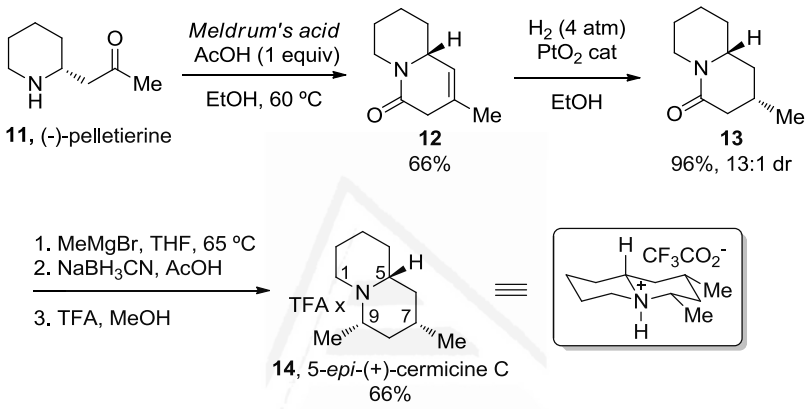


Scheme 6

As previously reported for racemic 5-*epi*-cermizine C,[80] the Knoevenagel condensation of the ammonium acetate salt of (*R*)-pelletierine **11** with Meldrum's acid took place with concomitant lactam formation, followed by decarboxylation and kinetic protonation to provide the unconjugated lactam **12** in good yield (**Scheme 7**). Hydrogenation of **12** at 4 atm of H_2 occurred mainly on the convex face, affording the desired lactam **13** in excellent yield and good selectivity (13:1 dr). Addition of MeMgBr to compound **13** was followed by *in situ* stereoselective reduction of the iminium intermediate to afford 5-*epi*-cermizine C in good overall

[96] Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192.

yield, which was further transformed to its trifluoroacetate salt **14**. It is worth pointing out that protonation of 5-*epi*-cermizine C should render a stereogenic nitrogen via equilibration through the most stable *trans*-quinolizidine conformation of the free amine.[97] Importantly, since 2-allyl piperidines **3** and *ent*-**3** are available using the present methodology, formally all four diastereoisomers of senepodine G and the corresponding cermizine C diastereoisomers could be prepared following the pathways described in **Schemes 5** and **7**.



Scheme 7

Synthesis of N-tert-Butylsulfinyl-2-(2'-piperidyl)acetaldehyde

It is reported that the addition of organometallic reagents to *N*-carbamates derivatives of 2-(2'-piperidyl)acetaldehyde give rise to a range of Sedum alkaloids. With an appropriate choice of the organometallic specie, the formation of a chelate involving both carbonyl groups could exert an efficient stereocontrol in the addition step.[98] With these precedents we considered of interest to prepare *N*-*tert*-butylsulfinyl-2-(2'-piperidyl)acetaldehyde and examine the addition of some organometallic reagents.

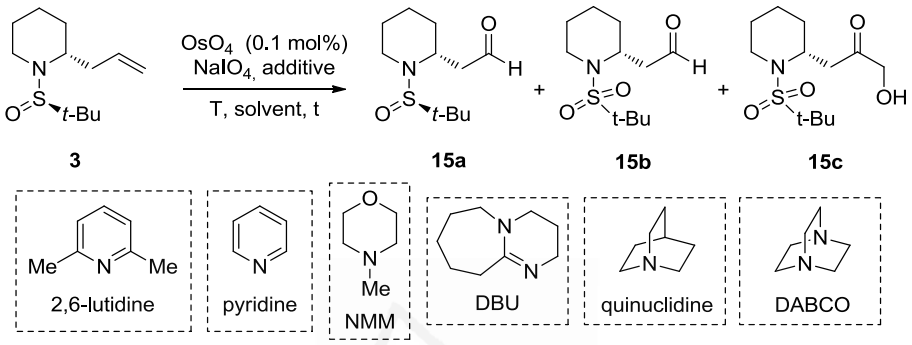
The oxidative cleavage of an alkene containing a sulfinamine group seems to be complicated by the possible oxidation of the sulfinamine moiety as well as

[97] Neutralization of trifluoroacetate ammonium salt **14** gave the corresponding free amine, which exhibited the characteristic Bohlmann band at 2783 cm^{-1} of the IR spectra, supporting the *trans*-quinolizidine conformation as the most stable.

[98] (a) Passarella,D.; Barilli, A.; Belinghieri, F.; Fassi, P.; Riva, S.; Sacchetti, A.; Silvani, A.; Danieli B. *Tetrahedron: Asymmetry* **2005**, *16*, 2225. (b) For similar stereocontrolled addtions to ketones: see ref.96.

different double bond oxidation pathways. Indeed, to the best of our knowledge, this chemoselective transformation has not been reported today.

Table 1



Entry	Additive	eq. additive/ eq. $NaIO_4$	1,4-dioxane/ H_2O	time (min)	T (°C)	Ratio[a] 15a[b]/15b/15c/3
1	no additive	0/4	3/1	30	25	0/65/35/0
2	2,6-lutidine	2/4	3/1	60	25	66/34/0/0
3	2,6-lutidine	2/4	3/1	10	25	0/0/0/100
4	2,6-lutidine	2/4	3/1	360	25	31/69/0/0
5	pyridine	2/4	3/1	30	25	28/15/0/57
6	NMM	2/4	3/1	30	25	38/28/5/28
7	DBU	2/4	3/1	30	25	39/18/0/43
8	quinuclidine	2/4	3/1	30	25	62/32/0/6
9	DABCO	2/4	3/1	30	25	87/13/0/0
10	DABCO	2/4	3/1	60	25	88/11/0/1
11	DABCO	2/2	3/1	30	25	71/14/4/11
12	DABCO	1/2	3/1	30	25	75/22/3/0
13	DABCO	2/4	6/1	30	25	65/29/0/6
14	DABCO	2/4	1/1	30	25	12/88/0/0
15	DABCO	2/4	6/1 ($MeCN/H_2O$)	30	25	71/4/25
16[c]	**DABCO**	**2/4**	**3/1**	**60**	**0**	**96/4/0/0**

[a] Relationship of all reaction products of the reaction, measured by ^{1}H-NMR.
[b] 94:6 dr observed in all cases in the ^{1}H NMR spectra of the crude reaction. [c] The product **15a** was isolated in a 60% yield.

When we examined the oxidative cleavage of the double bond on substrate **3** under originally Jonhson-Lemieux conditions,[99] the corresponding sulfonyl aldehyde **15b** and the sulfonyl α-hydroxy ketone **15c**[100] were the only products isolated (**Table 1**, entry 1). To improve the chemoselectivity, 2,6-lutidine[101] was added to the reaction mixture and in fact the formation of the sulfonyl α-hydroxy ketone **15c** was efficiently suppressed and the desired aldehyde was obtained but mixed with the sulfonyl derivative **15b** (**Table 1**, entries 2-4). We thus screened different amines as possible additive (**Table 1**, entries 5-9), obtaining the best chemoselection with DABCO. Different ratios of DABCO/$NaIO_4$ as well as different solvent mixtures were tested but without significant improvements (**Table 1**, entries 10-15). However, a decrease in the reaction temperature to 0 ^oC produced an important positive impact on the desired chemoselective oxidation (**Table 1**, entry 16). Unfortunately, despite the high chemoselectivity observed by ^1H-NMR of the crude reaction mixture we were not able to isolate the product in more than 60% yield after column chromatography (three attempts with similar results).

Despite the low yield obtained in the isolation of compound **15a**, an indium-mediated allylation of the aldehyde was performed in order to evaluate the diastereoselectivity of the reaction (**Scheme 8**). Allylindium reagent was prepared in THF at 65 ^oC from In(0) and allyl bromide. The addition of allylindium reagent to aldehyde **15a** was carried out at 25 ^oC in THF under argon atmosphere for 4 h, and the corresponding homoallylalcohol was isolated in 78% yield. Acidic deprotection of the amine followed by catalytic hydrogenation of the double bond allowed the formation of halosaline **17** as a 4:1 mixture of diastereoisomers, being the natural (-)-halosaline the minor component.[102] In order to improve the obtained diastereoselectivity, the addition of the allylindium was performed at -60 ^oC and the synthesis was completed following the same reaction sequence. However, contrary to expected, the diastereoselectivity turned to be worse and a 2:1 mixture of halosaline **17** diastereoisomers was observed. Further experiments, for instance increasing the temperature to 60 ^oC, need to be performed to improve the diastereoselectivity of the addition step.

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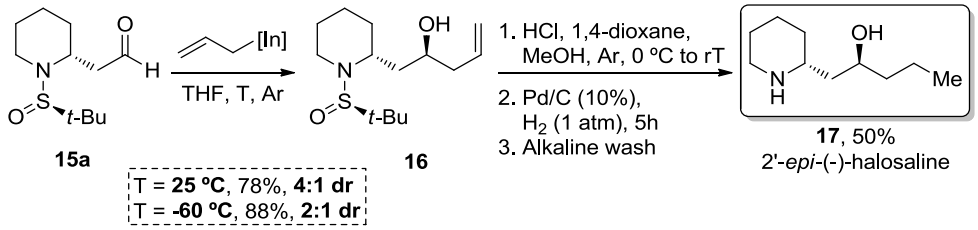
[99] Pappo, R.; Alen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem*. **1956**, *21*, 478.
[100] For origin of α-hydroxy ketones in the presence of OsO_4 see: Lohray, B. B.; Bhusham, V.; Kumar, R. K. *J. Org. Chem*. **1994**, *59*, 1375.
[101] Use of 2,6-lutidine in order to avoid overoxidation: Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett*. **2004**, *6*, 3217.
[102] Krishna, P. R.; Reddy, B. K.; Srinivas, P. *Tetrahedron*, **2012**, *68*, 841.



Scheme 8

As a summary of this chapter, we have developed a highly efficient two-step process for the synthesis of enantioenriched 2-allylpiperidine **3** in 4 g scale. Because of its operational simplicity, we believe this method provides a useful complement to existing methods for the preparation of both enantiomers of **4**. The usefulness of **3** as a building block was illustrated by the total synthesis of alkaloids such as (+)-coniine, (−)-pelletierine, and 5-*epi*-(+)-cermizine C as well as in the formal synthesis of (−)-cermizine C, (+)-allosedridine, and (+)-lasubine II. The chemoselective oxidative C-C bond cleavage of *N*-*tert*-butylsulfinyl-2-allylpiperidine was also examined with promising good results, followed by a modest diasteroselective addition of allylindium reagent. Further optimization of these two steps could provide a straightforward entry to enantioenriched halosarine and other structurally related Sedum alkaloids.

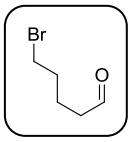
I.4. EXPERIMENTAL SECTION

General Remarks.

(R_S)-*N*-*tert*-Butylsulfinamide and its enantiomer were a gift of Medalchemy (> 99% ee by chiral HPLC on a Chiracel AS column, 90:10 *n*-hexane/*i*-PrOH, 1.2 mL/min, λ=222 nm). TLC was performed on silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) stain. Flash chromatography was carried out on handpacked columns of silica gel 60 (230- 400 mesh). CSP-GC 20% β-cyclodextrin-permethlated capillary column 30 m x 0.25 mm i.d., hydrogen carrier at 12 psi; temperature at 80 ºC over 60 min, then a ramp of 10 ºC/min. Melting points are uncorrected. Optical rotations were measured using a polarimeter with a thermally jacketted 5 cm cell at approximately 20 ºC and concentrations (c) are given in g/100 mL. Infrared analysis was performed with a spectrophotometer equipped with an ATR component; wavenumbers are given in cm^{-1}. Mass spectra (EI) were obtained at 70 eV; and fragment ions in m/z with relative intensities (%) in parentheses. HRMS analyses were also carried out in the electron impact mode (EI) at 70 eV. ^1H NMR spectra were recorded at 300 or 400 MHz for ^1H NMR and 75 or 100 MHz for ^{13}C NMR, using $CDCl_3$ as

the solvent and TMS as internal Standard (0.00 ppm). The data is being reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded with ^{1}H-decoupling at 100 MHz and referenced to $CDCl_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH_2 and CH_3.

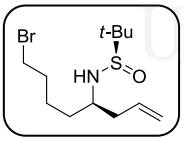
5-bromopentanal



A solution of DIBAL-H in toluene (23 mL, 1.2 M, 27.5 mmol) was added dropwise via syringe to a solution of ethyl 5-bromovaleronate (3.7 mL, 25.0 mmol) in dry CH_2Cl_2 (46 mL) at -78 ºC under Ar. The mixture was stirred for 2 h at the same temperature, observing full conversion of 5-bromovaleronate (t_r = 9.6 min) into the expected product (t_r = 6.7 min) by GC. The reaction mixture was quenched with 0.67 M HCl (37 mL), and allowed to reach room temperature. After phase separation, the aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were successively washed with saturated aqueous $NaHCO_3$ and brine. The organic solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide the product as of colorless oil (2.89 g, 78%)[103]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.5 Hz, 1H), 3.42 (t, *J* = 6.4 Hz, 2H), 2.50 (td, *J* = 7.0, 1.4 Hz, 2H), 1.97 – 1.86 (m, 2H), 1.85 – 1.73 (m, 2H); GC t_R = 6.7 min; LRMS (EI) *m/z* (%) 164 (M^+, 0.9), 137 (3), 135 (3), 85 (100), 84 (15), 67 (47), 57 (65), 55 (67), 53 (18).

Procedure for the synthesis of compounds 2 to 14.

(4*R*,*R*$_S$)-*N*-(*tert*-Butylsulfinyl)-8-bromooct-1-en-4-amine (2).

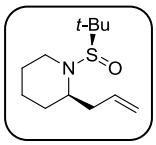


To a dry flask were added (*R*$_S$)-*N*-*tert*-butylsulfinamide (**1**, 2.109 g, 17.40 mmol) followed by indium powder (2.485 g, 21.80 mmol), and the mixture was evacuated and put under Ar. Then a solution of 5-bromopentanal (3.141 g, 19.15 mmol) in dry THF (34.9 ml) and $Ti(OEt)_4$ (7.8 mL, 34.80 mmol,) were added successively and the reaction mixture was stirred under Ar for 1 h at 23 ºC. At this time allyl bromide (2.3 mL, 26.10 mmol) was added to the mixture and it was heated to 60 ºC for 5 h. The mixture was allowed to reach room temperature and was carefully added over a stirring mixture of 4:1 EtOAc/brine (200 mL). The resulted white suspension was filtered through a short pad of Celite, washed with EtOAc and organics were concentrated *in vacuo*. The resulted suspension was diluted in 4:1 EtOAc/Hexane (200 mL) and filtered again through Celite. Organics were concentrated to afford the expected compound **2** (5.050 g, 94%, 94:6 dr according ^{1}H NMR) as a yellow oil, pure enough to be used in the next step. To provide the spectroscopy data, a sample of compound **2** was purified by column chromatography (7:3 hexane/EtOAc): R_f 0.15 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 - 5.71 (m, 1H), 5.18 - 5.31 (m,

[103] According to ^{1}H-NMR the aldehyde was contaminated with toluene and the yield was corrected. However, the aldehyde was used without further purification.

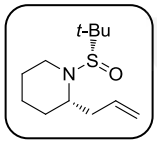
2H), 3.41 (t, *J* = 6.6 Hz, 2H), 3.32 (dt, *J* = 11.3, 5.8 Hz, 1H), 3.23 (d, *J* = 6.1 Hz, 1H), 2.42 (dt, *J* = 13.0, 5.9 Hz, 1H), 2.33 (dt, *J* = 13.8, 6.8 Hz, 1H), 1.92 - 1.80 (m, 2H), 1.62 - 1.46 (m, 4H), 1.21 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1 (CH), 119.3 (CH_2), 56.0 (C), 54.7 (CH), 40.5 (CH_2), 34.1 (CH_2), 33.8 (CH_2), 32.6 (CH_2), 24.1 (CH_2), 22.8 (CH_3); GC t_R = 14.6 min; LRMS (EI) *m/z* (%) 237 (M^+-C_4H_8, 19), 235 (M^+-C_4H_8, 20), 213 (67), 211 (67), 156 (100).

(2*R*,*R*s)-2-Allyl-(*N*-*tert*-butylsulfinyl)piperidine (3).



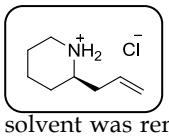
A titrated solution of KHMDS in THF (33 mL, 0.79 M, 26.10 mmol) was added via syringe to a cold solution (0 °C) of crude **2** (5.050 g, 16.30 mmol) in dry THF (36.5 mL). The reaction mixture was stirred for 2 h at 0 °C under Ar and then quenched with saturated NH_4Cl solution. The aqueous phase was extracted with EtOAc (3 times) and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (75:25 hexane/EtOAc) to provide the product as a pale-yellow oil (3.608 g, 15.76 mmol, 90% from **1**): $[\alpha]_D^{20}$ + 20.7 (*c* 1.0, $CHCl_3$); R_f 0.30 (7:3 hexane/EtOAc); IR ν 3075, 2939, 1639, 1074, 986, 906 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 - 5.70 (m, 1H), 5.15 - 5.04 (m, 2H), 3.46 - 3.28 (m, 1H), 3.20 - 3.11 (m, 1H), 2.99 - 2.90 (m, 1H), 2.59 - 2.43 (m, 2H), 1.72 - 1.49 (m, 6H), 1.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5 (CH), 117.4 (CH_2), 58.3 (C), 56.4 (CH), 40.8 (CH_2), 34.4 (CH_2), 28.1 (CH_2), 25.8 (CH_2), 23.2 (CH_3), 19.5 (CH_2); GC t_R = 12.7 min; LRMS (EI) *m/z* (%) 229 (M^+, 0.1), 173 (28), 132 (100), 83 (11), 57 (17), 55 (20); HRMS (EI) calcd for $C_{12}H_{23}NOS$ 229.1500, found 229.1507.

(2*S*,*S*s)-2-Allyl-(*N*-*tert*-butylsulfinyl)piperidine (*ent*-3).



It was prepared from (S_S)-*N*-*tert*-butylsulfinamide (*ent*-**1**, 0.45 mmol), following the same procedure described above for compound **3** (90 mg, 0.40, 88% from *ent*-**1**). Physical and spectroscopic data were found to be same than for (2*R*,R_S)-**3**, except for the optical rotation: $[\alpha]_D^{20}$ - 22.0 (*c* 1.1, $CHCl_3$).

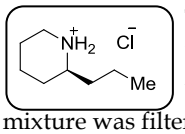
(*R*)-2-Allylpiperidine hydrochloride (4).



A solution of HCl in dioxane (6.8 mL, 4 M) was added dropwise to a solution of **3** (1.557 g, 6.80 mmol) in dry MeOH (40 mL) at 0 °C under Ar. The reaction mixture was allowed to reach 23 °C while stirring for 2 h. The solvent was removed *in vacuo* and the resulting solid was grinded with Et_2O (2 x 5 mL). The Et_2O was removed, and the solid was dried under reduced pressure to give a white crystalline solid (1.040 g, 95%): mp 159 – 161 °C (2-propanol-ethyl acetate) [lit.[77a] 175 – 178 °C]; $[\alpha]_D^{20}$ +2.4 (*c* 0.8, EtOH) [lit.[77a] $[\alpha]_D^{25}$ +2.1 (*c* 1.3, EtOH)]; IR ν 3082, 2947, 2931, 2724, 1642, 1016, 922 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (br s, 1H), 9.27 (br s, 1H), 5.79 (td, *J* = 16.8, 7.4 Hz, 1H), 5.22 (d, *J* = 10.8 Hz, 1H), 5.18 (d, *J* = 3.1 Hz, 1H), 3.48 (br d, *J* = 10.4 Hz, 1H), 2.99 (br s, 1H), 2.92 - 2.75 (m, 2H), 2.60 – 2.44 (m, 1H), 2.09 – 1.77 (m, 4H), 1.77 – 1.55

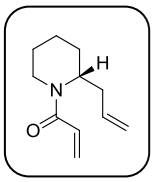
(m, 1H), 1.54 – 1.33 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9 (CH), 119.9 (CH_2), 56.9 (CH), 45.0 (CH_2), 37.9 (CH_2), 28.0 (CH_2), 22.5 (CH_2), 22.3 (CH_2).

(*S*)-Coniine hydrochloride (5).



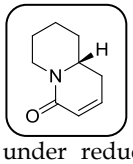
To a solution of **4** (154 mg, 0.95 mmol) in dry MeOH (20 mL) was added 10% Pd/C (50 mg). A balloon of H_2 gas was fitted to the equipment, and the reaction mixture was stirred under H_2 for 20 h at 23 °C. The reaction mixture was filtered through a short pad of Celite and washed successively with Et_2O and a 4 M solution of HCl in dioxane. The residue was concentrated *in vacuo* and the solid obtained was grinded with Et_2O (2 x 1 mL) and recrystalized from 3:1 EtOAc/EtOH (2 mL) to afford a white solid (120 mg, 78%): mp 226 - 230 °C [lit.[91b] 216-218 °C]; $[\alpha]_D^{20}$ +7.2 (*c* 1.0, EtOH) [lit.[77a] $[\alpha]_D^{25}$ +5.2 (*c* 0.35, EtOH)]; IR ν 2788, 2762, 2727, 1592 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (br s, 1H), 9.20 (br s, 1H), 3.45 (br d, *J* = 11.6 Hz, 1H), 3.06 - 2.71 (m, 2H), 2.10 - 1.54 (m, 7H), 1.54 - 1.33 (m, 3H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.4 (CH), 45.0 (CH_2), 35.6 (CH_2), 28.4 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 18.8 (CH_2), 13.8 (CH_3).

(*R*)-*N*-Acryloyl-2-allylpiperidine (6).



A mixture of **4** (230 mg, 1.42 mmol) in a 10% solution of NaOH (1.4 mL) was cooled to 0 °C and a solution of acryloylchloride (290 µL, 3.60 mmol) in CH_2Cl_2 (3.6 mL) was then added dropwise. The solution was allowed to reach room temperature and was stirred for 20 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (7:3 hexane/EtOAc) to provide the product **6** as a pale-yellow oil (208 mg, 82%): $[\alpha]_D^{20}$ +62.4 (c 0.7, $CHCl_3$) [lit.[85] for *ent*-**6** $[\alpha]_D^{20}$ –70.6 (c 0.42, $CHCl_3$)]; R_f 0.15 (6:4 hexane/EtOAc); IR ν 3078, 2936, 2858, 1640, 1607, 1430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (dd, *J* = 16.8, 10.7 Hz, 1H), 6.22 (d, *J* = 16.7 Hz, 1H), 5.72 (br s, 1H), 5.63 (dd, *J* = 10.6, 2.0 Hz, 1H), 5.10 - 5.00 (m, 2H), 4.74 (br d, *J* = 106.7Hz, 1H), 3.94 (br d, *J* =104.8 Hz, 1H), 2.91 (br d, *J* =123.5Hz, 1H), 2.46 (br s, 1H), 2.33 (dt, *J* = 14.2, 7.3 Hz, 1H), 1.77 - 1.53 (m, 6H), 1.53 - 1.34 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (C), 135.6 (CH), 134.3 (CH), 128.7 (CH), 127.1 (CH_2), 118.1 (CH_2), 116.9 (CH_2), 53.1 (CH), 47.9 (CH), 41.6 (CH_2), 37.1 (CH_2), 35.0 (CH_2), 34.4 (CH_2), 28.8 (CH_2), 27.4 (CH_2), 26.3 (CH_2), 25.4 (CH_2), 19.1 (CH_2); GC t_R = 10.8 min; LRMS (EI) m/z (%) 179 (M^+, 0.5), 138 (55), 84 (100), 55 (27); HRMS (EI) calcd for $C_{11}H_{17}NO$ 179.1310, found 179.1299.

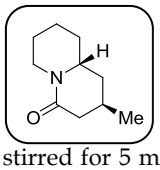
(*R*)-1,6,7,8,9,9a-Hexahydro-4*H*-quinolizin-4-one (7).



To a solution of **6** (188 mg, 1.24 mmol) in dry CH_2Cl_2 (10 mL) was added the Hoveyda-Grubbs catalyst (23 mg, 0.04 mmol) at room temperature. The reaction mixture was put under Ar and heated to 40 °C with stirring. After 30 min, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography (6:4

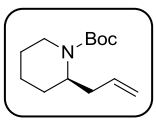
hexane/EtOAc) to provide the product as a pale-yellow oil (150 mg, 80%): $[\alpha]_D^{20}$ -39.0 (c 0.64, $CHCl_3$), [lit.[85] for *ent*-**7** $[\alpha]_D^{20}$ +45.7 (c 0.42, $CHCl_3$)]; R_f 0.17 (6:4 hexane/EtOAc); IR ν 3055, 2932, 2855, 1662, 1607, 1425 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (ddd, *J* = 9.8, 5.0, 3.4 Hz, 1H), 5.88 (ddd, *J* = 9.8, 2.5, 1.4 Hz, 1H), 4.50 (br d, *J* = 13.3 Hz, 1H), 3.43 (dtd, *J* = 9.7, 6.7, 3.3 Hz, 1H), 2.60 - 2.42 (m, 2H), 2.19 (dddd, *J* = 18.2, 9.5, 3.3, 2.6 Hz, 1H), 1.90 - 1.78 (m, 1H), 1.78 - 1.62 (m, 2H), 1.58 - 1.37 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 (C), 138.1 (CH), 124.7 (CH), 54.9 (CH), 43.0 (CH_2), 33.5 (CH_2), 31.2 (CH_2), 24.9 (CH_2), 24.0 (CH_2). GC t_R = 10.6 min; LRMS (EI) m/z (%) 151 (M^+, 93), 150 (25), 136 (12), 122 (50), 84 (100), 81 (82), 68 (40), 55 (22); HRMS (EI) calcd for $C_9H_{13}NO$ 151.0997, found 151.0973.

(2*R*,9*aR*)-2-Methyloctahydro-4*H*-quinolizin-4-one (8).



A solution of MeLi in Et_2O (2.4 mL, 1.2 M, 2.80 mmol) was added dropwise to a suspension of CuI (273 mg, 1.40 mmol) in dry THF (9.1 mL) at 0 °C. The resulting solution was stirred for 30 min and then cooled to -78 °C. $BF_3{\cdot}OEt_2$ was added dropwise and the resulting solution was stirred for 5 min at -78 °C. A solution of **7** (106 mg, 0.70 mmol) in dry THF (4.2 mL) was carefully added to the stirring mixture and the resulting solution was slowly allowed to reach room temperature (30 min). Saturated NH_4Cl solution (20 mL) was then added and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (98:2 to 95:5 CH_2Cl_2/MeOH) to give the product as a yellow oil (90 mg, 78%): $[\alpha]_D^{20}$ +21.0 (c 0.36, $CHCl_3$) [lit.[80] for *ent*-**8** $[\alpha]_D^{23}$ –21 (c 1.0, $CHCl_3$)]; R_f 0.36 (9:1 CH_2Cl_2/MeOH). IR ν 2929, 2855, 1624, 1442 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (ddt, *J* = 13.0, 4.0, 2.1 Hz, 1H), 3.40 – 3.29 (m, 1H), 2.53 – 2.35 (m, 2H), 2.14 – 1.84 (m, 3H), 1.72 – 1.29 (m, 7H), 0.99 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7 (C), 55.7 (CH), 43.2 (CH_2), 40.7 (CH_2), 37.0 (CH_2), 33.7 (CH_2), 25.6 (CH_2), 25.2 (CH_2), 24.6 (CH), 20.6 (CH_3); t_R = 11.7 min; LRMS (EI) m/z (%) 167 (M^+, 100), 166 (70), 152 (81), 125 (24), 97 (84), 83 (41), 69 (30), 55 (18); HRMS (EI) calcd for $C_{10}H_{17}NO$ 167.1310, found 167.1305.

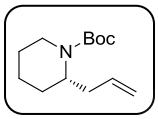
(*R*)-*N*-(*tert*-butoxicarbonyl)-2-allylpiperidine (9).



To a solution of **4** (614 mg, 3.80 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added aqueous NaOH solution (40 mL, 2 M) followed by Boc_2O (997 mg, 4.56 mmol). The reaction mixture was left stirring for 16 h while the temperature reached to 23 °C. The mixture was extracted with CH_2Cl_2 (3 times), washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was obtained as a colorless oil (905 mg contaminated with 12 mol% of Boc_2O according to GC, resulted in 93% estimated yield) and was used as it in the next step. A sample of compound **9** was purified by column chromatography (98:2 hexane/EtOAc) for characterization: $[\alpha]_D^{20}$ +46.5 (*c* 1.0, $CHCl_3$) [lit.[77c] for *ent*-**3c** $[\alpha]_D^{25}$ -39.96 (*c* 1.23, $CHCl_3$)]; R_f 0.60 (9:1 hexane/EtOAc); IR ν 2933, 1686, 1033, 912 cm^{-1}; ^1H NMR

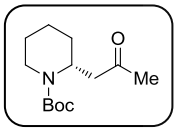
(400 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.00 (dd, *J* = 10.1, 0.9 Hz, 1H), 4.28 (br s, 1H), 3.97 (br d, *J* = 12.8 Hz, 1H), 2.77 (td, *J* = 13.2, 2.2 Hz, 1H), 2.39 (dt, *J* = 15.2, 7.7 Hz, 1H), 2.23 (dt, *J* = 15.0, 7.8 Hz, 1H), 1.65 - 1.51 (m, 6H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3 (C), 135.8 (CH), 116.7 (CH_2), 79.3 (C), 50.2 (CH), 39.0 (CH_2), 34.6 (CH_2), 28.6 (CH_3), 27.8 (CH_2), 25.6 (CH_2), 19.0 (CH_2); t_R = 10.4 min; LRMS (EI) *m/z* (%) 184 (M^+ - C_3H_5, 5), 128 (50), 84 (100), 57 (28), 56 (25); HRMS (EI) calcd for $C_{10}H_{18}NO_2$ (M^+ - C_3H_5) 184.1338, found 184.1343. CSP-GC analysis showed 93:7 er.[104]

(*S*)-*N*-*tert*-Butyl-2-allylpiperidine-carboxylate (*ent*-9).



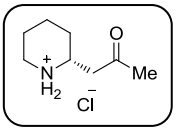
It was prepared from *ent*-**9** (0.30 mmol), following the same procedure described above for compound **9**. Physical and spectroscopic data were found to be same than for (*R*)-**9**, except for the optical rotation: $[\alpha]_D^{20}$ -41.7 (*c* 1.0, $CHCl_3$); CSP-GC analysis showed 93:7 er.

(*R*)-*N*-*tert*-Butoxycarbonyl-pelletierine (10).



A mixture of **9** (905 mg with 88 % of purity, 3.42 mmol), $PdCl_2$ (60 mg, 0.34 mmol) and $Cu(OAc)_2$ (126 mg, 0.68 mmol) in 7:1 DMF:H_2O (27 mL) was stirred for 24 h under O_2 (1 atm.) at 50 °C. The reaction was quenched with 1 M solution of $KHSO_4$ (27 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were successively washed with saturated $NaHCO_3$ solution (15 mL) and H_2O (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (9:1 hexane/EtOAc) to provide the product as a colorless oil (577 mg, 70%): $[\alpha]_D^{20}$ +10.5 (*c* 0.95, $CHCl_3$) [lit.[96] $[\alpha]_D^{25}$ +8.2 (*c* 2.0, $CHCl_3$)]; R_f 0.18 (9:1 hexane/EtOAc); IR ν 2978, 2930, 2854, 1710, 1684, 1409, 1363, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (br s, 1H), 3.97 (br d, *J* = 10.3 Hz, 1H), 2.78 (t, *J* = 13.0 Hz, 1H), 2.67 (dd, *J* = 12.4, 5.1 Hz, 1H), 2.62 (dd, *J* = 12.3, 5.6 Hz, 1H), 2.19 (s, 3H), 1.71 - 1.50 (m, 6H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3 (C), 154.9 (C), 79.8 (C), 47.4 (CH), 44.5 (CH_2), 39.5 (CH_2), 30.2 (CH_3), 28.6 (CH_2), 28.5 (CH_3), 25.4 (CH_2), 19.0 (CH_2); t_R = 12.3 min; LRMS (EI) *m/z* (%) 241 (M^+, 0.1), 184 (22), 168 (13), 140 (49), 128 (49), 98 (13), 84 (100), 57 (55); HRMS (EI) calcd for $C_{13}H_{23}NO_3$- CO 241.1678, found 213.1715.

(*R*)-(-)-Pelletierine hydrochloride (11).

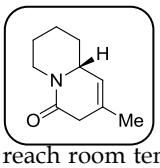


A solution of HCl in dioxane (2.5 mL, 4 M) was added dropwise to a solution of **10** (870 mg, 3.60 mmol) in dry CH_2Cl_2 (36 mL) at 0 °C and the reaction mixture was stirred at 23 °C for 2 h under Ar. After removal of the solvent under vacuum, the resulting solid was grinded with Et_2O (2

[104] See Supporting Information of Chapter I for more detail.

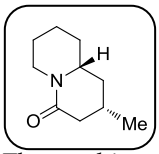
x 3 mL) to afford a pale brown amorphous solid (600 mg, 94%): $[\alpha]_D^{20}$ -12.0 (*c* 0.60, EtOH) [lit.[105] $[\alpha]_D^{25}$ –18.0 (*c* 0.5, EtOH)]. IR ν 2798, 2763, 2717, 1717, 1586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (br s, 1H), 9.19 (br s, 1H), 3.59 - 3.40 (m, 2H), 3.34 (dd, *J* = 18.3, 4.6 Hz, 1H), 2.99 (dd, *J* = 18.3, 8.0 Hz, 1H), 2.90 (dd, *J* = 23.3, 12.4 Hz, 1H), 2.22 (s, 3H), 2.10 - 1.82 (m, 4H), 1.80 - 1.68 (m, 1H), 1.60 - 1.46 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3 (C), 53.2 (CH), 46.0 (CH_2), 45.1 (CH_2), 30.7 (CH_3), 28.4 (CH_2), 22.4 (CH_2), 22.2 (CH_2).

(*R*)-2-Methyl-3,6,8,9,9a-hexahydro-(4*H*)-quinolizin-4-one (12).



Meldrum's acid (478 mg, 3.32 mmol) and acetic acid (156 µL, 2.70 mmol) were successively added to a stirring solution of (*R*)-Pelleterine[106] (380 mg, 2.69 mmol) in EtOH (2.7 mL) at room temperature. The resulting solution was heated to 60 ºC and stirred for 24 h. The solution was allowed to reach room temperature and more Meldrum's acid (388 mg, 2.69 mmol) was added. The solution was heated to 60 ºC and stirred for another 24 h. The reaction mixture was allowed to reach room temperature and concentrated under reduced pressure. The residue was diluted in EtOAc (18 mL), washed with a saturated solution of Na_2CO_3, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 hexane/EtOAc) to provide the product as a yellow oil (292 mg, 66%): $[\alpha]_D^{20}$ –8.7 (c 0.90, $CHCl_3$); R_f 0.50 (EtOAc). IR ν 2932, 2855, 1628, 1468, 1444, 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (dd, *J* = 2.8, 1.4 Hz, 1H), 4.85 (ddt, *J* = 13.0, 3.8, 2.0 Hz, 1H), 3.75 (br d, *J* = 10.0 Hz, 1H), 2.93 – 2.84 (m, 1H), 2.80 (dd, *J* = 20.6, 2.9 Hz, 1H), 2.46 (td, *J* = 12.8, 2.8 Hz, 1H), 1.94 – 1.76 (m, 3H), 1.70 (s, 3H), 1.62 – 1.33 (m, 2H), 1.22 (ddd, *J* = 25.1, 12.5, 3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (C), 129.1 (C), 120.3 (CH), 58.4 (CH), 42.3 (CH_2), 36.5 (CH_2), 34.5 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 21.9 (CH_3); t_R = 11.4 min; LRMS (EI) m/z (%) 165 (M^+, 36), 164 (19), 151 (10), 150 (100), 136 (34), 122 (21), 94 (15), 81 (11), 80 (16); HRMS (EI) calcd for $C_{10}H_{15}NO$ 165.1154, found 165.1150.

(2*S*,9*aR*)-2-Methyl-1,6,7,8,9,9a-hexahydro-quinolizin-4-one (13).

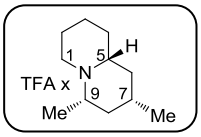


PtO_2 (9 mg, 0.04 mmol) was added to a solution of **12** (282 mg, 1.71 mmol) in EtOH (8.5 mL). The resulting suspension was shaken under H_2 atmosphere (50 psi) for 6 h at 23 ºC. The reaction mixture was diluted in EtOAc (3 mL) and the catalyst was removed by filtration through Celite. The resulting solution was concentrated under reduced pressure to give the product as a colorless oil (274 mg, 96%, 13:1 dr by ^1H NMR): $[\alpha]_D^{20}$ – 33.2 (c 1.00, $CHCl_3$); R_f 0.24 (1:1 hexane/EtOAc). IR ν 2929, 2854, 1635, 1444 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.81 – 4.72 (m, 1H), 3.18 (tdd, *J* = 11.1, 4.7, 2.6 Hz, 1H), 2.45 (dt, *J* = 16.1, 3.3 Hz, 1H), 2.36 (dd, *J* = 12.9, 2.7 Hz, 1H), 2.11 – 1.56 (m, 6H), 1.54 – 1.04 (m, 4H), 0.97 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (C), 56.8 (CH), 41.9 (CH_2), 41.4 (CH_2), 39.7 (CH_2), 34.7 (CH_2), 26.6

[105] Carlson, E. C.; Rathbone, L. K.; Yang, H.; Collett, N. D.; Carter, R. G. *J. Org. Chem.* **2008**, *73*, 5155.
[106] (*R*)-Pelleterine was released from hydrochloride **11** with NaOH 6 M and extracted with CH_2Cl_2 using conventional aqueous work-up.

(CH), 25.5 (CH_2), 24.4 (CH_2), 21.4 (CH_3); t_R = 11.0 min; LRMS (EI) m/z (%) 167 (M^+, 85), 166 (50), 152 (73), 125 (22), 124 (10), 98 (18), 97 (100), 84 (38), 83 (50), 69 (40), 68 (15), 56 (18), 55 (28); HRMS (EI) calcd for $C_{10}H_{17}NO$ 167.1310, found 167.1311.

(+)-5-*epi*-cermizine C-TFA salt (14).



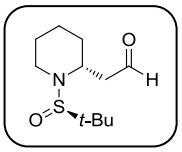
To a stirring solution of **13** (151 mg, 0.90 mmol) in dry THF (9 mL), was added dropwise a solution of MeMgBr in THF (3.8 mL, 0.95 M, 3.60 mmol). The mixture was heated to 60 ºC for 3 h and then allowed to cool to 0 ºC. $NaBH_3CN$ (340 mg, 5.40 mmol) and glacial acetic acid (450 µL, 7.86 mmol) were successively added and the mixture was stirred for 30 min at 0 ºC followed by another 30 min at 23 ºC. The reaction mixture was diluted with 5% aqueous solution of Na_2CO_3 (20 mL), verifying pH 10, and extracted with EtOAc (3 x 40 mL). The combined extracts were dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (90:9:1 $CHCl_3$/MeOH/NH_4OH). The obtained oil was dissolved in MeOH (2 mL) and treated with TFA (0.50 mL). The solution was concentrated under reduced pressure and the latter process was repeated to afford 180 mg (66%) of the TFA salt as a yellow oil: $[\alpha]_D^{20}$ +5.0 (c 0.53, MeOH); R_f 0.32 (90:9:1 $CHCl_3$/MeOH/NH_4OH); IR ν 2962, 1666, 1781, 1451, 1142, 797 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 3.79 (br d, *J* = 12.5 Hz, 1H), 3.23 – 3.12 (m, 1H), 3.06 (br t, *J* = 11.5 Hz, 1H), 2.73 (br t, *J* = 12.9 Hz, 1H), 2.04 – 1.90 (m, 3H), 1.90 – 1.62 (m, 4H), 1.62 – 1.48 (m, 2H), 1.37 (d, *J* = 6.4 Hz, 3H), 1.33 – 1.12 (m, 2H), 0.98 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, MeOD) δ 65.6 (CH), 62.5 (CH), 52.0 (CH_2), 41.8 (CH_2), 40.5 (CH_2), 32.3 (CH_2), 30.1 (CH), 24.9 (CH_2), 23.2 (CH_2), 21.4 (CH_3), 18.0 (CH_3).

A sample of compound **14** was dissolved in EtOAc, washed with NaOH 2 M (3 times), dried over $MgSO_4$ and concentrated under reduced pressure: IR ν 2924, 2857, 2782, 1453, 1198, 1120, 741 cm^{-1}; LRMS (EI) m/z (%)167 (M^+, 7), 166 (10), 151 (11), 152 (100), 124 (5), 110 (13), 83 (4), 69 (5), 55 (5); HRMS (EI) calcd for $C_{11}H_{22}N$ 167.1674, found 167.1674.

General procedure for the C=C double bond oxidative cleavage of compound 3.

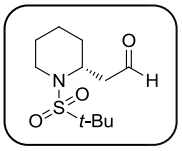
To a solution of **3** (115 mg, 0.5 mmol) in the correspondent solvent were successively added the corresponding amounts of 2,6-lutidine, $NaIO_4$ and an OsO_4 solution in ^{t}BuOH (2.5 % wt in *t*-BuOH, 50µL). The mixture was stirred at 0 ºC for 1 h before being quenched with water (20 mL). The mixture was extracted with EtOAc (3times) and the collected organic layers were washed with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was analyzed by ^1H-NMR and the products **15a** and/or **15b** and/or **15c** were purified by column chromatography (4:1 hexane/EtOAc).

(*R*,*R*$_S$)-*N*-(*tert*-Butylsulfinyl)-2-(2'-oxoethyl)piperidine (15a)



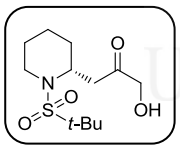
Compound **15a** (69 mg, 60%) was obtained as a colorless oil: $[\alpha]_D^{20}$ + 2 (c 1.50, $CHCl_3$); R_f 0.17 (1:1 hexane/EtOAc). IR ν 2933, 2862, 2721, 1719, 1456, 1387, 1359, 1066, 911 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (t, *J* = 1.6 Hz, 1H), 3.96 (dd, *J* = 118.3, 4.0 Hz, 1H), 3.18 (d, *J* = 12.7 Hz, 1H), 3.01 (ddd, *J* = 16.9, 9.4, 2.2 Hz, 1H), 2.95 – 2.80 (m, 2H), 1.92 – 1.46 (m, 6H), 1.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3 (CH), 58.6 (C), 51.7 (CH), 44.6 (CH_2), 41.1 (CH_2), 29.6 (CH_2), 25.5 (CH_2), 23.2 (CH_3), 19.7 (CH_2); t_R = 13.6 min; LRMS (EI) m/z (%) 232 (M^+, 0.1), 175 (12), 132 (13), 131 (100), 99 (6), 84 (19), 83 (21), 57 (23), 55 (11); HRMS (EI) calcd for $C_{11}H_{21}NO_2S$ - C_4H_8 175.0667, found 175.0664.

(*R*,*R*$_S$)-*N*-(*tert*-Butylsulfonyl)-2-(2'-oxoethyl)piperidine (15b)



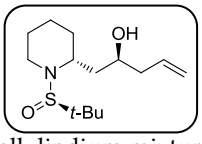
Compound **15b** was obtained as a colorless oil: R_f 0.54 (1:1 hexane/EtOAc); IR ν 2932, 2866, 2726, 1720, 1393, 1309, 1119, 931 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.8 Hz, 1H), 4.50 - 4.38 (m, 1H), 3.59 (d, *J* = 14.0 Hz, 1H), 3.09 - 3.00 (m, 1H), 2.96 (ddd, *J* =11.2, 6.5, 2.2 Hz, 1H), 2.85 (dd, *J* = 16.7, 4.7 Hz, 1H), 2.02 - 1.47 (m, 6H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1 (CH), 61.3 (C), 49.7 (CH), 45.3 (CH_2), 43.2 (CH_2), 28.8 (CH_2), 25.7 (CH_2), 24.4 (CH_3), 18.3 (CH_2); t_R = 13.9 min; LRMS (EI) m/z (%) 247 (M^+, 0.1), 204 (3), 148 (9), 126 (8), 112 (8), 99 (18), 84 (100), 83 (9), 57 (62), 56 (13).

(*R*,*R*$_S$)-*N*-(*tert*-Butylsulfonyl)-2-(2'-oxo-3'-hydroxypropyl)piperidine (15c)



Compound **15c** was obtained as a colorless oil: R_f 0.30 (1:1 hexane/EtOAc); IR ν 2928, 1719, 1308, 1120, 1051, 930 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (d, *J* = 19.1 Hz, 1H), 4.23 (d, *J* = 19.1 Hz, 1H), 3.57 (d, *J* = 14.0 Hz, 1H), 3.02 (dd, *J* = 19.7, 8.4 Hz, 1H), 2.96 – 2.88 (m, 1H), 2.80 (dd, *J* = 15.6, 3.8 Hz, 1H), 1.81 – 1.46 (m, 6H), 1.36 (s, 9H), 1.30 – 1.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9 (C), 68.8 (C), 51.3 (CH), 43.2 (CH_2), 40.0 (CH_2), 28.7 (CH_2), 25.6 (CH_2), 24.7 (CH_2), 24.3 (CH_3), 18.3 (CH_2).

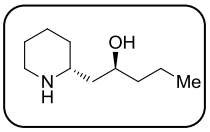
(*S*,*R*$_S$)-*N*-(*tert*-Butylsulfinyl)-2-(2'-hydroxy-4'-propenyl)piperidine (16)



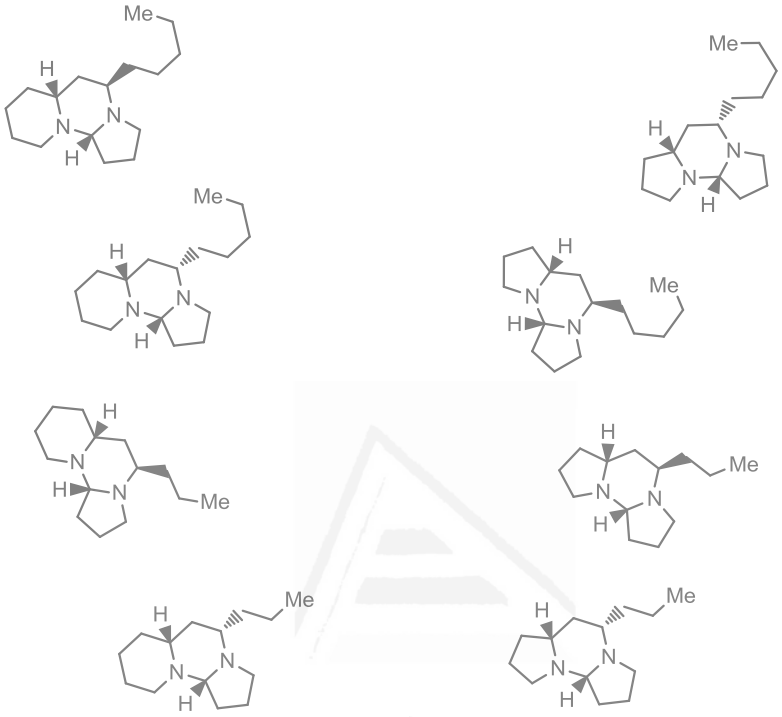
Indium (0) (36mg, 0.31 mmol) was suspended in dry THF (0.3 mL) and allyl bromide was added. The mixture was heated at 60 ºC for 1 h and then was allowed to reach 23 ºC. In a separate flask, aldehyde **15a** (44 mg, 0.26 mmol) was solved in dry THF (0.2 mL) and the allylindium mixture was dropwised whilst stirring. Then, the reaction mixture was stirred for 4h at 25 ºC. The reaction was quenched with brine and extracted with EtOAc (3 x 5 mL). The organics were dried over $MgSO_4$, concentrated and purified by column chromatography (1:1 Hexane/EtOAc) obtaining the corresponding product as a mixture of the corresponding diasteroisomers (55mg, 78 %, 1:4 dr): R_f 0.15 (1:1 Hexane/EtOAc); ^{1}H

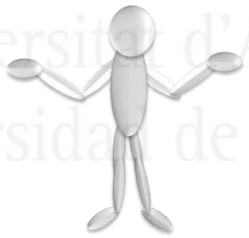
NMR (300 MHz, $CDCl_3$) δ 5.95 – 5.75 (m, 1H), 5.20 – 5.08 (m, 2H), 4.03 – 3.84 (m, 0.20H, minor), 3.82 – 3.70 (m, 0.80H), 3.70 – 3.57 (m, 1H), 3.20 (d, *J* = 14.1 Hz, 1H), 2.97 (dd, *J* = 12.5, 9.8 Hz, 0.8H, major), 2.77 (t, *J* = 12.7 Hz, 0.2H, minor), 2.39 – 2.17 (m, 2H), 1.90 – 1.82 (m, 2H), 1.73 – 1.42 (m, 6H), 1.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) for major compound δ 134.9 (CH), 118 (CH_2), 68.4 (CH), 58.4 (C), 55.2 (CH), 43.0 (CH_2), 40.3 (CH_2), 36.8 (CH_2), 28.7 (CH_2), 25.7 (CH_2), 23.4 (CH_3), 19.6 (CH_2).

Procedure for the synthesis of 2'-epi-halosaline (17).



A solution of HCl in dioxane (200μL) was dropwised into a mixture of homoallylalcohol **16** (54 mg, 0.2 mmol) in dry MeOH (2.4 mL) at 0 ºC. The reaction was stirred for 1 h at 23 ºC and then was concentrated under vacuum. The crude was diluted in dry MeOH (4mL) and Pd/C (10%, 60 mg) was added to the reaction. The reaction atmosphere was replaced by H_2 atmosphere (1 atm) and the reaction was shacked for 24 h at 25 ºC. Then the crude was filtrated through a short pad of Celite, washed with saturated K_2CO_3 solution and extracted with EtOAc (3 x 5 mL). Organics were dried over Na_2SO_4, concentrated and purified by column chromatography (95:5:0.05 $CHCl_3$:MeOH:NH_4OH) obtaining the corresponding product in 50% yield as a 4:1 mixture of the corresponding diasteroisomers (2'-*epi*-halosaline/(-)-halosaline): R_f 0.16 (95:5:0.05 $CHCl_3$:MeOH:NH_4OH); ^1H NMR (300 MHz, $CDCl_3$) δ 3.98 – 3.87 (m, 0.20H, minor), 3.87 – 3.78 (m, 0.80H, major), 3.02 (dd, *J* = 9.8, 7.7 Hz, 3H), 2.93 – 2.80 (m, 0.20H, minor), 2.71 (tt, *J* = 10.8, 2.4 Hz, 0.80H, major), 2.65 – 2.49 (m, 1H), 1.82 (d, *J* = 7.6 Hz, 1H), 1.70 – 1.00 (m, 10H), 0.92 (2x t, *J* = 6.9Hz, 3H).





Chapter II:

Tetraponerines:

a singular family of alkaloids.

PART OF THE CONTENT OF THIS CHAPTER HAS BEEN PUBLISHED IN:

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J. Org. Chem. **2012**, *77*, 10340.

A SECOND MANUSCRIPT WILL BE SUBMITTED IN DUE COURSE.

II.1. INTRODUCTION

Tetraponerines are a family of alkaloids segregated by *Pseudomyrmecine* ants of the genus *Tetraponera*, for which more than 80 species can be found in Asia, Africa or Australia. In 1987 Braekman and co-workers reported the first isolation and structural elucidation of these natural products.[107] These tricyclic alkaloids, named tetraponerines **T1** to **T8**, own a very uncommon aminal structure in alkaloids[108] and can be divided in two groups depending on the size of ring A (5 or 6). In each group, the tetraponerines differ in the length of the alkyl chain located in C_5 (propyl or pentyl groups) and in the configuration of this stereocenter(**Figure 1**). It has been determined that **T8** is the major tetraponerine isolated from the New Guinean ant *Tetraponera*, whilst **T1** and **T2** are very minor naturally occurring products. The structure of **T8** was unequivocally assigned by X-ray diffraction analysis.[107]

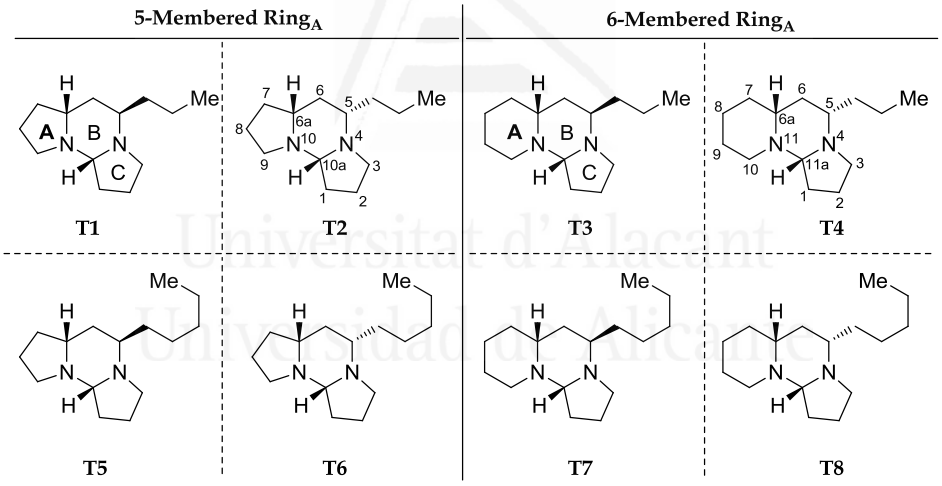


Figure 1

On the other hand, the structures of the other natural tetraponerines were proposed by comparison of their spectroscopical data, in particular one-dimensional ^{1}H-and ^{13}C-NMR spectra, with those of **T8**.[109] However, structures of **T3**, **T5**, **T6** and **T7** were mistakenly described at first and corrected then by massive studies involving nuclear magnetic resonance (NMR) and circular

[107] Braekman, J. C.; Daloze, D.; Pasteels, J. M.; Vanhecke, P.; Declercq, J. P.; Sinnwell, V.; Francke, W.; *Z Naturforsch. Teil* **1987**, *42c*, 627.
[108] Very few alkaloids possess an aminal carbon: Ban, Y.; Kimura, M.; Oishi, T. *Heterocycles* **1974**, *2*, 323.
[109] Merlin, P., Braekman, J. C., Daloze, D., Pasteels, J. M. *J. Chem. Ecol.* **1988**, *14*, 517.

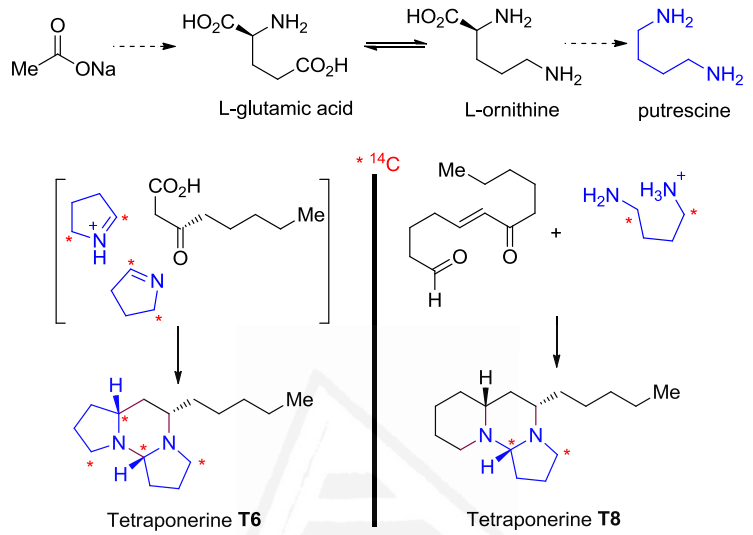
dicroism (CD).[110,111] It is worth mentioning that the combined use of infrared spectroscopy (IR) and mass spectrometry (MS) has been recently described to easily identify each isolated tetraponerine from their natural source.[112] In the study the authors conclude that the assignment of the C_5 configuration is possible by a simple analysis of the Bohlmann bands in the infrared spectra of the tetraponerines. Thus, it was observed that tetraponerines with 5-(*S*) configuration showed a less energetic and more intense vibrational C-H band than epimers with 5-(*R*) configuration.

It was early recognized that tetraponerines are paralyzing venoms segregated by the host ants against their enemies. Not surprisingly, it was found that they exhibit important insecticidal and neurotoxic biolological activities.[107] Recent studies categorize them as efficient inhibitors of a range of nAChRs (nicotinic acetycholine receptors).[113] However, despite their interesting biological profile, the actual mechanisms of interaction with their corresponding receptors are still unknown. More recently, cytotoxic activities have also been described for these natural products as well as for some synthetic analogs containing long hydrocarbon chains at C_5 position. [114]

The natural origin of the tetraponerines has been studied by the Braekman's group with **T6** and **T8** and they suggest different biosynthetic routes depending on the A ring size.[115,116] The analysis was carried out by feeding *Tetraponera* ants with a sucrose solution containing [^{14}C]-radiolabelled sodium acetate, glutamic acid, ornithine hydrochloride or [1,4-^{14}C]-putrescine dihydrochloride. Radiactive tetraponerines were thus extracted and submitted to a chemical degradation process. For compound **T8**, the distribution of ^{14}C was consistent with a pyrrolidine ring derived from L-glutamic acid vía L-ornithine and putrescine. Condensation of this diamine with a 12-carbon poliacetate precursor (six acetate units) is the biosynthetic pathway proposed. Similar studies with **T6** suggest that

[110] Macours, P.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *Tetrahedron* **1995**, *51*, 1415.
[111] The structures of **T5** and **T6** were also confirmed in this article by chemical synthesis: Devijver, C.; Macours, P.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *Tetrahedron* **1995**, *51*, 10913.
[112] Garrafo, M. H.; Spande, T. F.; Jain, P.; Kaneko, T.; Jones, T. H.; Blum, M. S.; Ali, T. M. M.; Snelling, R. R.; Isabell, L. A.; Robertson, H. G.; Daly, J. W. *Rapid Commun Mass Spectrom.* **2001**, *15*, 1409.
[113] Kem, W. R.; Wildeboer, K.; LeFrancois, S.; Raja, M.; Marszalec, W.; Braekman, J. C. *Cell Mol. Neurobiol.* **2004**, *24*, 535.
[114] Rouchaud, A.; Braekman, J. C. *Eur. J. Org. Chem.* **2009**, 2666.
[115] Devijver, C.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *Chem. Comm.* **1997**, 661.
[116] Renson, B.; Merlin, P.; Daloze, D.; Braekman, J. C.; Roisin, Y.; Pasteels, J. M. *Can J. Chem.* **1994**, *72*, 105.

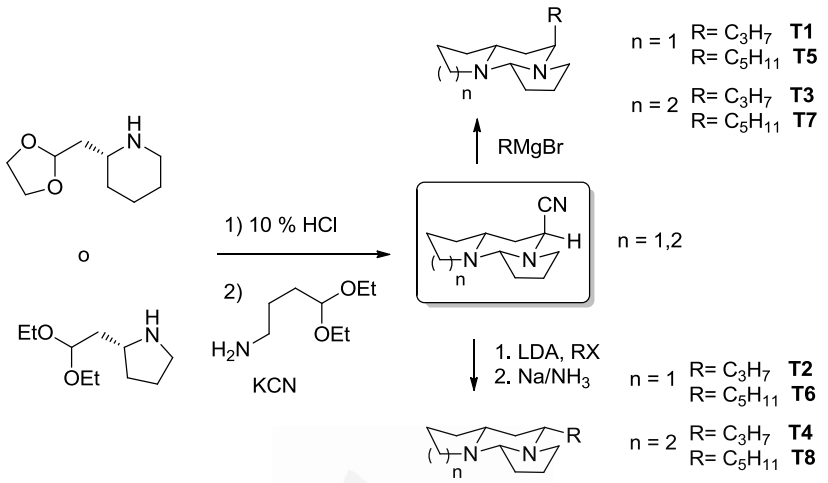
this alkaloid is formed by reaction of two putrescine units with an eight-carbon polyacetate precursor followed by decarboxylation (**Scheme 9**).



Scheme 9

The first total synthesis of (±)-**T8** was reported one year after the first isolation and structural elucidation of the tetraponerines by the same research group.[117] However, the first enantioselective synthesis of (+)-**T8** was not achieved until 1990 and based on that, the absolute configuration of the natural alkaloid was firmly established.[118] Later on, the group of Royer applied the same CN (*R*,*S*) strategy to the synthesis of all natural tetraponerines known, being the only general method to prepare this family of alkaloids to date.[119] The methodology allows a rapid stereoselective construction of the tricyclic tetraponerines core with a nitrile group in C_5 axial position (anomeric effect with Nα). Based on previous results from the same group, two alternative routes allowed the nitrile group substitution by the corresponding alkyl chain with complementary stereochemical results (**Scheme 10**).[120]

[117] Merlin, P.; Braekman, J.-C.; Daloze, D. *Tetrahedron Lett.* **1988**, *29*, 1691.
[118] Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1990**, *55*, 1140.
[119] Yue, C. W.; Gauthier, I.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1996**, *61*, 4949.
[120] Guerrier, L.; Roger, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.



Scheme 10

The singular tricyclic skeleton with an aminal moiety along with their interesting biological activities have made the tetraponerines very attractive targets for total synthesis.[121] Despite all the synthetic efforts that have been made in this field, a general and straightforward route to this family of alkaloids, that can be easily adapted to the synthesis of analogues, is still needed. Moreover, gain insight into the configurational spectrum of tetraponerines could be important to understand their mode of action in any activity displayed as well as to perform a rationale search of structure-activity for tetraponerine derived compounds.

II.2. OBJECTIVES

A computational study of the configurational spectrum of **T3** and **T4** by DFT calculations was planned. With the help of these theoretical calculations, a general divergent route to all natural tetraponerines was designed, in which our indium mediated α-aminoallyllation of aldehydes methodology occupies a central role.

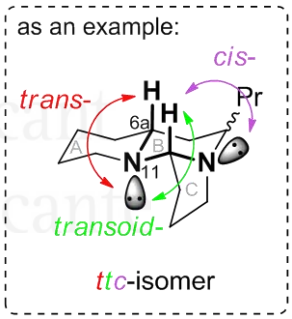
[121] Other representative examples for enantioselective syntheses: (a) see ref. 77b. (b) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584. (c) Airiau, E.; Girard, N.; Pizzeti, M.; Salvadori, M.; Taddei, M.; Mann, A. *J. Org. Chem.* **2010**, *75*, 8670.

II.3. RESULTS AND DISCUSSION

Stereochemical Analysis of T3 and T4 by Computational Studies.

To our best knowledge, a comprehensive study on the conformational and configurational analysis of tetraponerines has not been reported to date. To fulfill the lack of detailed structural information of tetraponerines, we consider all possible isomers of **T3** and **T4** for a configurational analysis by DFT calculations.

A few remarks on the stereochemical nomenclature and notation used are pertinent for a better understanding. Concerning the nitrogen atoms, the relevant configurational descriptors of the pyramidal nitrogen were specifically defined, in coherence with the calculation inputs. Until now, this task has been always overlooked, probably on the basis of the expected low nitrogen inversion barriers. Thus, we speak of configuration of the pyramidal nitrogen regardless of its inversion barrier. Both **T3** and **T4** share a bicyclic quinolizidine (rings AB) as well as an indolizidine fragment (rings BC). As a starting anchor point the (*R*)-configuration was used for carbon C_{6a}, which is invariably in these natural products. The configuration of the nearest nitrogen N_{11}, defines the type of ring fusion of the AB fragment, either *cis*- or *trans*-. Next, the relative stereochemistry of the quinolizidine and indolizidine frameworks (i.e., the rings AB and BC) was defined as either *cisoid*- or *transoid*-. Finally the indolizidine ring fusion BC was again defined as either *cis*- or *trans*-. Thus, as depicted in the example, the *ttc*-isomer would correspond to a *trans*-*transoide*-*cis* relative configuration.



Considering that *cis*-quinolizidines present two conformers in equilibrium with the same relative configuration (just as in *cis*-decalin), a total of 12 possible isomers are conceivable for each tetraponerine (**Figure 2**).

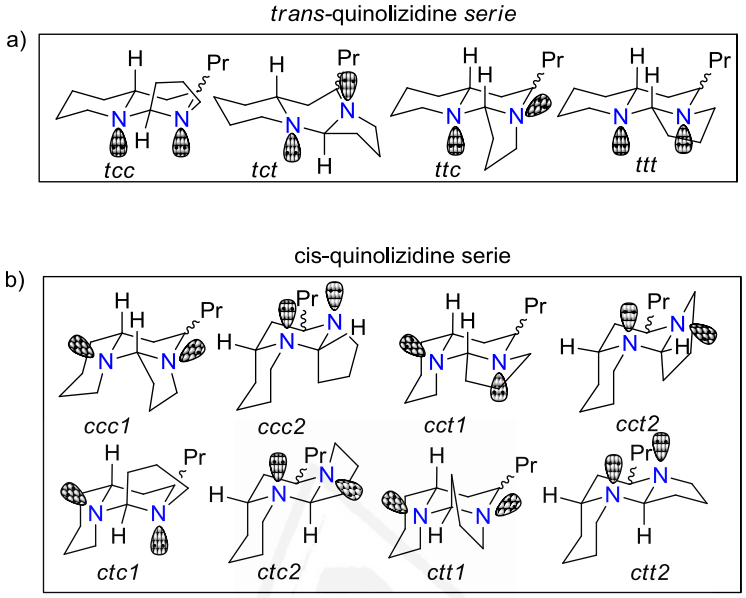


Figure 2

By using DFT calculations, the energies for the optimized structures were obtained for each isomer (**Chart 1**).[122] Considering only the structures within 3 kcal/mol from the absolute minimum, we estimated the population of the major isomers for each compound. For **T3** the most stable isomer was *ttc*- representing about 65% of the population at 25 °C, closely followed by *ttt*- with a 34% (ΔE = 0.38 kcal/mol) of the population. The third more stable configuration was *ctt2*-**T3**, with only 0.47% of the population (ΔE = 2.72 kcal/mol).[123] The configurational spectrum of **T4** is dominated by its *ttt*- isomer with about 95% of the population, whereas the second most stable isomer is *ttc*- with a representation of only 4.5% (ΔE = 1.81 kcal/mol).

[122] All optimized structures are described in detail in the Supporting Information file of Chapter II. The accuracy of these results has been estimated by comparision with a preliminary study at the B3LYP/6-31G(d) level. Both calculations have identical profiles, with an average absolute deviation of the energies in the whole set of ±0.4 and ±0.7 kcal·mol^{-1}for **T3** and **T4** respectively.

[123] $\Delta G^{o} = -RT \cdot \ln K_{eq}$ (K_{eq} = equilibrium constant between the possible configurations).

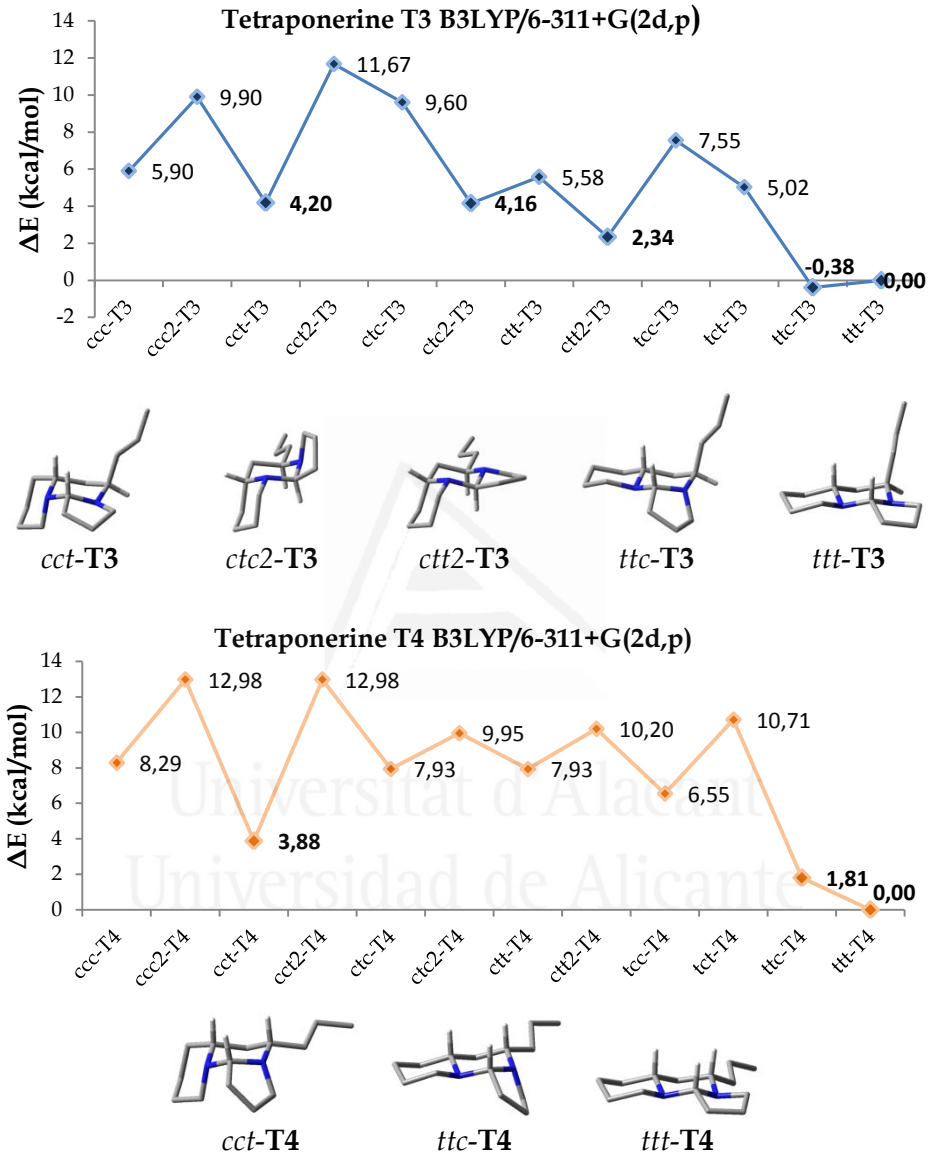


Chart 1. DFT energy profiles (Δ*E* including *ZPE* corrections in kcal mol^{-1}) of local minima for all the **T4** configurations. The structures with Δ*E* < 5 kcal mol^{-1} for each compound are drawn. The stereochemically non-relevant hydrogens have been removed. During geometry optimization, the *ccc*2-**T4** became *cct*2-**T4**, and the *ctt*-**T4** became *ctc*-**T4**. Both are consistent with a spontaneous release of strain through nitrogen inversion at the indolizidine framework.

The first conclusion from these calculations is that for both **T3** and **T4**, at least 99% of the population is represented by either its *ttc*- or *ttt*- isomer. A closer examination of these two configurational isomers shows that, despite the different fusions at the indolizidine frameworks, the same (*S*)-configuration at the aminal carbon center is observed. *Remarkably, this configuration at C_{11a} is observed not only for natural **T3** and **T4**, but also for all the other natural tetraponerines.*

The reasons for the relative stabilities of the isomers considered for **T3** and **T4** are a combination of tensional, steric, and stereoelectronic effects. Concerning tensional and steric effects, two important patterns of destabilization are easily identified. The methylene-methylene (or alkyl-alkyl) 1,3-diaxial interactions, as occurring in *ccc1*-**T3**-**4**, *ccc*2-**T3**, *ctc1*-**T3**, *ctc*2-**T4**, *ctt*2-**T4**, *tcc*-**T3**, is one of them. The second, even more severe, is a ring B deformation from chair into other distorted conformations such as twisted boat, which occurs when a tentative *trans*-diaxial fusion with ring C is imposed, e.g. *cct*2-**T3-4**, *ctt1*-**T3**, *tct*-**T3-4**. None of these destabilizing elements are found in the more stable configurations of **T3** and **T4** (*ttc* and *ttt*). The main stereochemical elements of these configurations follow. For **T3**, a small gauche interaction is appreciated between C_3 and Pr in the *ttt* configuration. This interaction can be avoided by nitrogen inversion at N_4, becoming the more stable *ttc*-**T3**, at the expense of an additional 1,3-diaxial methylene interaction with only 1 hydrogen. Importantly, *ttc*-**T3** takes advantage of one anomeric stabilization between the N_4 lone pair and the σ* C_{11a}-N_{11}. The geometric effect of this hyperconjugation is patent in the calculated bond lengths for C_{11a}-N_4 (1.455 Å) and C_{11a}-N_{11} (1.489 Å). For **T4**, the most stable configuration is *ttt* where a small gauche interaction between C_3 and Pr cannot be relieved by nitrogen inversion at N_4. In this case *ttc*-**T4** has also a gauche interaction and the anomeric stabilization (calculated C_{11a}-N_4 and C_{11a}-N_{11} bond lengths are 1.454 and 1.489 Å, respectively) seems not to compensate the appearance of an additional 1,3-diaxial methylene interaction with one hydrogen.

On the other hand, although **T3** and **T4** do not interconvert spontaneously, a comparison of the intrinsic stability of both tetraponerines was performed. Overall, the tetraponerine **T4** is calculated to be intrinsically some 2.52 kcal mol^{-1} more stable than **T3**.[124] This issue was crucial in a reported stereoselective

[124] This ΔG was determined from the calculated standard free energies taking into consideration that both, **T3** and **T4** are actual mixtures of conformations:

$$G^0 = -\mathrm{RT}[\ln \sum_i \mathrm{e}^{-\mathrm{G}_i^0(\mathbf{T4})/\mathrm{RT}} - \ln \sum_j \mathrm{e}^{-\mathrm{G}_j^0(\mathbf{T3})/\mathrm{RT}}]$$

synthesis of **T4**, where the final step implied the conversion of a fast inverting radical at C_5 into the more stable carbanion and its fast protonation.[119]

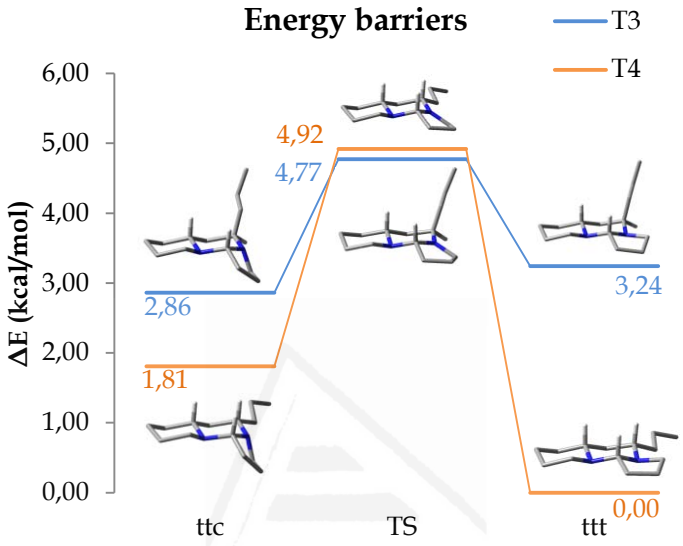


Chart 2: Calculated activation barriers for N_4 inversion in **T3** (ΔE = 1.90 kcal·mol^{-1}) and **T4** (ΔE = 4.92 kcal·mol^{-1}) at the B3LYP/6-311+G-7(2d,p) level. Notice the trigonal planar nitrogen at the inverting nitrogen; ν = 126.27*i* cm^{-1} for the transition state TS_**T3** (bottom centered) and ; ν = 163.64*i* cm^{-1} for the transition state TS_**T4** (top centered).

Inversion at N_4 of the indolizidine fragment should allow the interconversion between the two most populated stereoisomers for **T3** and **T4** (*ttc*- and *ttt*-). We thus decided to calculate these inversion barriers for each tetraponerine and the results are summarized in **Chart 2**. Visual examination of the imaginary frequency mode passing through the transition state confirmed the correct nature of the calculated saddle points TS-**T3-4**. In both cases the nitrogen atom examined (N_4) displays a trigonal planar geometry at the transition state. Importantly, the calculated energy barriers are low (4.92 and 1.90 kcal·mol^{-1} for **T4** and **T3**, respectively) implying a fast interconversion between these two isomers for each tetraponerine. It is worth noting that this barrier is *ca.* 3 kcal·mol^{-1} higher for **T4** than for **T3**, presumably because during the inversion process of **T4,** C_3 has to overcome a gauche interaction with the propyl group. Moreover, coalescence barriers of 106-112 ^{o}K for **T4** and 43-45 ^{o}K for **T3** were

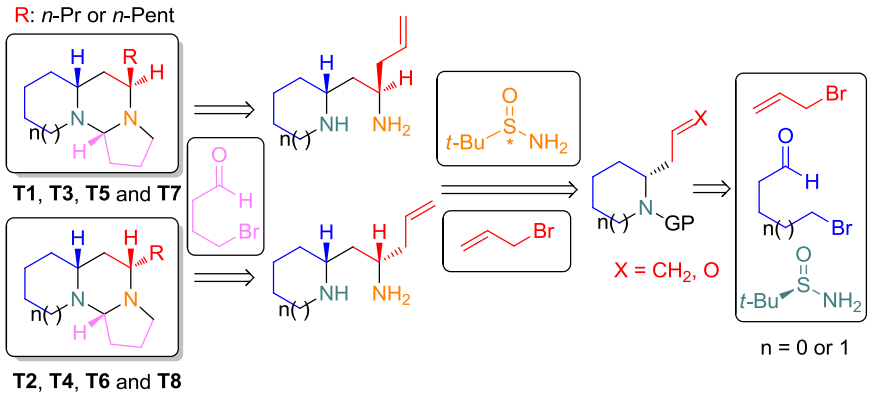
estimated, which unfortunately makes their experimental measurements very difficult.

Retrosynthetic Analysis.

During degradation studies of **T6** and **T8**, catalytic hydrogenation under acidic media produced the selectively cleavage the N_{11}-C_{11a} bond , presumably via the corresponding iminium ion.[115] Our stereochemical analysis of **T3** and **T4** by DFT calculations estimates that at least 99% of the population of its compound exhibit the same (*S*)-configuration at the aminal carbon center that is present in any natural tetraponerine. Based on these facts, we speculated that the aminal core of tetraponerines is susceptible of being in equilibrium with the corresponding iminium ion and the *natural alkaloids might correspond to the most stable aminals possible*. With this in mind we anticipated that rings B and C of tetraponerines could be formed, with the right stereochemistry at C_{11a}, by reaction of 4-bromobutanal[125] with the corresponding diamines.

As depicted in **Scheme 11**, the required enantioenriched diamines include two stereogenic carbon centers in adjacent positions to the nitrogen atoms. We thus envisioned an iterative use of our stereoselective indium-mediated aminoallylation. Hence, we traced back the synthesis of diamine precursors to 2-allyl piperidine/pyrrolidine derivatives, which could be prepared by aminoallylation of 5-bromopentanal or 4-bromobutanal with chiral *tert*-butylsulfinamide and *in situ* generated allylindium. Oxidative cleavage of the double bond would give rise to the corresponding aldehydes that could be submitted to a second aminoallylation step to prepare the required diamines. Importantly, the stereochemistry at the new carbon center should be independently controlled by the chiral *tert*-butylsulfinamide used in order to give access to all tetraponerines. Reduction of these homoallylic diamines, followed by reaction with 4-bromobutanal should give rise to all C_5-propyl tetraponerines (**T1**-**T4**), *if the hypothesis of the thermodynamic control at the aminal center is correct*. On the other hand, a five-carbon chain at C_5 could be constructed by cross-methatesis of the the same homoallylic diamines intermediates with 3-hexene. Finally, a similar protocol from this new C_5-elongated homoallylic diamines should furnish the other C_5-penthyl tetraponerines (**T5**-**T8**).

[125] The use of 4-bromobutanal was already reported in a concise synthesis of (±)-**T8**. However, the origin of the stereochemical result was not discussed by the authors. See: Barluenga, J.; Tomás, M.; Kouznetsov, V.; Rubio, E. *J. Org. Chem.* **1994**, *59*, 3699.

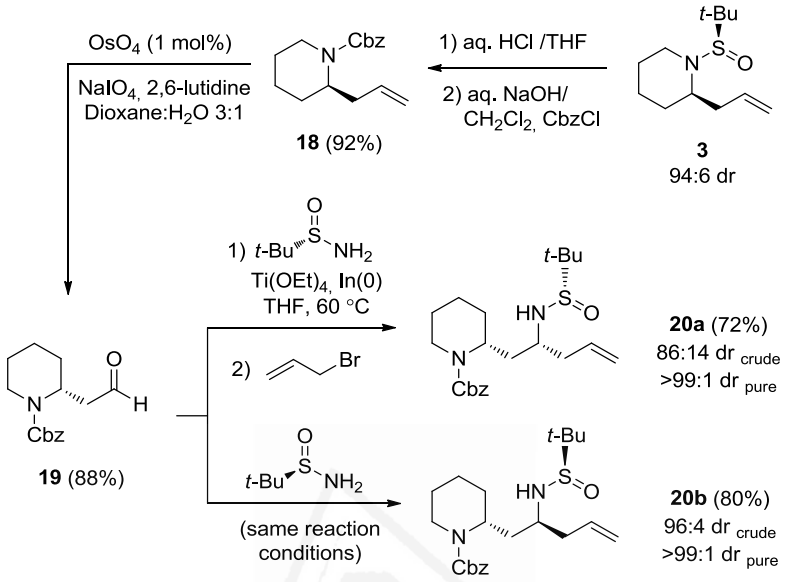


Scheme 11

It is worth noting that all the required starting materials for this approach - allyl bromide, 5-bromopentanal, 4-bromobutanal, 3-hexene and both enantiomers of *tert*-butylsulfinamide- are commercially available or easily prepared.

Synthesis of all Known Natural Tetraponerines (T1 to T8).

N-tert-Butylsulfinyl-2-allylpiperidine **3** was prepared as shown in the previous chapter. The sulfinyl group was removed under aqueous acidic conditions, and after basifying with NaOH, the addition of benzyloxicarbonyl chloride allowed the one-pot preparation of the corresponding Cbz-protected amine **18** in excellent yield. The oxidative cleavage of the double bond was examined under ozonolysis conditions; however, better results (**19**, 88% yield) were obtained with the use of OsO_4 (1 mol%)/2,6-lutidine (**Scheme 12**).[101] Aminoallylation of this aldehyde **19**, under the same reaction conditions used in the first aminoallylation step, gave **20a** as the major product when (S_s)-*tert*-butylsulfinamide was used, and **20b** when (R_s)-*tert*-butylsulfinamide was employed. In both cases the desired products were obtained as single diastereoisomers (>99:1 dr judged by HPLC for each compound) after purification by column chromatography. On the other hand, the analyses of both crude products showed that the diasteroselection was greater for **20b** (96:4 dr) than for **20a** (86:14 dr). This result must be a consequence of a cooperative effect between the chiral aldehyde **19** and the (R_s)-*tert*-butylsulfinamide in the observed chiral induction (match effect). Remarkably, the chiral induction of the sulfinyl group overcome the induction of the chiral aldehyde **19** and even in the case of the mismatched combination, the product **20a** could be isolated in good yield (72%). *This element was crucial for the success of the proposed strategy in the synthesis of all natural tetraponerines*.

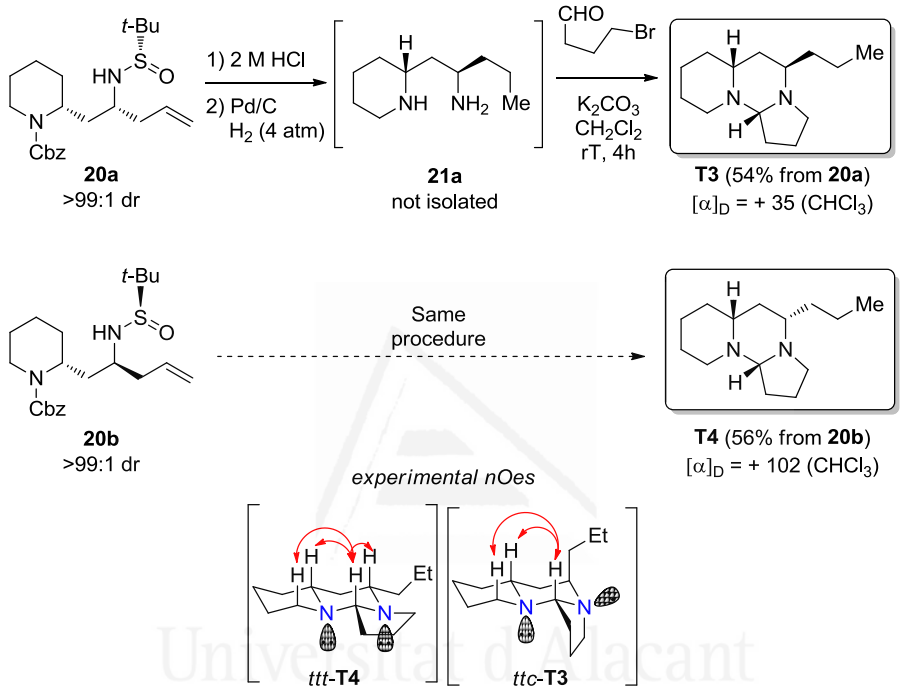


Scheme 12

The corresponding free saturated diamines were prepared by aqueous acidic removal of the chiral auxiliary followed by catalytic hydrogenation at 4 atm of the alkene framework with concomitant hydrogenolysis of the carbamate group (**Scheme 13**). Compounds **21a** and **21b** were identified by ^{1}H-NMR but their isolation was avoided due to its difficult handling. It is worth mentioning that Cbz was chosen as protecting group of the nitrogen atom since the hydrogenation of the double bond was inevitable and this would allow the *in situ* removal of the Cbz group without any additional step. The stage was then set to complete the synthesis of **T3** and **T4**. After explored some reaction conditions of diamines **21a** or **21b** with 4-bromobutanal, like Na_2SO_4 in CH_2Cl_2 at 25 ^{o}C / Na_2SO_4 in $CHCl_3$ at 25 ^{o}C / or Na_2SO_4 in THF at 60 ^{o}C, the best results were obtained in a suspension of K_2CO_3 in CH_2Cl_2. In both cases, after only 4 h at 25 ^{o}C the GC-MS showed the formation of major products with identical mass spectra to tetraponerines **T3** and **T4**. Purification by column chromatography allowed the isolation of the final products with good global yields and excellent diasteroselectivities (>99:1 dr by GC in both cases). Most importantly, the spectroscopical as well as the physical data for these synthetic products (^{1}H-NMR, ^{13}C-NMR, IR and optical rotation) perfectly matched with the literature data described for the natural tetraponerines.[126] The relative stereochemistry was

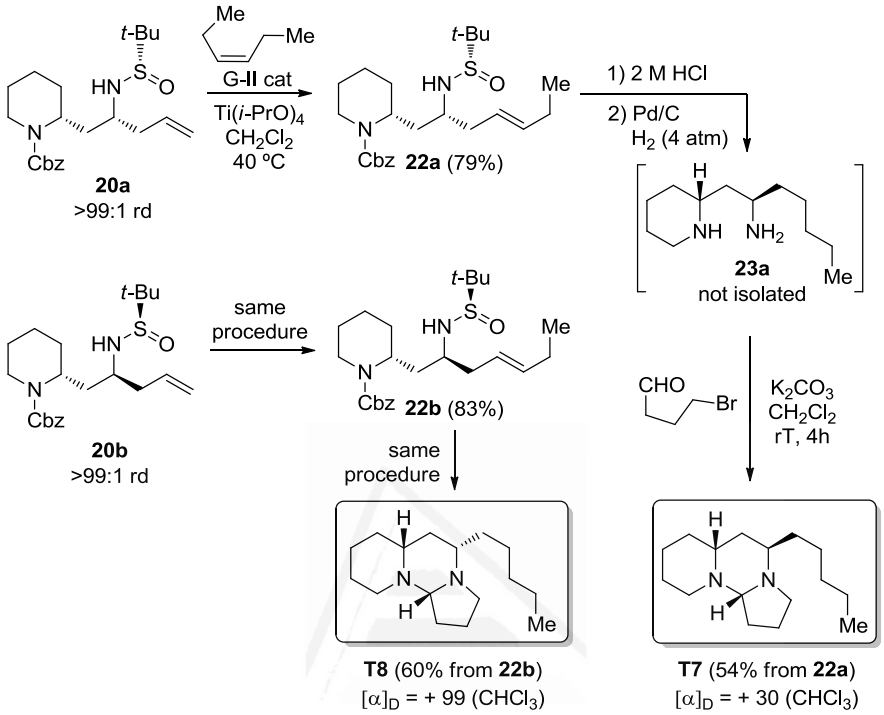
[126] See Supporting Information of Chapter II for more detail.

ascertained by ^{1}H-NMR, observing the nOes depicted in **Scheme 13** for the major isomers. *These results clearly support our hypothesis of a thermodynamic control for the aminal carbon stereocenter of the natural tetraponerines.*



Scheme 13

On the other hand, the allyl group in the intermediates **20a** and **20b** provides a handle to prepare analogues of **T3** and **T4** using the same synthetic sequence. In particular, we decided to enlarge the hydrocarbonated side-chain up to 5 carbons by cross-metathesis with 3-hexene in order to prepare tetraponerines **T7** and **T8** (**Scheme 14**). Indeed, the reactions took place in good yields with *cis*-3-hexene in the presence of Grubbs 2nd generation catalyst and substoichiometric amounts of Ti(*i*-PrO)$_4$. After this single modification, the same reaction sequence applied to the synthesis of **T3** and **T4** was followed to obtain tetraponerines **T7** and **T8**, with good overall yields and excellent diasteroselectivities (>99:1 dr by GC-MS).

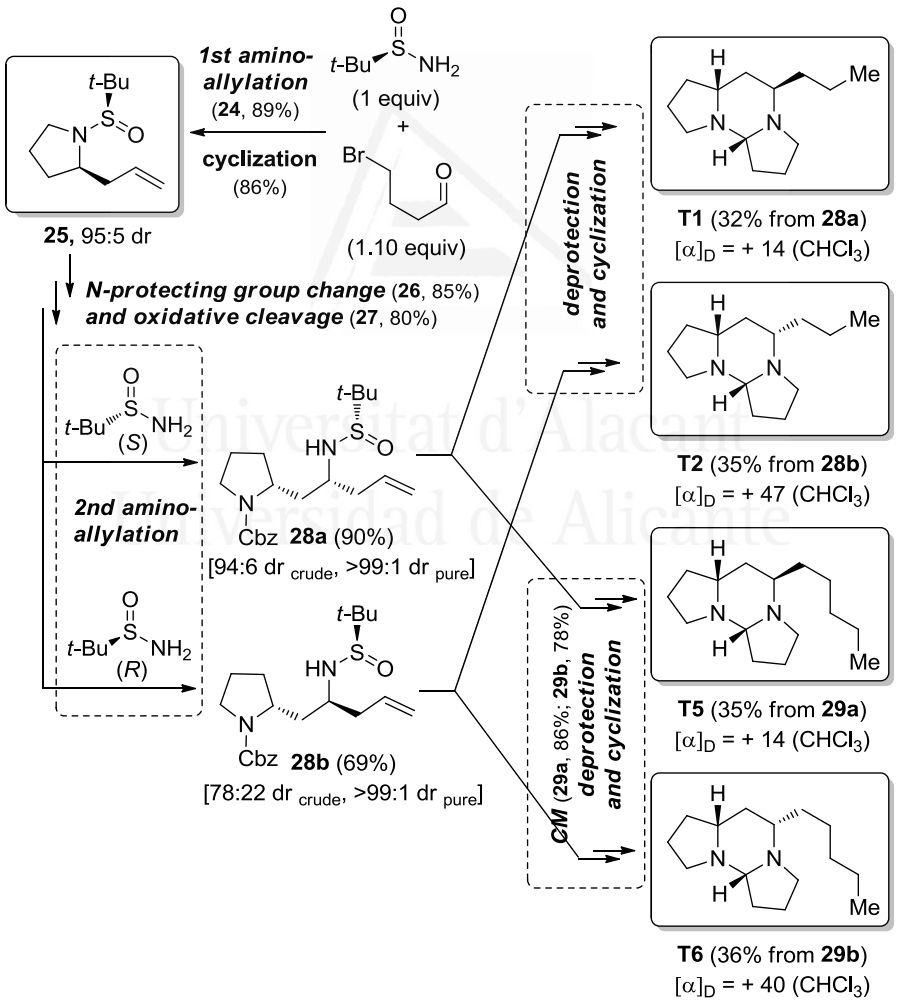


Scheme 14

Our next goal was to extend this methodology to the synthesis of the remaining natural tetraponerines (**T1**, **T2**, **T5** and **T6**) which differ in the size of ring A. With this in mind, the indium-mediated aminoallylation of 4-bromobutanal was accomplished with (R_S)-*tert*-butylsulfinamide (compound **24**), followed by cyclization with KHMDS, to obtain the corresponding 2-allylpyrrolidine **25** in good yield and 95:5 dr (**Scheme 15**).

After protecting group exchange and oxidative cleavage of the terminal double bond with good yields, the obtained aldehyde was submitted to a second aminoallylation with (*R*)- or (*S*)-*N*-*tert*-butylsulfinamides. In this case the match-mismatched effect was stronger than with piperidine substrates, achieving a 90% yield of **28a** (94:6 dr of the crude product) and a 69% yield of **28b** (with only 78:22 dr of the crude product). Contrary to what was observed for the piperidine aldehyde **19**, in this case the matched product was obtained when (*S*)-*N*-*tert*-butylsulfinamide was used. As previously shown for **T3** and **T4**, the synthesis of tetraponerines **T1** and **T2** was completed after acidic deprotection, catalytic hydrogenation and reaction of free diamines with 4-bromobutanal. Additionally,

tetraponerines **T5** and **T6** were prepared by including in the reaction sequence a cross-metathesis step with 3-hexene, as previously described for **T7** and **T8**. It is worth saying that the final steps (formation of rings B and C) during the synthesis of tetraponerines with a 5-membered A ring (**T1**, **T2**, **T5** and **T6**) were less efficient (32 - 36% yields) compared to the 6-membered A ring family (**T3**, **T4**, **T7** and **T8**; 54 - 60% yields). Moreover, it is also worthy of mention to our best knowledge, there are not NMR spectra available in the literature for the two smaller and very minor tetraponerines (**T1** and **T2)**, although their NMR data were reported.[119]



Scheme 15

Interestingly, a single crystal X-ray analysis could be performed for the mismatched product of the second aminoallylation step (**28b).** We were pleased to confirm that the configuration observed for the new carbon stereocenter agreed with the stereochemistry predicted by our working model for the aminoallylation step (**Figure 3**). Furthermore, spectroscopical and physical data of these new four tetraponerines were also in accordance with those reported for the corresponding natural products.

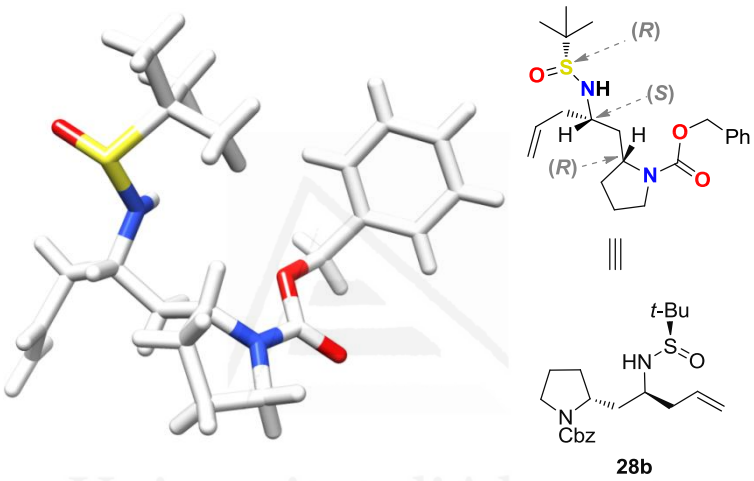


Figure 3: X-ray structure of compound **28b**[127]

In summary, the iterative use of stereoselective aminoallylation of aldehydes with chiral *N-tert*-butylsulfinamide and in situ generated allyl indium reagent was successfully applied to the synthesis of all natural tetraponerines from easily available starting materials. Furthermore, this synthetic approach clearly supports the hypothesis of a thermodynamic control for the configuration at the aminal carbon center of tetraponerines.

[127] CDCC 971540.

The Bolhmann Bands in IR Spectra of Tetraponerines.

A brief comment is in order here related to the use of the Bohlmann bands to assign the configuration at C_5 of tetraponerines. These bands are commonly used to elucidate the structure of alkaloids.[128] As shown in **Figure 4**, the experimental IR obtained for the synthesized tetraponerines show bands for C-H stretching at relatively low vibrational frequencies (2780-2810 cm^{-1}). The origin of these bands is not accurately known but has been related to the lengthening of $C\text{-}H_{axial}$ bonds due to the hyperconjugation of the adjacent nitrogen lone pair with the antiperiplanar antibonding C-H orbitals (n → σ* C-H).[129]

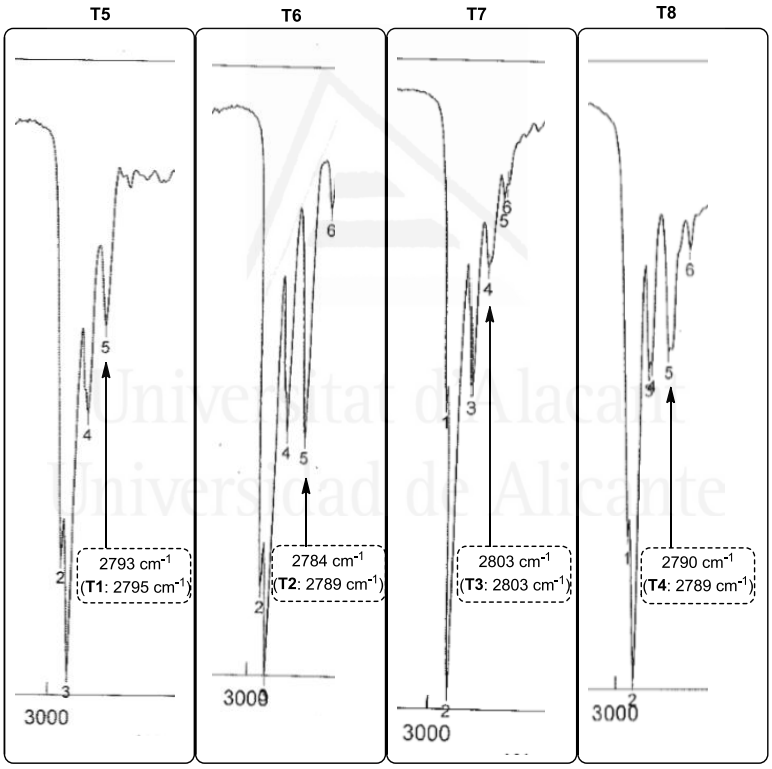


Figure 4

Interestingly, the even-numbered tetraponerines (**T2**, **T4**, **T6** and **T8**) with (*S*)-configuration at C_5 show a more severe deviation on this C-H bands which appear at lower vibrational frequencies and more intense, compare to the odd-

[128] Gribble, G. W.; Nelson, R. B. *J. Org. Chem.* **1973**, *38*, 2831.
[129] Wolfe, S.; Schlegel, B.; Whangbo, M.-H. *Can. J. Chem.* **1974**, *52*, 3787.

numbered tetraponerines (**T1**, **T3**, **T5** and **T7**). This pattern has been already used to assign the configuration at C_5 of isomeric tetraponerines.[112] To the light of our configurational analysis of **T3** and **T4** by DFT calculations we can offer a reasonable explanation to this different Bohlmann band patterns. It was conclude that both **T3** and **T4** are mainly populated (>99%) by *ttc*- or *ttt*- configurational isomers that are under rapid equilibration by inversion at N_4. Furthermore, in the case of **T4** the contribution of the *ttt*-isomer is more relevant (95%) than in **T3** (34%). As shown in **Table 2**, *ttt*-isomers present two nitrogens with electron pairs antiperiplanar to 4 or 5 C-H bonds, whereas *ttc*-isomers exhibit only one nitrogen with a lone pair antiperiplanar to 3 C-H bonds. Thus, the major contribution of *ttt*-isomer to **T4** (95% according DFT calculations) and *ttc*-isomer to **T3** (65% according DFT calculations) is in accordance with the Bohlmann patterns observed in the IR spectra for both **T3** and **T4**. A similar analysis can be done to compare the rest of odd-numbered and even-numbered tetraponerines.

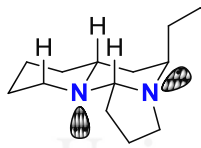
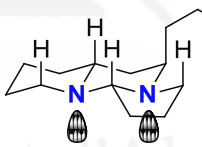
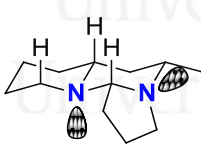
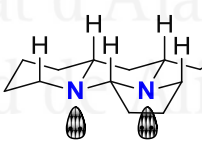
	ttc	*ttt*	ν C-H (IR)
T3	 65%	 34%	2803 cm^{-1}
T4	 4.5%	 95%	2789 cm^{-1} more intense

Table 2

II.4. EXPERIMENTAL SECTION

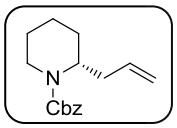
General Remarks.

(R_s)-*N*-*tert*-Butylsulfinamide and its enantiomer were a gift of Medalchemy (>99% ee by chiral HPLC on a Chiracel AS column, 90:10 *n*-hexane/*i*-PrOH, 1.2 mL/min, λ=222 nm). TLC was performed on silica gel 60 F_{254}, using aluminum plates and visualizad with phosphomolybdic acid (PMA) stain. Flash chromatography was carried out on handpacked columns of silica gel 60 (230- 400 mesh). Melting points are uncorrected. Optical rotations were measured using a polarimeter with a thermally jacketted 5 cm cell at approximately 20 ºC and concentrations (c) are given in g/100 mL. Infrared analysis was performed with a spectrophotometer equipped with an ATR component;

wavenumbers are given in cm^{-1}. Mass spectra (EI) were obtained at 70 eV; and fragment ions in m/z with relative intensities (%) in parentheses. HRMS analyses were also carried out in the electron impact mode (EI) at 70 eV. GC analyses were obtained with an HP-5 column (30 m × 0.25 mm, ID × 0.25 μm) and an EI (70 EV) detector. The temperature program: hold at 60 °C for 3 min, ramp from 60 °C to 270 °C at 15 °C/min, hold at 270 °C for 10 min. ^{1}H NMR spectra were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR, using $CDCl_3$ as the solvent and TMS as internal Standard (0.00 ppm). The data is being reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded with ^{1}H-decoupling at 100 MHz and referenced to $CDCl_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH_2 and CH_3.

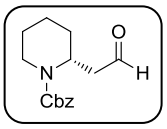
Procedure for the synthesis of compounds 18 - 20, 22 and tetraponerines T3, T4, T7 and T8.

(R)-2-Allyl-(*N*-benzyloxicarbonyl)piperidine (18)



An aqueous 6 M solution of HCl (1.5 mL, 9.00 mmol) was added dropwise to a solution of **3** (687 mg, 3.00 mmol) in dry THF (3 mL) at 0 °C under Ar. The solution was allowed to reach 23 °C and was stirred for 1.5 h. After cooled again to 0 °C, an aqueous 2 M solution of NaOH (14 mL, 27.00 mmol) was added dropwise and the resulting mixture was stirred at the same temperature. After 5 min, a solution of benzyloxicarbonil chloride (515 μL, 3.60 mmol) in CH_2Cl_2 (11 mL) was added to the stirring solution. The resulting mixture was then allowed to reach 23 °C and stirred for 3 h. The reaction mixture was extracted with EtOAc (3 times) and the combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatograpy (95:5 hexane/EtOAc) to provide the desired product **18** as a colorless oil (715 mg, 92%): $[\alpha]_D^{20}$ + 43.9 (*c* 0.50, $CHCl_3$); R_f 0.26 (9:1 hexane/EtOAc); IR ν 3035, 2937, 2859, 1691, 1641, 1445, 1421, 1258, 1240 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 5H), 5.71 (td, *J* = 16.5, 7.3 Hz, 1H), 5.19 – 4.95 (m, 4H), 4.37 (br s, 1H), 4.05 (d, *J* = 12.3 Hz, 1H), 2.86 (td, *J* = 12.8, 2.5 Hz, 1H), 2.43 (dddd, *J* = 10.5, 7.4, 2.4, 1.2 Hz, 1H), 2.25 (dt, *J* = 14.0, 7.1 Hz, 1H), 1.73 –1.54 (m, 5H), 1.54 –1.31 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (C), 137.2 (C), 135.4 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 117.0 (CH_2), 67.0 (CH_2), 50.5 (CH), 39.4 (CH_2), 34.6 (CH_2), 27.7 (CH_2), 25.6 (CH_2), 18.9 (CH_2); GC t_R = 15.1 min; LRMS (EI) *m/z* (%) 259 (M^+, 0.1), 219 (19), 218 (100), 175 (32), 174 (100), 92 (40), 91 (100), 65 (35), 55 (20); HRMS (EI) calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1601.

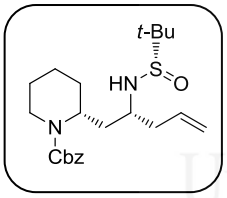
(*R*)-(*N*-Benzyloxicarbonyl)-2-(2′-oxoethyl)piperidine (19).



To a solution of **18** (684 mg, 2.64 mmol) in 1,4-dioxane:H_2O (3:1, 27 mL) were successively added 2,6-lutidine (615 μL, 5.28 mmol), $NaIO_4$ (2.30 g, 10.56 mmol) and a solution of OsO_4 in *t*-BuOH (2.5 % wt in *t*-BuOH, 260

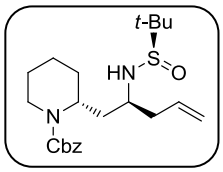
μL). The mixture was stirred at 23 ºC for 1.5 h before being quenched with water (20 mL). The mixture was extracted with EtOAc (3times) and the collected organic layers were washed with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatograpy (4:1 hexane/EtOAc) to provide the pure product as a colorless oil (610 mg, 88%): $[\alpha]_D^{20}$ + 42.0 (*c* 0.34, $CHCl_3$); R_f 0.30 (7:3 hexane/EtOAc); IR ν 3026, 2939, 2860, 2731, 1721, 1687, 1445, 1418, 1257, 1238 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.42 – 7.29 (m, 5H), 5.12 (s, 2H), 4.93 (dd, *J* = 13.0, 6.9 Hz, 1H), 4.08 (d, *J* = 13.1 Hz, 1H), 2.85 (t, *J* = 13.0 Hz, 1H), 2.75 (ddd, *J* = 15.6, 8.1, 3.0 Hz, 1H), 2.60 (ddd, *J* = 15.7, 6.9, 2.0 Hz, 1H), 1.81 –1.32 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7 (CH), 155.4 (C), 136.7 (C), 128.6 (CH), 128.2 (CH), 128.0 (CH), 67.4 (CH_2), 46.3 (CH), 44.6 (CH_2), 39.8 (CH_2), 28.8 (CH_2), 25.3 (CH_2), 19.0 (CH_2); GC t_R = 15.9 min; LRMS (EI) *m/z* (%) 261 (M^+, 3), 233 (27), 218 (20), 175 (13), 174 (100), 170 (18), 126 (27), 108 (20), 92 (29), 91 (100), 65 (30), 55 (13); HRMS (EI) calcd for $C_{15}H_{19}NO_3$ 261.1365, found 261.1351.

(2*R*,2'*S*,*S*$_S$)-(*N*-Benzyloxicarbonyl)-2-[(2'-*tert*-butylsulfinamide)-4'-pentenyl]piperidine (20a).



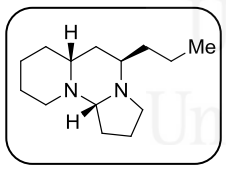
To a dry flask were added (*S*$_S$)-*tert*-butylsulfinamide, *ent*-**1** (220 mg, 1.82 mmol) and indium powder (259 mg, 2.27 mmol) under Ar. Then was added a solution of aldehyde **19** (496 mg, 1.90 mmol) in dry THF (4.5 ml) followed by $Ti(OEt)_4$ (818 μL, 3.64 mmol) and the reaction mixture was stirred under Ar for 1 h at 23 ºC . At this time allyl bromide (236 μL, 2.73 mmol) was added to the mixture and it was heated to 60 ºC for 5 h. The mixture was allowed to reach 23 ºC and was carefully added over a stirring mixture of 4:1 EtOAc/brine (15 mL). The resulted white suspension was filtered through a short pad of Celite, washed with EtOAc and organics were concentrated *in vacuo*. According to HPLC analysis (Chiralcel AD-H column 25 cm x 0.46 cm, isocratic elution with 95:5 *n*-hexane/*i*-PrOH, 1.0 mL/min, UV detection at 217 nm), the crude reaction mixture showed a major diastereoisomer at 15.93 min (86%) and other diastereoisomers at 20.76 - 23.39 min (14%). After column chromatography (3:2 hexane/EtOAc), the major isomer was isolated pure (>99:1 dr according to HPLC) as a white solid (532 mg, 72%): mp 31.6 – 32.9 ºC; $[\alpha]_D^{20}$ + 75.6 (c 0.62, $CHCl_3$); R_f 0.26 (1:1 hexane/EtOAc); IR ν 3242, 3033, 2936, 1674, 1641, 1421, 1260, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 5.72 (dt, *J* = 16.6, 8.4 Hz, 1H), 5.26 – 5.01 (m, 4H), 4.88 (br s, 1H), 4.65 (br s, 1H), 4.03 (m, 1H), 2.94 (br s, 1H), 2.77 (t, *J* = 12.7 Hz, 1H), 2.53 (br s, 1H), 2.34 (dt, *J* = 13.9, 6.9 Hz, 1H), 2.02 (t, *J* = 12.7 Hz, 1H), 1.84 – 1.36 (m, 7H), 1.31 – 0.98 (2 x br s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0 (C), 137.0 (C), 135.4 (CH), 128.6 (CH), 128.1 (CH), 127.9 (CH), 117.6 (CH_2), 67.3 (CH_2), 55.8 (C), 53.3 (CH), 47.6 (CH), 39.4 (CH_2), 39.1 (CH_2), 36.4 (CH_2), 29.4 (CH_2), 25.7 (CH_2), 22.9 (CH_3), 19.3 (CH_2); GC t_R = 23.4 min; LRMS (EI) *m/z* (%) 350 (M^+ - C_4H_8, 5), 218 (10), 174 (29), 91 (100), 84 (19); HRMS (EI) calcd for $C_{22}H_{34}N_2O_3S$ - C_4H_8 350.1664, found 350.1665.

(2*R*,2'*R*,*R*S)-(*N*-Benzyloxicarbonyl)-2-[(2'-*tert*-butylsulfinamide)-4'-pentenyl]piperidine (20b).



It was prepared from (*R*S)-*tert*-butylsulfinamide **1** (282 mg, 2.33 mmol), and aldehyde **19** (610 mg, 2.34 mmol) following the same procedure described above for compound **20a**. According to HPLC analysis (conditions described above for compound **20a**) the crude reaction mixture showed a major diastereoisomer at 19.25 min (96%) and a minor diastereoisomer at 17.88 min (4%). After column chromatography (3:2 hexane/EtOAc) the major isomer was isolated pure (>99:1 dr according to HPLC) as a white solid (757 mg, 80%): mp 88.9 – 89.5 ºC; $[\alpha]_D^{20}$ – 25.6 (*c* 0.80, $CHCl_3$); R_f 0.21 (1:1 hexane/EtOAc); IR ν 3219, 3032, 2947, 1664, 1642, 1438, 1267, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.29 (m, 5H), 5.73 (dt, *J* = 16.6, 8.4 Hz, 1H), 5.21 – 5.03 (m, 5H), 4.48 (br s, 1H), 4.07 (d, *J* = 13.3 Hz, 1H), 3.27 (dd, *J* = 12.8, 6.3 Hz, 1H), 2.89 (t, *J* = 12.5 Hz, 1H), 2.54 – 2.28 (m, 2H), 1.88 – 1.32 (m, 8H), 1.17 (br s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (C), 136.9 (C), 134.0 (CH), 128.6 (CH), 128.1 (CH), 128.0 (CH), 119.2 (CH_2), 67.2 (CH_2), 56.0 (C), 53.0 (CH), 47.8 (CH), 40.7 (CH_2), 39.6 (CH_2), 34.7 (CH_2), 27.8 (CH_2), 25.6 (CH_2), 22.7 (CH_3), 18.9 (CH_2); GC t_R = 23.6 min; LRMS (EI) *m/z* (%) 350 (M^+ - C_4H_8, 7), 218 (12), 174 (30), 128 (10), 91 (100), 84 (20); HRMS (EI) calcd for $C_{22}H_{34}N_2O_3S$ - C_4H_8 350.1664, found 350.1680.

Tetraponerine T3:

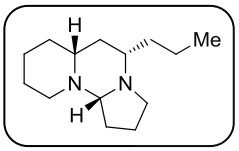


To a solution of compound **20a** (510 mg, 1.26 mmol) in THF (3.2 mL) was added dropwise aqueous 6 M HCl (628 µL, 3.77 mmol) at 0 ºC under Ar. The reaction mixture was stirring for 1 h while reaching 23 ºC. Aqueous 2 M NaOH (5 mL) was added to the mixture and the free amine was extracted with EtOAc (3 x 10 mL) and washed with brine (1 x 10 mL). Organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then disolved in dry MeOH (24 mL) and Pd/C 10% (420 mg) was added to the mixture. The suspension was shacked under hydrogen atmosphere (4 atm.) for 12 h at 23 ºC, filtered though Celite and the obtained solution was concentrated under reduced pressure. The residue (free diamine) was then dissolved in dry CH_2Cl_2 (13 mL) and K_2CO_3 (520 mg, 3.77 mmol) was added, followed by 4-bromobutanal[130] (285 mg, 1.89 mmol). The mixture was stirred at 23 ºC for 4 h, after which time inorganic salts were removed by filtration. The filtrate was washed twice with aqueous $NaHCO_3$, followed by brine and then dried over $MgSO_4$. Organics were concentrated under reduced pressure and the residue was purified by column chromatography (96:4:0.05 CH_2Cl_2/ MeOH/ 20% NH_4OH) to provide the desired product as an oil (151 mg, 54 % from **20a**): $[\alpha]_D^{20}$ + 35 (*c* 0.49, $CHCl_3$) {lit.[110] $[\alpha]_D^{20}$ + 27 (*c* 0.07,

[130] 4-Bromobutanal is commercially available, but we prepared it by DIBAL-H reduction of the corresponding methyl esther.

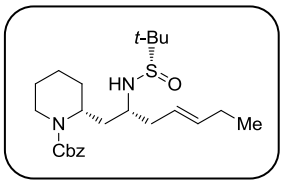
$CHCl_3$), lit.[77b] $[\alpha]_D^{20}$ + 34.57 (*c* 0.505, $CHCl_3$)}; R_f 0.40 (9:1 CH_2Cl_2/MeOH); IR ν 2952, 2927, 2869, 2803, 1455, 1390, 1354, 1157, 1129, 1113 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 3.28 (dd, *J* = 4.8, 2.2 Hz, 1H), 3.20 (dd, *J* = 14.6, 7.4 Hz, 1H), 2.85 – 2.69 (m, 3H), 2.08 – 1.98 (m, 1H), 1.97 – 1.87 (m, 1H), 1.86 – 1.50 (m, 8H), 1.50 – 1.01 (m, 8H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 75.7 (CH), 56.8 (CH), 52.8 (CH), 50.8 (CH_2), 50.7 (CH_2), 33.9 (CH_2), 33.2 (CH_2), 32.0 (CH_2), 30.4 (CH_2), 26.2 (CH_2), 25.1 (CH_2), 22.2 (CH_2), 20.7 (CH_2), 14.5 (CH_3); GC t_R = 12.4 min; LRMS (EI) *m/z* (%) 222 (M^+, 39), 221 (64), 194 (14), 193 (100), 180 (8), 179 (14), 152 (44), 138 (19), 137 (14), 124 (12), 110 (12), 97 (10), 96 (51), 84 (19); HRMS (EI) calcd for $C_{14}H_{26}N_2$ 222.2096, found 222.2076.

Tetraponerine T4:



Tetraponerine **T4** was prepared from **20b** (199 mg, 0.49 mmol) and 4-bromobutanal (111 mg, 0.74 mmol), following the same procedure described above for tetraponerine **T3**. The expected product was obtained as an oil (61 mg, 56 % from **20b**): $[\alpha]_D^{20}$ + 102 (*c* 0.34, $CHCl_3$) {lit.[110] $[\alpha]_D^{20}$ + 94 (*c* 0.2, $CHCl_3$), lit.[77b] $[\alpha]_D^{20}$ + 107.25 (*c* 1.155, $CHCl_3$)}; R_f 0.43 (9:1 CH_2Cl_2/MeOH); IR ν 2953, 2930, 2870, 2789, 1646, 1454, 1377, 1337, 1190, 1157, 1025 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 3.16 (td, *J* = 8.2, 2.2 Hz, 1H), 2.83 (d, *J* = 8.1 Hz, 1H), 2.35 (t, *J* = 6.3 Hz, 1H), 2.13 (ddd, *J* = 10.7, 7.1, 3.4 Hz, 1H), 2.04 (dd, *J* = 15.9, 8.5 Hz, 1H), 1.86 – 1.55 (m, 7H), 1.55 – 1.05 (m, 11H), 0.88 (t, *J* = 7.1 Hz, 3H) ; ^{13}C NMR (101 MHz, C_6D_6) δ 86.0 (CH), 63.3 (CH), 61.4 (CH), 51.9 (CH_2), 49.2 (CH_2), 37.9 (CH_2), 37.3 (CH_2), 33.2 (CH_2), 30.0 (CH_2), 26.5 (CH_2), 25.5 (CH_2), 20.8 (CH_2), 19.3 (CH_2), 15.3 (CH_3); GC t_R = 12.7 min; LRMS (EI) *m/z* (%) 222 (M^+, 49), 221 (100), 194 (14), 193 (98), 180 (15), 179 (15), 152 (58), 151 (20), 138 (22), 137 (14), 124 (14), 110 (13), 96 (35), 84 (19); HRMS (EI) calcd for $C_{14}H_{26}N_2$ 222.2096, found 222.2064.

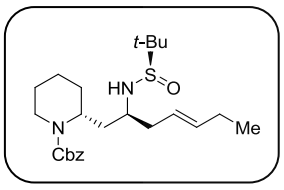
(2*R*,2'*S*,S_S,*E*)-(*N*-Benzyloxicarbonyl)-2-[(2'-*tert*-butylsulfinamide)-4'-heptenyl]piperidine (22a).



The corresponding homoallylamine **20a** (464mg, 1.16 mmol) was placed in 4 different oven dried Schlencks under Argon atmosphere (116 mg each, 0.29 mmol each). In each flask, the homoallylamine was disolved in dry CH_2Cl_2 (5 mL). Then Ti(*i*-PrO)$_4$ (27 µL, 0.09 mmol), *cis*-3-hexene (143 µL, 1.16 mmol) and Grubbs 2nd Gen. catalyst (7 mg, 0.009 mmol) were added sequentially. The reaction mixtures were heated at 40 ^oC for 6 h. After that time, all reactions were collected together and the solvent removed by reduced pressure. The residue obtained was purified by column chromatography (3:2 Hexane/EtOAc). The reactions were performed in parallel with 0.3 mmol maximum in each Schlenck to avoid the rapid inactivation of the catalyst. The expected product **22a** was obtained as a colorless wax (391 mg, 79%): $[\alpha]^{20}_D$ + 50.5 (*c* 1.01, $CHCl_3$); R_f 0.21 (1:1 Hexane/EtOAc); IR ν 3242, 2935, 2867, 1677, 1421, 1352, 1260, 1173, 1142, 1064, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ

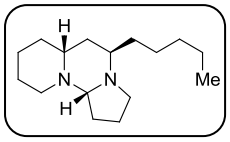
7.43 – 7.30 (m, 5H), 5.62 – 5.42 (m, 1H), 5.37 – 5.26 (m, 1H), 5.14 (t, *J* = 12.5 Hz, 2H), 4.91 – 4.33 (m, 2H), 4.05 (br d, *J* = 12.9 Hz, 1H), 2.91 (s, 1H), 2.77 (t, *J* = 12.4 Hz, 1H), 2.39 (br s, 1H), 2.35 – 2.19 (m, 1H), 2.11 – 1.89 (m, 3H), 1.82 – 1.33 (m, 7H), 1.20 (s, 9H), 1.02 – 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (C), 136.9 (C), 135.4 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 125.4 (CH), 67.1 (CH_2), 55.6 (C), 53.4 (CH_3), 47.6 (CH), 39.3 (CH_2), 39.2 (CH_2), 36.2 (CH_2), 29.3 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 22.8 (CH), 19.2 (CH_2), 13.9 (CH_3); GC t_R = 20.0 min; LRMS (EI) *m/z* (%) 378 (M^+ - C_4H_8, 0.1), 328 (3), 241 (8), 218 (31), 175 (8), 174 (58), 92 (8), 91 (100); HRMS (TOF) calcd for $C_{24}H_{39}N_2O_3S$ (M^++1) 435.2664, found 435.2681.

(2*R*,2'*R*,*R*$_S$,*E*)-(*N*-Benzyloxicarbonyl)-2-[(2′-*tert*-butylsulfinamide)-4′-heptenyl]piperidine (22b).



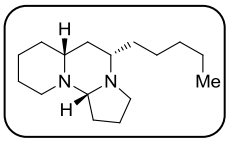
The expected product **22b** was obtained from **20b** (337 mg, 0.83 mmol) as a colorless wax (299 mg, 83%) following the same procedure described for **20a**: $[\alpha]^{20}_D$ – 17.6 (*c* 1.05, $CHCl_3$); R_f 0.21 (1:1 Hexane/EtOAc); IR ν 3239, 2932, 2867, 1692, 1422, 1259, 1172, 1065, 1053, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 5.70 – 5.47 (m, 1H), 5.41 – 5.24 (m, 1H), 5.20 – 5.03 (m, 2H), 4.48 (s, 1H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.22 (dd, *J* = 12.4, 6.1 Hz, 1H), 2.89 (t, *J* = 13.1 Hz, 1H), 2.40 (s, 1H), 2.29 (s, 1H), 2.11 – 1.91 (m, 3H), 1.88 – 1.53 (m, 7H), 1.50 – 1.32 (m, 2H), 1.17 (s, 9H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (C), 137.4 (C), 136.9 (CH), 128.6 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 67.1 (CH_2), 55.9 (C), 52.9 (CH), 47.8 (CH), 39.5 (CH_2), 39.3 (CH_2), 34.5 (CH_2), 27.9 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 22.7 (CH_3), 18.9 (CH_2), 14.1 (CH_3); GC t_R = 19.9 min; LRMS (EI) *m/z* (%) 378 (M^+ - C_4H_8, 0.1), 328 (3), 241 (8), 218 (31), 175 (8), 174 (58), 92 (8), 91 (100); HRMS (TOF) calcd for $C_{24}H_{39}N_2O_3S$ (M^++1) 435.2664, found 435.2681.

Tetraponerine T7



Tetraponerine **T7** was obtained from **22a** (317 mg, 0.75 mmol) as a yellow oil (102 mg, 54%) following the same procedure described for **T3**: $[\alpha]^{20}_D$ + 30 (*c* 0.82, $CHCl_3$); R_f 0.50 (9:1 CH_2Cl_2/MeOH); IR ν 2954, 2926, 2855, 2803, 1455, 1389, 1346, 1156, 1129, 1118 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 3.03 (dd, *J* = 4.4, 2.7 Hz, 1H), 2.90 (dd, *J* = 14.6, 7.5 Hz, 1H), 2.57 – 2.46 (m, 3H), 1.83 – 1.73 (m, 1H), 1.68 (dd, *J* = 12.5, 5.2 Hz, 1H), 1.58 – 1.20 (m, 9H), 1.16 – 0.90 (m, 10H), 0.87 – 0.81 (m, 1H), 0.64 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 75.5 (CH), 56.7 (CH), 53.3 (CH), 50.9 (CH_2), 50.6 (CH_2), 34.1 (CH_2), 32.5 (CH_2), 32.2 (CH_2), 31.0 (CH_2), 30.5 (CH_2), 27.3 (CH_2), 26.4 (CH_2), 25.1 (CH_2), 23.2 (CH_2), 22.2 (CH_2), 14.4 (CH_3); GC t_R = 13.8 min; LRMS (EI) *m/z* (%) 251 (M+1, 6), 250 (M^+, 44), 249 (82), 207 (19), 194 (14), 193 (100), 180 (14), 179 (10), 165 (6), 152 (34), 151 (11), 138 (10), 110 (12), 96 (30), 84 (10), 55 (6); HRMS (TOF) calcd for $C_{16}H_{31}N_2$ (M^++1) 251.2487, found 251.2486.

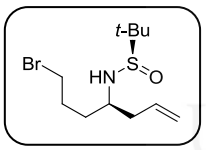
Tetraponerine T8



Tetraponerine **T8** was obtained from **22b** (205 mg, 0.49 mmol) as a yellow oil (74 mg, 60%) following the same procedure described for **T3**: $[\alpha]^{20}_D$ + 99 (*c* 0.70, $CHCl_3$); R_f 0.40 (9:1 CH_2Cl_2/MeOH); IR ν 2928, 2857, 2790, 2775, 1631, 1454, 1377, 1338, 1188, 1156, 1035 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 3.26 (td, *J* = 8.1, 2.2 Hz, 1H), 2.98 – 2.91 (m, 1H), 2.42 (t, *J* = 6.8 Hz, 1H), 2.23 (ddd, *J* = 11.0, 7.3, 3.7 Hz, 1H), 2.19 – 2.08 (m, 1H), 1.91 – 1.66 (m, 8H), 1.65 – 1.24 (m, 14H), 1.01 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 85.6 (CH), 62.7 (CH), 61.4 (CH), 51.5 (CH_2), 49.0 (CH_2), 38.0 (CH_2), 34.6 (CH_2), 32.9 (CH_2), 32.8 (CH_2), 29.7 (CH_2), 26.2 (CH_2), 25.2 (CH_2), 25.1 (CH_2), 23.1 (CH_2), 20.2 (CH_2), 14.3 (CH_3); GC t_R = 14.2 min; LRMS (EI) *m/z* (%) 251 (M+1, 6), 250 (M^+, 45), 249 (100), 207 (19), 194 (13), 193 (95), 180 (20), 179 (11), 165 (12), 152 (45), 151 (15), 138 (12), 137 (10), 110 (14), 96 (30), 84 (16), 55 (9); HRMS (TOF) calcd for $C_{16}H_{31}N_2$ (M^++1) 251.2487, found 251.2493.

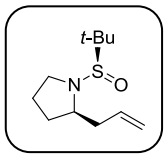
Procedure for the synthesis of compounds 24 - 29 and tetraponerines T1, T2, T5 and T6.

(4*R*,*R*S)-*N*-(*tert*-Butylsulfinyl)-7-bromohept-1-en-4-amine (24).



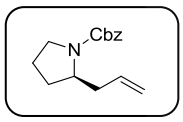
As described in Chapter I for homoallylamine **2**, to a dry flask were added (*R*S)-*N*-*tert*-butylsulfinamide (**1**, 829 mg, 6.79 mmol) followed by indium powder (968 g, 8.489 mmol) under Ar. Then a solution of 4-bromobutyraldehyde (1.121 g, 7.470 mmol) in dry THF (15.9 ml) and $Ti(OEt)_4$ (3.1 mL, 13.582 mmol,) were added successively and the reaction mixture was stirred under Ar for 1 h at 23 °C. At this time allyl bromide (897 µL, 10.186 mmol) was added to the mixture and the reaction was allowed to reach 60 °C and stirred at that temperature for 5 h. The mixture was allowed to reach room temperature and was carefully added over a stirring mixture of 4:1 EtOAc/brine (100 mL). The resulted white suspension was filtered through a short pad of Celite, washed with EtOAc and organics were concentrated *in vacuo*. The resulted suspension was diluted in 4:1 EtOAc/Hexane (50 mL) and filtered again through Celite. Organics were concentrated to afford the expected compound **24** (1.783 g, 89%, 95:5 dr according ^1H NMR) as a colorless wax, pure enough to be used in the next step. To provide the spectroscopy data, a sample of homoallylamine **24** was purified by column chromatography: R_f 0.13 (7:3 hexane/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 19.6, 9.4, 7.2 Hz, 1H), 5.20 (d, *J* = 0.7 Hz, 1H), 5.16 (d, *J* = 3.6 Hz, 1H), 3.41 (t, *J* = 6.6 Hz, 3H), 3.27 (d, *J* = 6.2 Hz, 1H), 2.55 – 2.25 (m, 2H), 2.03 – 1.82 (m, 2H), 1.82 – 1.56 (m, 2H), 1.22 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8 (CH), 119.5 (CH_2), 56.2 (C), 54.5 (CH), 40.7 (CH_2), 33.7 (CH_2), 33.6 (CH_2), 29.0 (CH_2), 22.8 (CH_3); GC t_R = 14.1 min; LRMS (EI) *m/z* (%) 200 (40), 199 (100), 198 (39), 197 (95), 118 (15), 91 (13), 70 (80), 68 (16), 57 (66).

(2*R*,*R*s)-2-Allyl-(*N*-*tert*-butylsulfinyl)pyrrolidine (25).



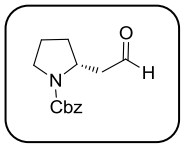
As described in Chapter I for homoallylamine **3**, a titrated solution of KHMDS in THF (7.9 mL, 1.03 M, 8.136 mmol) was added via syringe to a cold solution (0 °C) of crude **24** (1.600 g, 5.424 mmol) in dry THF (13.8 mL). The reaction mixture was stirred for 1.5 h at 0 °C under Ar, quenched with saturated NH_4Cl solution and allowed to reach room temperature. The aqueous phase was extracted with EtOAc (3 times) and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (80:20 hexane/EtOAc) to provide the product as a colorless oil (1.008 g, 86%, dr 95:5 according to ^{1}H NMR): $[\alpha]_D^{20}$ – 17.1 (*c* 1.038, $CHCl_3$); R_f 0.30 (7:3 hexane/EtOAc); IR ν 3076, 2658, 2871, 1639, 1474, 1456, 1361, 1065, 994, 911 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 – 5.66 (m, 1H), 5.11 – 5.01 (m, 2H), 3.74 (ddd, *J* = 10.1, 6.6, 3.7 Hz, 1H), 3.51 – 3.43 (m, 1H), 3.14 (dt, *J* = 10.7, 7.0 Hz, 1H), 2.52 – 2.43 (m, 1H), 2.17 (ddd, *J* = 14.0, 9.4, 8.2 Hz, 1H), 1.87 – 1.73 (m, 3H), 1.71 –1.60 (m, 1H), 1.19 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3 (CH), 117.3 (CH_2), 58.1 (C), 57.5 (CH), 48.6 (CH_2), 39.0 (CH_2), 30.4 (CH_2), 24.2 (CH_2), 23.7 (CH_3); GC t_R = 11.9 min; LRMS (EI) *m/z* (%) 215 (M^+, 0.1), 159 (16), 118 (100), 117 (29), 70 (10), 57 (13); HRMS (EI) calcd for $C_{12}H_{24}NOS$ 215.1344, found 215.1368.

(R)-2-Allyl-(*N*-benzyloxicarbonyl)pyrrolidine (26)



Compound **26** was prepared from **25** (860 mg, 4.0 mmol) following the same procedure described above for compound **18**, affording the expected product as a colorless oil (831 mg, 85%). Rotamers are present: $[\alpha]_D^{20}$ + 53.1 (*c* 0.617, $CHCl_3$); R_f 0.60 (7:3 hexane/EtOAc); IR ν 3035, 2972, 2876, 1696, 1639, 1446, 1407, 1355, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 5.83 – 5.64 (m, 1H), 5.21 – 4.96 (m, 4H), 3.92 (br s, 1H), 3.52 – 3.35 (m, 2H), 2.51 (br d, *J* = 54.4 Hz, 1H), 2.15 (td, *J* = 14.8, 8.1 Hz, 1H), 1.96 – 1.70 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (C), 154.9 (C), 137.3 (C), 137.1 (C), 135.2 (CH), 135.0 (CH), 128.6 (CH), 127.9 (CH), 117.4 (CH_2), 66.8 (CH_2), 66.6 (CH_2), 57.4 (CH), 56.9 (CH), 47.0 (CH_2), 46.7 (CH_2), 39.1 (CH_2), 38.2 (CH_2), 30.2 (CH_2), 29.3 (CH_2), 23.8 (CH_2), 23.0 (CH_2); GC t_R = 14.6 min; LRMS (EI) *m/z* (%) 245 (M^+, 0.1), 204 (26), 160 (28), 91 (100); HRMS (EI) calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1427.

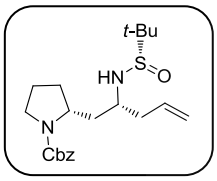
(*R*)-(*N*-Benzyloxicarbonyl)-2-(2-oxoethyl)pyrrolidine (27).



Compound **27** was prepared from **26** (790 mg, 3.224 mmol) following the same procedure described above for compound **19**, affording the expected product as a colorless oil (639 mg, 80%): $[\alpha]_D^{20}$ + 40.4 (*c* 1.44, $CHCl_3$); R_f 0.24 (7:3 hexane/EtOAc); IR ν 3031, 2956, 2879, 2726, 1718, 1692, 1497, 1448, 1409, 1356, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (br s, 0.6H), 9.67 (br s, 0.4H), 7.44 – 7.29 (m, 5H), 5.24 – 5.01 (m, 2H), 4.32 (dt, *J* = 12.1,

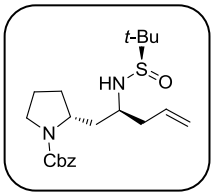
5.9 Hz, 1H), 3.58 – 3.27 (m, 2H), 2.99 (dd, *J* = 16.5, 3.1 Hz, 0.6H), 2.83 (br d, *J* = 16.8 Hz, 0.4H), 2.53 (d, *J* = 7.6 Hz, 0.6H), 2.48 (d, *J* = 7.6 Hz, 0.4H), 2.14 (dq, *J* = 12.5, 7.9 Hz, 1H), 1.92 – 1.81 (m, 2H), 1.74 – 1.61 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9 (CH), 200.6 (CH), 155.0 (C), 154.7 (C), 136.9 (C), 136.6 (C), 128.6 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 67.1 (CH_2), 66.9 (CH_2), 53.1 (CH), 52.3 (CH), 49.4 (CH_2), 48.7 (CH_2), 46.9 (CH_2), 46.5 (CH_2), 32.1 (CH_2), 31.3 (CH_2), 23.9 (CH_2), 23.1 (CH_2); GC t_R = 15.4 min; LRMS (EI) *m/z* (%) 247 (M^+, 0.6), 219 (10), 160 (10), 156 (10), 112 (10), 91 (100), 65 (10); HRMS (EI) calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1213.

(2*R*,2'*S*,*S*$_S$)-(*N*-Benzyloxicarbonyl)-2-[2'-(*tert*-butylsulfinamide)-4'-pentenyl]pyrrolidine (28a).



Compound **28a** was prepared from aldehyde **27** (301 mg, 1.218 mmol) and (*S*$_S$)-*N*-*tert*-butylsulfinamide (*ent*-**1**, 134 mg, 1.107 mmol) following the same procedure described above for compound **20a**. According to HPLC analysis (Chiralcel AD-H column 25 cm x 0.46 cm, isocratic elution with 95:5 *n*-hexane/*i*-PrOH, 1.0 mL/min, UV detection at 217 nm), the crude reaction mixture showed a major diastereoisomer at 16.17 min (94%) and other diastereoisomers at 20.80 - 23.50 min (6%). After column chromatography (3:2 hexane/EtOAc), the major isomer was isolated pure (>99:1 according to HPLC) as a colorless wax product as a unique diastereoisomer after purification by column chromatography (391 mg, 90%): $[\alpha]_D^{20}$ + 83.2 (*c* 1.220, $CHCl_3$); R_f 0.20 (1:1 hexane/EtOAc); IR ν 3243, 3065, 2957, 2888, 1685, 1452, 1409, 1360, 1099, 1062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5H), 5.80 (dq, *J* = 10.0, 6.9 Hz, 0.8H), 5.62 (dd, *J* = 15.8, 8.3 Hz, 0.2H), 5.27 – 5.00 (m, 5H), 4.34 (dd, *J* = 13.0, 7.6 Hz, 0.8H), 3.99 (br s, 0.2H), 3.42 (dt, *J* = 11.4, 8.5 Hz, 2H), 3.20 (qd, *J* = 10.1, 5.5 Hz, 1H), 2.52 (dt, *J* = 14.5, 7.4 Hz, 1H), 2.42 – 2.27 (m, 1H), 2.09 – 1.81 (m, 3H), 1.81 – 1.54 (m, 3H), 1.24 (s, 7H), 1.12 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3 (C), 137.0 (C), 135.6 (CH), 134.1 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 119.0 (CH_2), 117.5 (CH_2), 67.3 (CH_2), 66.9 (CH_2), 55.6 (C), 54.9 (CH), 53.3 (CH), 46.6 (CH_2), 42.4 (CH_2), 41.3 (CH_2), 39.8 (CH_2), 39.2 (CH_2), 31.4 (CH_2), 23.8 (CH_2), 23.0 (CH_3), 22.7 (CH_3); GC t_R = 22.7 min; LRMS (EI) *m/z* (%) 336 (M^+, 0.8), 287 (6), 218 (14), 204 (10), 174 (10), 160 (20), 114 (6), 91 (100), 70 (23); HRMS (EI) calcd for $C_{21}H_{32}N_2O_3S$ – C_4H_8 336.1507, found 336.1510.

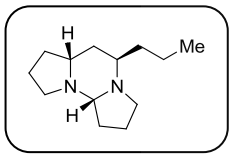
(2*R*,2'*R*,*R*$_S$)-(*N*-Benzyloxicarbonyl)-2-[(2'-*tert*-butylsulfinamide)-4'-pentenyl]pyrrolidine (28b).



Compound **28b** was prepared from aldehyde **27** (301 mg, 1.218 mmol) and (*R*$_S$)-*N*-*tert*-butylsulfinamide (**1**, 134 mg, 1.107 mmol) following the same procedure described above for compound **20a**. According to HPLC analysis (Chiralcel AD-H column 25 cm x 0.46 cm, isocratic elution with 95:5 *n*-hexane/*i*-PrOH, 1.0 mL/min, UV detection at 217 nm), the crude reaction mixture showed a major

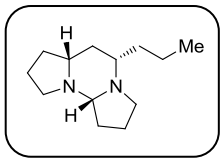
diastereoisomer at 21.4 min (78%) and other diastereoisomers at 14.4 - 17.0 min (22%). After column chromatography (3:2 hexane/EtOAc), the major isomer was isolated pure (>99:1 according to HPLC) as a colorless wax (301 mg, 69%): mp 76.5 – 77.1 °C; $[\alpha]_D^{20}$ - 31.8 (*c* 0.929, $CHCl_3$); R_f 0.16 (1:1 Hexane/EtOAc); IR ν 3203, 3075, 2958, 2883, 1689, 1471, 1453, 1407, 1096, 1045, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.32 (m, 5H), 5.94 – 5.58 (m, 1H), 5.27 – 4.94 (m, 4H), 4.04 (br d, *J* = 35.6 Hz, 1H), 3.58 – 3.36 (m, 2.6H), 3.28 (br d, *J* = 32.9 Hz, 1H), 3.02 (d, *J* = 8.4 Hz, 0.4H), 2.58 – 2.31 (m, 2H), 2.09 – 1.80 (m, 4H), 1.68 (br d, *J* = 5.1 Hz, 1H), 1.51 – 1.35 (m, 1H), 1.22 (s, 5H), 1.06 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9 (C), 137.1 (C), 137.0 (C), 134.0 (CH), 133.3 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 119.8 (CH_2), 119.2 (CH_2), 67.2 (CH_2), 66.6 (CH_2) 56.4 (C), 56.2 (C), 55.2 (CH), 54.6 (CH), 54.5 (CH), 54.3 (CH), 46.7 (CH_2), 46.4 (CH_2), 42.2 (CH_2), 42.0 (CH_2), 40.3 (CH_2), 39.5 (CH_2), 30.5 (CH_2), 30.1 (CH_2), 23.9 (CH_2), 23.1 (CH_2), 22.9 (CH_3), 22.7 (CH_3); GC t_R = 22.9 min; LRMS (EI) *m/z* (%) 336 (M^+, 0.8), 287 (6), 218 (14), 204 (10), 174 (10), 160 (25), 114 (12), 91 (100), 70 (23); HRMS (EI) calcd for $C_{21}H_{32}N_2O_3S$ – C_4H_8 336.1507, found 336.1508.

Tetraponerine T1



Tetraponerine **T1** was prepared from **28a** (300 mg, 0.765 mmol), and 4-bromobutanal (207 mg, 1.377 mmol) following the same procedure described above for compound **T3**, affording the expected product as an oil (51 mg, 32 % from **28a**); $[\alpha]_D^{20}$ + 14 (*c* 0.498, $CHCl_3$); R_f 0.15 (95:5 CH_2Cl_2/MeOH); IR ν 2954, 2928, 2871, 2792, 2639, 2585, 1457, 1381, 1349, 1191, 1167, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 – 3.74 (m, 1H), 3.46 – 3.15 (m, 2H), 3.14 – 2.88 (m, 2H), 2.77 – 2.36 (m, 1H), 2.31 – 1.78 (m, 8H), 1.79 – 1.16 (m, 7H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 77.0 (CH), 58.4 (CH), 53.7 (CH), 50.4 (CH_2), 49.8 (CH_2), 33.8 (CH_2), 30.8 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 21.3 (CH_2), 20.5 (CH_2), 20.1 (CH_2), 14.3 (CH_3); GC t_R = 11.6 min; LRMS (EI) *m/z* (%) 208 (M^+, 46), 207 (100), 180 (12), 179 (91), 165 (10), 138 (51), 137 (19), 124 (23), 110 (17), 96 (64), 70 (29); HRMS (EI) calcd for $C_{13}H_{24}N_2$ 208.1939, found 208.1929.

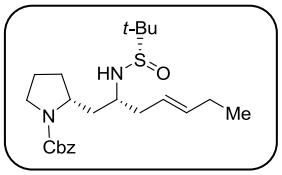
Tetraponerine T2



Tetraponerine **T2** was prepared from **28b** (230 mg, 0.587 mmol), and 4-bromobutanal (159 mg, 1.057 mmol) following the same procedure described above for compound **T3**, affording the expected product as an oil (42 mg, 35 % from **28b**); $[\alpha]_D^{20}$ + 47 (*c* 0.232, $CHCl_3$); R_f 0.15 (95:5 CH_2Cl_2/MeOH); IR ν 2955, 2931, 2871, 2787, 2695, 1457, 1379, 1362, 1190, 1162, 1099 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 3.17 – 2.93 (m, 3H), 2.60 – 2.51 (m, 1H), 2.43 (td, *J* = 8.7, 5.1 Hz, 1H), 2.07 – 1.83 (m, 5H), 1.83 – 1.60 (m, 4H), 1.60 – 1.25 (m, 7H), 1.01 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 83.0 (CH), 63.8 (CH), 59.1 (CH), 48.6 (CH_2), 45.5 (CH_2), 36.5 (CH_2), 32.7 (CH_2), 30.4 (CH_2), 28.9 (CH_2), 21.1 (CH_2), 20.8 (CH_2), 19.3 (CH_2), 14.6 (CH_3); GC t_R = 11.9 min; LRMS (EI) *m/z* (%) 208

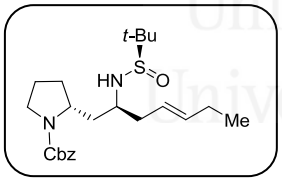
(M^+, 41), 207 (100), 180 (8), 179 (53), 165 (11), 138 (59), 137 (20), 124 (25), 110 (18), 96 (47), 70 (37); HRMS (EI) calcd for $C_{13}H_{24}N_2$ 208.1939, found 208.1909.

(2*R*,2'*S*,S_S,*E*)-(*N*-Benzyloxicarbonyl)-2-[(2'-*tert*-butylsulfinamide)-4'-heptenyl]pyrrolidine (29a).



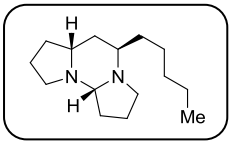
Compound **29b** was prepared from **28a** (513 mg, 1.31 mmol) following the same procedure described above for compound **22a**, affording the corresponding product as a colorless wax (473 mg, 86%): $[\alpha]^{20}_D$ + 81.6 (*c* 1.20, $CHCl_3$); R_f 0.31 (1:1 Hexane/EtOAc); IR ν 3248, 3031, 2958, 2931, 1685, 1453, 1409, 1359, 1099, 1062, 968, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.31 (m, 5H), 5.66 – 5.48 (m, 1H), 5.47 – 5.29 (m, 1H), 5.29 – 5.03 (m, 2H), 4.42 – 3.89 (m, 1H), 3.56 – 3.05 (m, 3H), 2.42 (dt, *J* = 14.1, 7.1 Hz, 1H), 2.34 – 2.19 (m, 1H), 2.19 – 1.50 (m, 9H), 1.18 (d, *J* = 34.3 Hz, 9H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C), 137.0 (C), 135.4 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 125.6 (CH), 66.9 (CH_2), 55.7 (C), 55.0 (CH), 53.5 (CH), 46.5 (CH_2), 42.2 (CH_2), 38.0 (CH_2), 31.3 (CH_2), 25.8 (CH_2), 23.8 (CH_2), 22.9 (CH_3), 22.7 (CH_3), 14.3 (CH_3), 13.9 (CH_3); GC t_R = 19.4 min; LRMS (EI) *m/z* (%) 314 (3), 227 (3), 204 (12), 173 (4), 161 (3), 160 (23), 145 (24), 92 (8), 91 (100), 70 (6), 69 (3), 65 (5); HRMS (TOF) calcd for $C_{23}H_{37}N_2O_3S$ (M^++1) 421.2525, found 421.2511.

(2*R*,2'*R*,R_S,*E*)-(*N*-Benzyloxicarbonyl)-2-[(2'-*tert*-butylsulfinamide)-4'-heptenyl]pyrrolidine (29b).



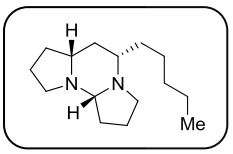
Compound **29b** was prepared from **28b** (358 mg, 0.90 mmol) following the same procedure described above for compound **22a**, affording the corresponding product as a colorless wax (295 mg, 78%): $[\alpha]^{20}_D$ – 20.5 (*c* 0.99, $CHCl_3$); R_f 0.30 (1:1 Hexane/EtOAc); IR ν 3232, 3030, 2959, 2873, 1691, 1454, 1412, 1359, 1102, 1057, 970, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 5H), 5.59 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.47 – 5.22 (m, 1H), 5.22 – 4.97 (m, 2H), 4.18 – 3.87 (m, 1H), 3.59 – 3.00 (m, 4H), 2.34 (br d, *J* = 21.0 Hz, 2H), 2.11 – 1.92 (m, 4H), 1.92 – 1.59 (m, 3H), 1.37 (dd, *J* = 24.1, 12.3 Hz, 1H), 1.14 (d, *J* = 55.3 Hz, 9H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7 (C), 137.7 (CH), 137.2 (CH), 136.9 (C), 136.8 (C), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 123.8 (CH), 123.1 (CH), 67.0 (CH_2), 66.5 (CH_2), 56.1 (C), 55.9 (C), 55.1 (CH), 54.6 (CH), 54.4 (CH), 46.6 (CH_2), 46.2 (CH_2), 40.6 (CH_2), 40.5 (CH_2), 40.2 (CH_2), 39.3 (CH_2), 30.4 (CH_2), 29.9 (CH_2), 25.7 (CH_2), 23.7 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.7 (CH_2), 14.2 (CH_3), 13.9 (CH_3); GC t_R = 19.4 min; LRMS (EI) *m/z* (%) 314 (3), 227 (3), 207 (3), 204 (11), 179 (3), 174 (4), 173 (4), 161 (3), 160 (23), 145 (9), 92 (8), 91 (100), 70 (6), 65 (4); HRMS (TOF) calcd for $C_{23}H_{37}N_2O_3S$ (M^++1) 421.2525, found 421.2510.

Tetraponerine T5



Tetraponerine **T5** was prepared from **29a** (460 mg, 1.10 mmol), and 4-bromobutanal following the same procedure described above for compound **T3**, affording the expected product as a yellow oil (90 mg, 35%); $[\alpha]^{20}_D$ + 14 (*c* 1.60, $CHCl_3$); R_f 0.35 (9:1 CH_2Cl_2/MeOH); IR ν 3414, 2953, 2927, 2857, 2793, 1457, 1384, 1348, 1233, 1162, 1114, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 – 3.45 (m, 1H), 3.40 – 2.64 (m, 4H), 2.62 – 2.15 (m, 1H), 2.16 – 1.43 (m, 12H), 1.40 – 0.98 (m, 7H), 0.89 (dd, *J* = 9.0, 4.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 59.9 (CH), 58.3 (CH), 53.9 (CH), 50.3 (CH_2), 49.5 (CH_2), 31.9 (CH_2), 31.3 (CH_2), 30.6 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 21.1 (CH_2), 20.0 (CH_2), 14.1 (CH_3); GC t_R = 13.0 min; LRMS (EI) *m/z* (%) 237 (5), 236 (M^+, 42), 235 (100), 193 (13), 180 (12), 179 (81), 166 (15), 165 (6), 152 (11), 138 (27), 137 (12), 124 (10), 110 (21), 96 (43), 70 (18), 55 (7); HRMS (TOF) calcd for $C_{15}H_{29}N_2$ (M^++1) 237.2331, found 237.2324.

Tetraponerine T6



Tetraponerine **T6** was prepared from **29b** (255 mg, 0.61 mmol), and 4-bromobutanal following the same procedure described above for compound **T3**, affording the expected product as a yellow oil (52 g, 36%); $[\alpha]^{20}_D$ + 40 (*c* 0.75, $CHCl_3$); R_f 0.50 (9:1 CH_2Cl_2/MeOH); IR ν 3395, 2954, 2928, 2858, 2784, 1458, 1378, 1204, 1188, 1161, 1064 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 3.11 – 3.01 (m, 1H), 2.94 (td, *J* = 8.4, 2.5 Hz, 1H), 2.85 (t, *J* = 5.3 Hz, 1H), 2.48 – 2.36 (m, 1H), 2.32 (dd, *J* = 8.4, 5.3 Hz, 1H), 2.00 – 1.84 (m, 2H), 1.83 – 1.52 (m, 7H), 1.50 – 1.19 (m, 11H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 83.4 (CH), 64.2 (CH), 59.7 (CH), 49.1 (CH_2), 45.9 (CH_2), 34.7 (CH_2), 33.5 (CH_2), 32.6 (CH_2), 30.6 (CH_2), 29.2 (CH_2), 25.9 (CH_2), 23.1 (CH_2), 21.3 (CH_2), 20.9 (CH_2), 14.4 (CH_3); GC t_R = 13.3 min; LRMS (EI) *m/z* (%) 237 (M+1, 5), 236 (M^+, 40), 235 (100), 207 (5), 193 (15), 180 (8), 179 (54), 166 (17), 165 (10), 152 (13), 151 (10), 138 (38), 137 (14), 124 (12), 123 (5), 110 (14), 97 (7), 96 (35), 70 (24), 68 (7), 55 (6); HRMS (TOF) calcd for $C_{15}H_{29}N_2$ (M^++1) 237.2331, found 237.2333.

Computational details.

All the 24 structures of **Charts 1** and **Chart 2** were built as explained in the text and were initially optimized using a MM2 force field before being submitted to density functional theory calculations (DFT). DFT calculations of the structures,[131] energies, and harmonic vibrational analysis were carried out using the Becke-Lee-Yang-Parr (B3LYP) exchange-correlation functional.[132] We relied on the widely used B3LYP functional, the performance

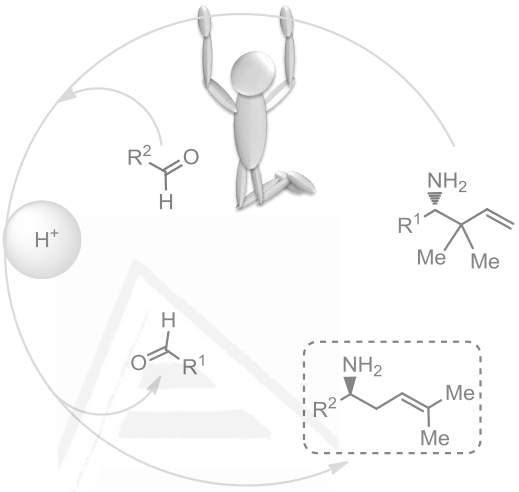
[131] (a) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, *136*, B864; (b) Kohn, W.; Sham, L. *J. Phys. Rev.* **1965**, *140*, A1133.

[132] (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; (b) Stephens, P. J.; Devlin, F. J.; Chablowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.

of which was reviewed recently with a collection of molecules of biological relevance on the basis of the reported errors in barrier height energy (for singlet transition states) and conformational energies,[133] and also specifically for this functional with a larger set of neutral, closed-shell organic molecules containing C, H, N and O atoms, on the basis of the isomerization energies for nitrogen-containing molecules.[134] Important correlation energy corrections due to non-covalent, medium-range interactions are not expected.[135] The geometries of the isolated species have been fully optimized in the gas phase using the split valence triple-ζ 6-311+G (2d,p) basis set.[136] When both polatization and diffuse gunctions are used, an improbement of the isomerization energies of amines was reported for this functional.[137] In addition, a double set of polatization functions was used to get a better description of the inersion barriers at the nitrogen. A preliminary study with a typical double-ζ 6-31G (d) basis set was also carried out to test the level of convergence of the energies with the size of the derivative calculations, which was considered adequate for our purposes. Analytic second derivative calculations, which yield the harmonic frequencies, were performed on the optimized geometries at the same level of theory to ensure that the optimized geometries were true minima, and to provide corrections for the zero-point energy (*ZPE*) effects. The Hessian matrices of the optimized geometries had only positive eigenvalues. The activation barriers were located using the synchronous transit-guided quasi-Newton (STQN) method,[138] requested both with the QST2 (two input structures) and QST3 (three input structures) formalism. Frequency analysis were carried out subsequently to make sure that true first order saddle points were located, giving rise to a one negative eigenvalue.

The calculations were carried out with the GAUSSIAN 09 suite of programs.[139] Graphic material was drawn with Chimera.[140]

[133] Riley, K. E.; Op't Holt, B. T.; Merz, K. M. Jr. *J. Chem. Theory Comput*. **2007**, *3*, 407.
[134] Tirado-Rives, J.; Jorgensen, W. L. *J. Chem. Theory Comput*. **2008**, *4*, 297.
[135] Zhao, Y.; Truhlar, D. G.; *J. Chem. Theory. Comput*. **2007**, *3*, 286.
[136] Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650.
[137] Tirado-Rives, J.; Jorgensen, W. L. *J. Chem. Theory Comput*. **2008**, *4*, 297.
[138] Peng, C.; Ayala, P. Y.; Schlegel, H. B.; Frisch, M. J. *J. Comp. Chem.*, **1996**, *17,* 49.
[139] Gaussian 09, Revision A.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian, Inc., Wallingford CT*, **2009**.
[140] UCSF Chimera version 1.5.3. http://www.cgl.ucsf.edu/chimera.



Chapter III :

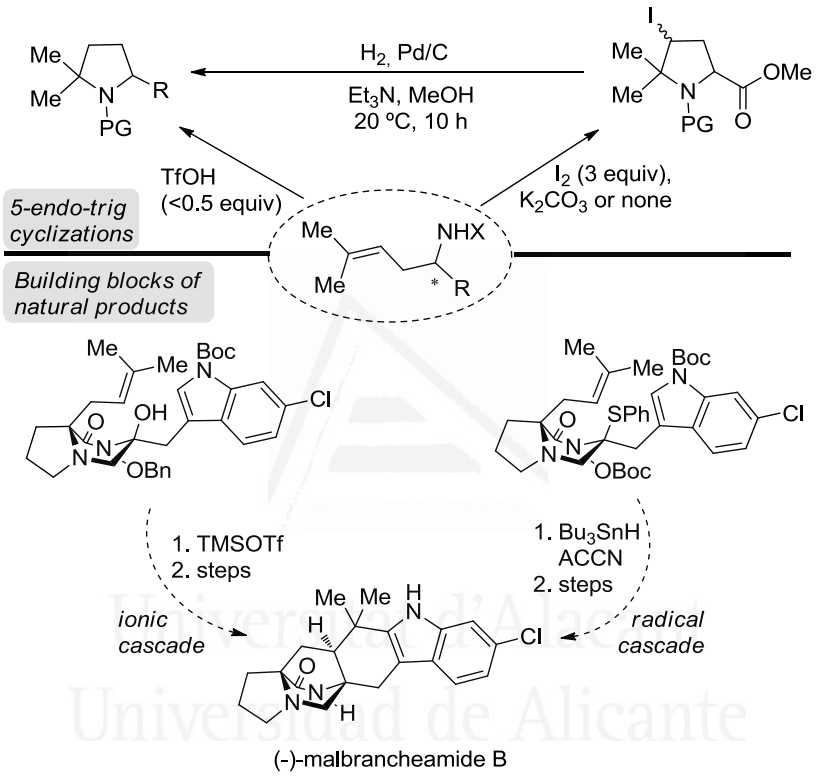
A General Procedure to Afford Enantioenriched Linear Homoprenylamines

PART OF THE CONTENT OF THIS CHAPTER HAS BEEN PUBLISHED IN:

Bosque, I.; Foubelo, F.; González-Gómez, J. C.
Org. Biomol. Chem. **2013**, *11*, 7507.

III.1. INTRODUCTION

Homoprenylsulfonamides have been extensively used for the synthesis of different substituted pyrrolidines through 5-*endo*-*trig* cyclizations.



Scheme 16

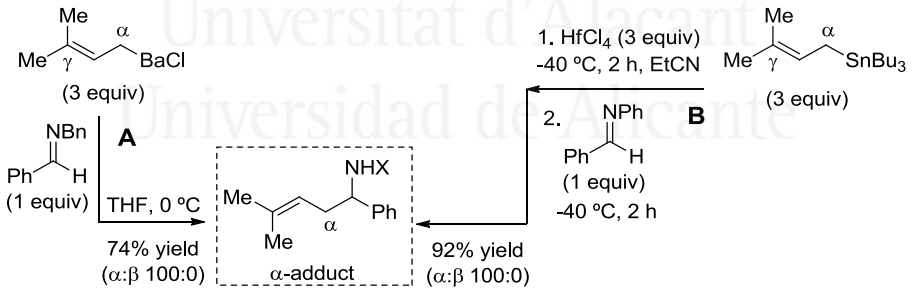
This reactivity is known to be promoted by triflic acid, obtaining the expected pyrrolidines with excellent regioselectivities, being the 4-*exo*-*trig* product never observed.[141] In addition, iodine promoted cyclizations have also been reported under basic (K_2CO_3) or acidic conditions with good yields and regioselectivities.[142] Interestingly, the reactivity of the homoprenyl amine moiety under cationic conditions has been successfully exploited in the synthesis of

[141] (a) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471. (b) Haskins, C. M.; Knight, D. W. *Chem. Commun.* **2002**, 2724. (c) Elaridi, J.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 2025. (d) Griffiths-Jones, C. M.; Knight, D. W. *Tetrahedron*, **2010**, *66*, 4150. (e) van Lierop, B. J.; Jackson, W. R.; Robinson, A. J. *Tetrahedron* **2010**, *66*, 5357.

[142] Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2006**, *47*, 2825.

bioactive natural products like (-)-nupharamine[143] and (±)-chemobtusin.[144] Elegant examples that illustrate the synthetic potential of this framework are the synthesis of (-)-malbrancheamide B by using a cascade of ionic[145] or radical cyclizations[146] (**Scheme 16**).

The regioselectivity in the addition of prenyl organometallic reagents to imines is a very important issue. Many examples can be found in the literature concerning the prenylation of carbonyl compounds with good α- or/and γ-regioselectivities.[147] However, only a few α-regioselective prenylation of imines are reported. The first efficient α-prenylation was achieved by H. Yamamoto in 1996 and consisted in the addition of an *in situ* generated prenyllic barium reagent to an imine at 0 ºC (**Scheme 17, A**).[148] Importantly it was found that when the reaction was conducted at -78 ºC, the γ-adduct was the major product (kinetic product) and upon warming to 20 ºC, gradual isomerization to the most stable α-adduct was observed. It was then assumed by the authors that the addition of the prenyllic barium reagent to the aldimine was reversible and that α-adduct is formed under thermodynamic control conditions. Although excellent regioselection could be achieved with this methodology, it has some practical limitations related to the manipulation of activated (Rieke) barium under careful anhydrous conditions.

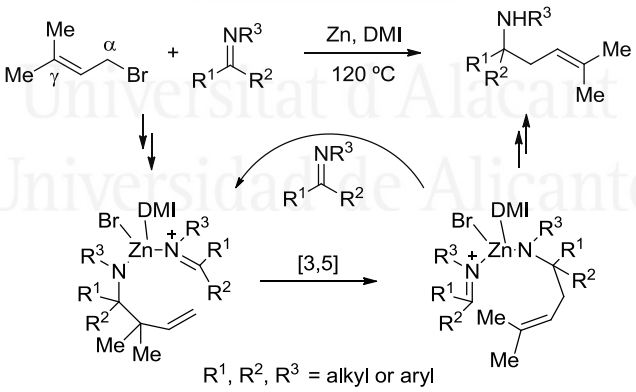


Scheme 17

[143] Gebauer, J.; Blechert, S. *Synlett* **2005**, 2826.
[144] Susuki, H.; Aoyagi, S. *Chem. Commun.* **2011**, *47*, 7878.
[145] Frebault, F.; Simpkins, N. S.; Fenwick, A. *J. Am. Chem. Soc.* **2009**, *131*, 4214.
[146] Simpkins, N.; Pavlakos, I.; Male, L. *Chem. Commun*. **2012**, *48*, 1958.
[147] (a) Mosli, R. M.; Jamison, T. F. *J. Org. Chem*. **2007**, *72*, 9736. (b) Habaue, S.; Yasue, K.; Yanagisawa, A.; Yamamoto, H. *Synlett* **1993**, 788. (c) Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc*. **1994**, *116*, 6130. (d) Hong, B.-C.; Hong, J.-H.; Tsai, Y.-C. *Angew. Chem. Int. Ed*. **1998**, *37*, 468. (e) Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 4990. (f) Zhao, L.-M.; Jin, H.-S-; Wan, L.-J.; Zhang, L.-M. *J. Org. Chem*. **2011**, *76*, 1831.
[148] Yanagisawa, A.; Ogasawara, K.; Yasue, K.; Yamamoto, H. *Chem. Commun*, **1996**, 367.

It was not until more than ten years later, when another efficient α-prenylation was achieved.[149] This time a prenylhafnium reagent, formed *in situ* from tributylprenylstannane-$HfCl_4$ in propionitrile, was added to aldimines to get the corresponding α-adducts with excellent regioselectivity for benzylidenaniline (**Scheme 17, B**). The authors proposed that upon transmetallation, the transient γ-prenylhafnium is more reactive and is trapped by most of the aromatic aldimines at the α-position. However, the use of more reactive aromatic aldimines with highly electron-withdrawing substituents (ie.: NO_2 or SO_2Ph) led selectively to γ-adducts by trapping the most stable α-prenylhafnium specie at the bulkier γ-position.

More recently it was reported a procedure for the allylation of imines that involves a prenyl zinc reagent in combination with 1,3-dimethyl-2-imidazolidinone (DMI) at 120 °C.[150] A variety of imines were tested obtaining exclusively the corresponding α-adduct with excellent yields. The authors propose that after a γ-prenyl addition to a Zn-activated imine, the same metal is coordinated to DMI and another imine, leading to an *in situ* [3,5]-sigmatropic rearrangement (**Scheme 18**).

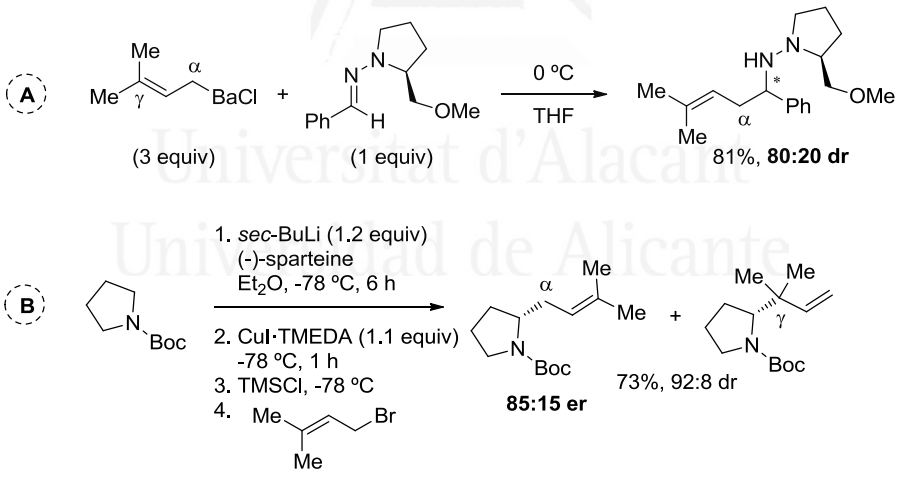


Scheme 18

Different approaches to linear homoprenylic amines have also been successfully accomplished. A recent representative example is the cross-coupling of imines with 2-methyl-3-buten-2-ol, mediated by an *in situ* formed low-valent titanium reagent.[7] Very recently the linear prenylation of imines has also been achieved

[149] Shibata, I., Miyamoto, S.; Tsunoi, S.; Sakamoto, K.; Baba, A. *Eur. J. Org. Chem.* **2009**, 3508.
[150] Zhao, L.-M.; Zhang, S.-Q.; Jin, H.-S.; Wan, L.-J.; Dou, F. *Org .Lett.* **2012**, *14*, 886.

under elegant transfer hydrogenation conditions.[151] However, to the best of our knowledge, only two methods for the preparation of enantioenriched α-homoprenylic amines have been reported to date. The first protocol involved the addition of prenyl barium reagent to a hydrazone bearing a chiral moiety attached to the nitrogen (**Scheme 19, A**). This method was only examined with the SAMP-hydrazone of benzaldehyde, leading to the corresponding product with moderate diasteroselectivity (80:20 dr).[148] The other methodology relied on the α-deprotonation of *N*-Boc-pyrrolidine by *s*-BuLi/(-)-sparteine to give a chiral organolithium that, after copper transmetalation, is quenched with prenylbromide (**Scheme 19, B**). This method gave good regioselectivity as well as good enantioselectivity for the α-homoprenyl pyrrolidine adduct (85:15 er).[77c] Moreover, good enantioselection was also achieved using similar conditions (1. *n*-BuLi/(-)-sparteine; 2. Prenylbromide) in the α-prenylation of *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamines.[152] However, it is worth noting that all the existing methods for the preparation of enantioenriched linear homoprenylic amines are limited to very specific substrates.



Scheme 19

[151] Schmitt, D. C.; Lee, J.; Dechert-Schmitt, A.-M. R.; Yamaguchi, E.; Krische, M. J. *Chem. Commun.* **2013**, *49*, 6096.
[152] Coldman, I.; Robinson, S. P.; Baxter, C. A. *Synlett* **2012**, 2405.

III.2. OBJECTIVES

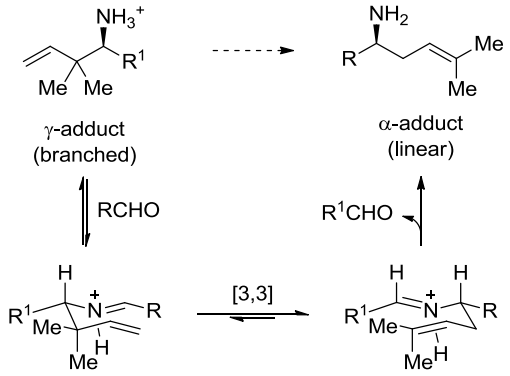
The aim of this chapter was to develop a general procedure for the preparation of linear enantioenriched homoprenylic amines. For this purpose we decided to explore the 2-azonia-Cope rearrangement of chiral branched iminium ions easily prepared by our α-aminoallylation protocol.

III.3. RESULTS AND DISCUSSION

Synthesis of the Chiral Donor.

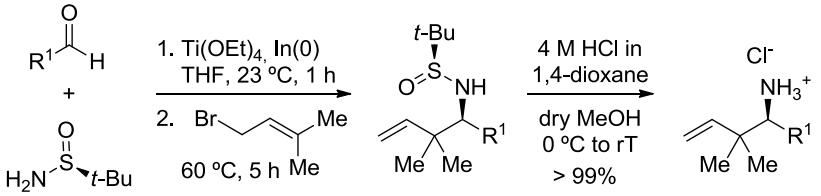
The 2-azonia-Cope rearrangement strategy was first employed by the group of Kobayashi using a chiral derivative of (1*R*)-camphorquinone as aminoallyl donor,[36] and more recently in catalytic versions that use Brønsted acids for the asymmetric induction *via* a chiral ion-pair.[38,153] To our surprise, this methodology has never been employed to generate homoprenylic amines. We reasoned that chiral γ-adducts, easily available from the addition of prenyl organometallic reagents to imine derivatives, could act as convenient aminoprenyl donors to other aldehydes. In our approach, the geminal methyl groups are expected to sterically promote the rearrangement to an iminium ion with an internal more stable double bond (**Scheme 20**). In this model, it is assumed that the (*E*)-iminium intermediate rearranges through a closed chair-like transition state in which the bulkier substituent (R^1) is placed in the equatorial position. The fact that this favored transition state involves two gauche interactions of the R^1 group with the geminal methyl groups anticipates a more challenging enantioselection than in other related transfer aminoallylations.

[153] Rueping, M.; Antonchick, P. *Angew. Chem. Int, Ed*. **2008**, *47*, 10090.



Scheme 20

The preparation of the aminoprenyl donors was carried out using our indium-mediated one-pot protocol. When 3-phenylpropanal and cinnamaldehyde were submitted to the aminoallylation conditions with (S_S)-*tert*-butylsulfinamide, the corresponding branched adducts were obtained in excellent yield, regio- and diasteroselectivities (**Scheme 21**). Importantly, the enantiomers were also successfully prepared in a similar way and an X-ray structure of *ent*-**30b** was obtained, confirming the configuration at the new carbon stereocenter predicted by our working model for this reaction (**Figure 5**). Moreover, we were also able to isolate the corresponding enantioenriched amine hydrochlorides in quantitative yield after treatment with HCl in dioxane/methanol. It is worth saying that although this acidic deprotection is a well-established methodology, we were aware of a possible protonation of the terminal double bond. In this case, a carbocationic intermediate could be involve in a [1,2]-methyl shift and/or in intermolecular alkylation of amines. Fortunately, our fears were unfounded.



a: R^1 = $PhCH_2CH_2$
b: R^1 = (*E*)-PhCH=CH

30a: 97%
30b: 80%

31a: ≥98:2 er
31b: ≥99:1 er

Scheme 21

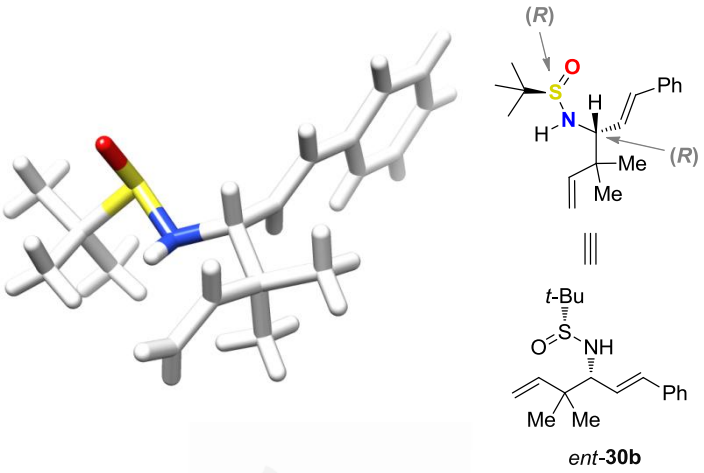


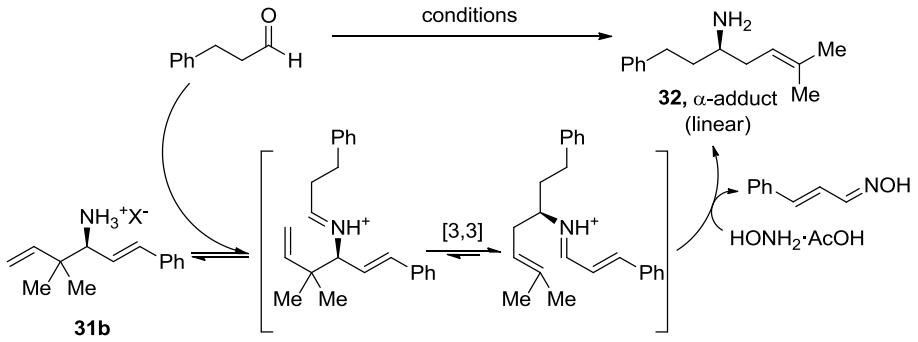
Figure 5: X-ray structure of *ent*-**30b** [154]

Optimization of the 2-Azonia-Cope Rearrangement Reaction Conditions.

Both potential donors were screened by using 3-phenylpropanal as acceptor. The conditions chosen were very simply: *in situ* deprotection of the corresponding donor under acidic conditions, removal of all volatile byproducts under vacuum, followed by the addition of 3-phenylpropanal in the appropriate solvent and submitted to the reaction conditions shown in **Table 3**. While the best yield for the α-adduct was obtained with donor **31a**,[155] the best enantiomeric ratio was obtained with **31b** (**Table 3**, entries 1 and 2). In the latter case, it was necessary to quench the reaction mixture with $HONH_2 \cdot AcOH$ in MeOH,[36] probably due to the better stability of the conjugate iminium formed after the rearrangement. We were encouraged by this result because this donor, which was obtained enantiomerically pure in excellent yield, could be used as a chiral aminoprenyl transfer agent to different aldehydes.

[154] CDCC 953178. For crystallographic data in CIF or other electronic format see: DOI: 10.1039/c3ob41804a.
[155] Starting compound **30a** was prepared as previously described by our research group in ref 62a.

Table 3:



Entry	31	Conditions[a]	t (h)	Yield[b]	er[c]
1	**31a**	CH_2Cl_2, 25 °C	24	80%[d]	83:17
2	**31b**	CH_2Cl_2, 25 °C	24	65%	88:12
3	**31b**	CH_2Cl_2,[d] 25 °C	24	0	-
4	**31b**	Toluene, 25 °C	24	50%	88:12
5	**31b**	**CH_2Cl_2, 40 °C**	**12**	**78%**	**88:12**
6	**31b**	CH_2Cl_2, 40 °C, 3 Å MS	12	70%	82:18
7	**31b**	CH_2Cl_2, 40 °C, 4 Å MS	12	74%	82:18
8	**31b**	CH_2Cl_2, 40 °C, 5 Å MS	12	71%	86:14
9	**31b** [e]	CH_2Cl_2, 40 °C	12	0	-
10	**31b** [f]	CH_2Cl_2, 40 °C, (+)-CSA	12	70%	82:18
11	**31b** [f]	CH_2Cl_2, 40 °C, (−)-CSA	12	74%	82:18

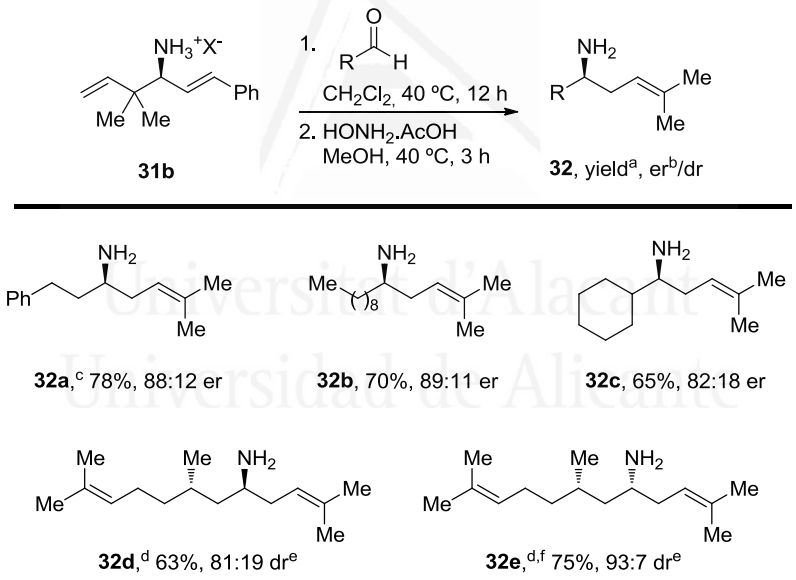
[a] Unless otherwise specified, all reactions were run in dry solvents and quenched with $HONH_2$·HCl in MeOH at 40 °C. [b] Isolated yield. [c] Determined by HPLC analysis of benzoyl derivative. [d] 5 equiv of H_2O were added. [e] Free amine of **31b** was used with no external acid. [f] Free amine of **31b** and 10 mol% of CSA was used.

In order to improve the enantiomeric ratio and the yield of the product, other reaction conditions were tested. In this regard we avoided the quenching of the reaction with $HONH_2$·AcOH by adding 5 equivalents of water to the reaction mixture, but no reaction was observed (**Table 3**, entry 3). Toluene was examined as solvent, but a significant decrease of the yield was observed with no improvement of the enantioselectivity (**Table 3**, entry 4). We were pleased to observe that increasing the temperature to 40 °C, produced a significant acceleration of the reaction with a positive impact in the isolated yield after 12 h and no deterioration of the enantioselectivity (**Table 3**, entry 5). Under these reaction conditions, the addition of different molecular sieves to the reaction mixture was explored observing no improvements in the results (**Table 3**, entries 6 to 8). Importantly, in a control experiment we checked it that the reaction did

not take place from the corresponding branched free amine with no acidic media (**Table 3**, entry 9). Even though stoichiometric amounts of HCl were used to promote this 2-azonia-Cope rearrangement, this was only a consequence of the conditions used to remove the sulfinyl group. We thus reasoned that substoichiometric amounts of chiral Brønsted acids could also promote the reaction with a positive (match case) or negative (mismatch case) impact in the enantioselection. Indeed when the reaction was accomplished with the corresponding free homoprenyl amine donor and 10 mol% of either enantiomer of camphorsulfonic acid, the product was obtained in similar yield but unfortunately with slightly lower enantioselectivity (**Table 3**, entries 10 and 11).

Scope and Limitations of the Procedure.

Table 4:



[a] Isolated yieds after column chromatography. [b] Determined by HPLC analysis (CHIRACEL OD-H). [c] The enantiomer was also obtained from *ent*-**31b** with the same selectivity. [d] (*S*)-Citronellal with 98:2 er was used. [e] Determined by ^{13}C-NMR analysis. [f] *ent*-**31b** was used as chiral donor.

Having found a simple and reliable set of conditions for the enantioselective aminoprenylation of aldehydes, we set about determining the scope and limitations of the procedure. A wide range of aldehydes were. Given that enolizable aldehydes would furnish iminium ions which are in equilibrium with their enamines, these substrates are commonly more challengers. *Remarkably, our*

developed protocol tolerates enolizable aliphatic aldehydes, affording the corresponding linear homoprenylic amines in good yields and moderate enantioselectivities (**Table 4**). Noteworthy, when a chiral aldehyde as (*S*)-citronellal was used with both enantiomeric forms of the chiral donor, matched (**32e**) and mismatched cases (**32d**) were obtained with a significant impact on both, isolated yield and diasteroselectivity. It is worthy to say that the diastereomeric ratios for these compounds were measured by ^{13}C-NMR.[156] For this purpose, the relative height was measured for each pair of well resolved signals corresponding to the same carbon and the average ratios were taken as diastereomeric ratios of amines **32d** (81:19 dr) and **32e** (93:7 dr).

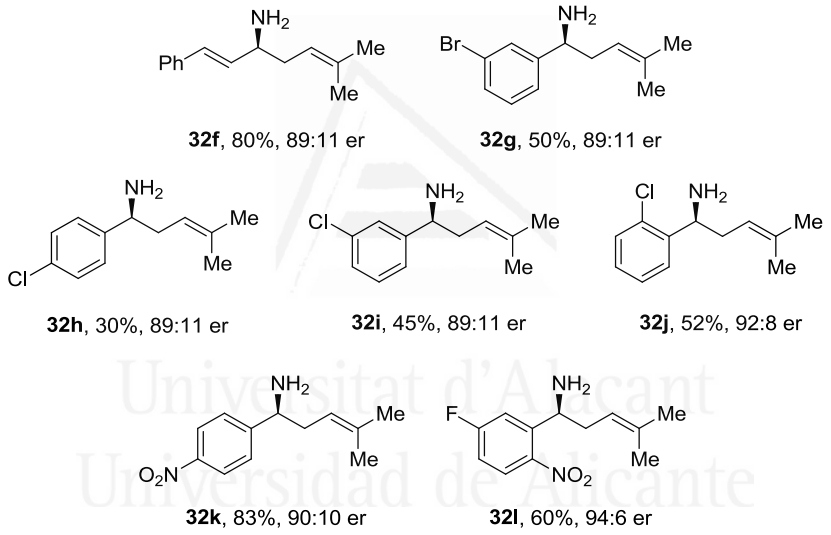


Figure 6: Isolated yields after column chromatography are given. The er for all compounds was determined by HPLC analysis (CHIRACEL OD-H).

Regarding aromatic aldehydes, this protocol was more limited and benzaldehyde, gave very little conversion into the desired product (<10%). However, cinnamaldeyde and aromatic aldehydes with electron-withdrawing substituents furnished the corresponding products in moderate to good yields and uniformly good enantioselectivities (≥ 89:11 er, **Figure 6**). These examples also serve to illustrate the tolerance of this methodology to the presence of different functional groups (i.e. nitro, halogens or α,β-unsaturated double bonds).

[156] The same method was used by Kobayashi in the diasteromeric ratio determination of the homoallylic amines obtained from (*S*)-citronellal. See the SI of ref 36 for more detail.

Consequently, we expanded the scope of this transformation by taking advantage of this chemoselectivity (**Figure 7**). When 3-methoxy- or 4-ethoxycarbonylpropanal was submitted to the optimized reaction conditions, the corresponding γ-lactam **32m** or δ-lactam **32n** was directly isolated. However, when 5-ethoxycarbonylpropanal was used, the cyclization did not take place *in situ* and the opened aminoester **32p** was obtained in excellent yield. The corresponding ε-lactam **33** was prepared in good yield after treatment with a solution of NaOMe in MeOH, keeping the same enantiomeric ratio. More interestingly, when 6-oxoheptanal was used, an *in situ* intramolecular iminium formation took place, which upon reduction with $NaCNBH_3$, furnished the *cis*-2,7-azepane derivative **32o** in reasonable overall yield.[157] Importantly, in most cases the corresponding enantiomers were prepared using the same protocol but the aminoprenyl donor ***ent*-31b** in order to unequivocally determine the enantiomeric ratio by HPLC. It is worth saying that the isolated yields and enantioselectivities were essentially the same for each enantiomeric aminoprenyl donor, but obtaining the opposite major enantiomer of the product.

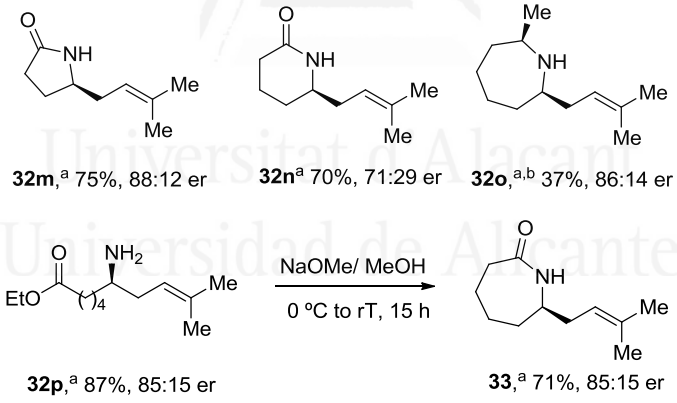


Figure 7: Isolated yields after column chromatography are given. The er for all compounds was determined by HPLC analysis (CHIRACEL OD-H). [a] The enantiomer was also obtained from *ent*-**31b** with the same selectivity.[b] $NaCNBH_3$ was used to quench the reaction.

[157] Its *cis* configuration was determined by nOe experiments.

Assignment of the absolute conficuration of the synthesized amines.

The assignment of the absolute configuration of the major enantiomer of amine **32a** was performed by ^{1}H-NMR analysis of its (*R*)-MPA amide derivative in the absence and in the presence of $Ba(ClO_4)_2$ in the NMR tube (**Figure 8**).[158]

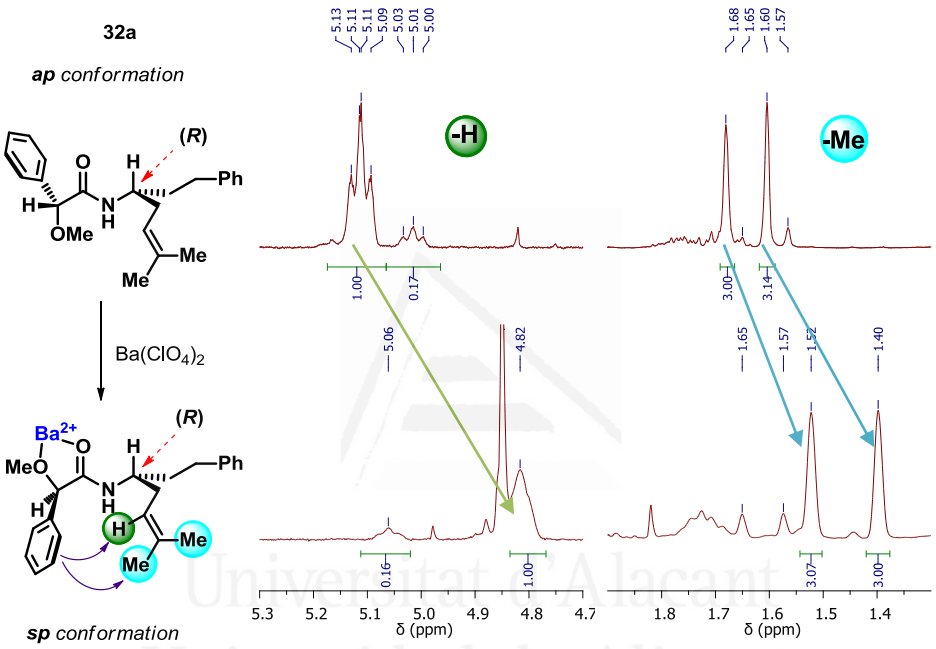


Figure 8

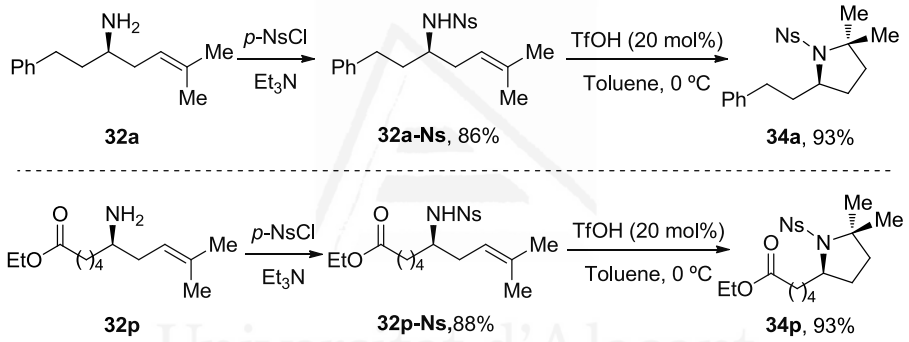
As described by the group of Riguera, MPA amides are mainly populated by conformers with an *antiperiplanar* disposition of the methoxy group related to the oxygen atom of the carbonyl. Upon the addition of Ba^{2+} to a sample of **32a**, the formation of a chelate shifts the equilibrium to a population where these groups are locked in a *synperiplanar* conformation. This conformational change can be easily appreciated by ^{1}H-NMR since it cause an increase in the shielding of the vinylic and methyl signals by the phenyl group of the MPA auxiliary. The same analysis was performed for compounds **32b** and **32k**, confirming the same stereochemistry for all aliphatic as well as aromatic synthesized amines.[159] Importantly, in all cases inversion of the configuration at the stereogenic center

[158] García, R.; Seco, J. M.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2006**, *71*, 1119.
[159] See Supporting Infromation of Chapter III.

from donor (*S*)-**31b** to the major enantiomer of **32** was observed, *which was correctly predicted by our working model depicted before in* ***Scheme 20***.

Synthetic Applications of the Linear Homoprenylamines.

The potential of this transformation as a valuable tool in organic synthesis has been briefly illustrated with the synthesis of the correspondent 2,2,5-trisubstituted pyrrolidines (**Scheme 22**). *p*-Nosylate derivatives of compounds **32a** and **32p** were prepared in excellent yields, and upon treatment with substoichiometric amounts of triflic acid at 0 ºC underwent very smooth and efficient intramolecular hydroamination to give compounds **34a** and **34p** in excellent yields.[141a]



Scheme 22

III.4. EXPERIMENTAL SECTION

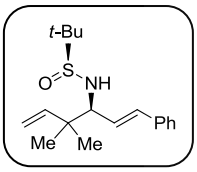
General Remarks.

(R_s)-*N*-*tert*-Butylsulfinyl amine and its enantiomer were a gift of Medalchemy (> 99% ee by chiral HPLC on a Chiracel AS column, *n*-Hexane/*i*-PrOH 90:10, 1 mL/min, λ=222 nm). TLCs were performed on silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) or ninhydrine stain. Flash chromatographies were carried out on handpacked columns of silica gel 60 (230- 400 mesh). Melting points are uncorrected. Optical rotations were measured using a polarimeter with a thermally jacketted 5 cm cell at approximately 20 ºC and concentrations (c) are given in g/100 mL. Infrared analyses were performed with a spectrophotometer equipped with an ATR component; wavenumbers are given in cm^{-1}. GC analyses were obtained with an HP-5 column (30 m × 0.25 mm, i.d. × 0.25 µm) and an EI (70 EV) detector; the temperature program was as follows: hold at 60 °C for 3 min, ramp from 60 to 270 °C at 15 °C/min, hold at 270 °C for 10 min. Mass spectra (EI) were obtained at 70 eV; and fragment ions in

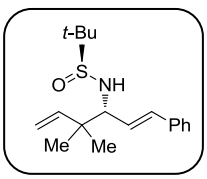
m/z with relative intensities (%) in parentheses. HRMS analyses were also carried out in the electron impact mode (EI) at 70 eV using a quadrupole mass analyzer or in the electrospray ionization mode (ES^+) using a TOF analyzer. ^1H NMR spectra were recorded at 300 or 400 MHz, using $CDCl_3$ or CD_3CN as the solvent and TMS as internal Standard (0.00 ppm); the data is being reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded with ^1H-decoupling at 101 MHz using the solvent signal as reference (77.16 ppm for $CDCl_3$). DEPT-135 experiments were performed to assign CH, CH_2 and CH_3.

Procedure for the synthesis of donors 30b and ent-30b.

(S_S,1*E*,3*S*)-N-*tert*-Butylsulfinyl-4,4-dimethyl-1-phenylhexa-1,5-dien-3-amine (30b)



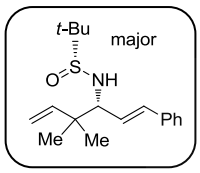
To a dry flask were added (R_S)-*N*-*tert*-Butylsulfinyl amine (605 mg, 5.00 mmol) followed by indium powder (713 mg, 6.25 mmol), and the mixture was evacuated and left under Ar atmosphere. Then a solution of cynnamaldehyde (726 mg, 5.5 mmol) in dry THF (10 mL) was added, followed by $Ti(OEt)_4$ (2.3 mL, 10.00 mmol) and the reaction mixture was stirred under Ar for 1 h at 23 °C. At this time, 3,3-Dimethylallyl bromide (873 µL, 7.5 mmol) was added and the reaction mixture was heated to 60 °C for 3 h. The mixture was allowed to reach room temperature and was carefully added over a stirring mixture of 4:1 EtOAc/brine (50 mL). The resulted white suspension was filtered through a short pad of Celite, washed with EtOAc and organics were concentrated *in vacuo*. The resulted suspension was diluted in 4:1 EtOAc/Hexane (50 mL) and filtered again through Celite. Organics were concentrated and the residue (92:8 dr according ^1H NMR) was purified by column chromatography (8:2 Hexane/EtOAc). The expected product was obtained as a white solid (1.218 g, 80%, >98:2 dr according ^1H NMR): mp 94.0 – 95.1 °C; $[\alpha]^{20}_D$ + 163.4 (*c* 1.10, $CHCl_3$); R_f 0.21 (7:3 Hexane/EtOAc); IR ν 3289, 3057, 2958, 2924, 1637, 1364, 1337, 1184, 1059, 996, 984, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 6.63 (d, *J* = 15.9 Hz, 1H), 5.96 (dd, *J* = 15.9, 8.8 Hz, 1H), 5.85 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.19 (dd, *J* = 10.7, 1.0 Hz, 1H), 5.13 (dd, *J* = 17.5, 1.1 Hz, 1H), 3.71 (d, *J* = 8.9 Hz, 1H), 3.59 (br s, 1H), 1.19 (s, 9H), 1.07 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9 (CH), 136.8 (C), 135.3 (CH), 128.7 (CH), 127.9 (CH), 126.7 (CH), 126.4 (CH), 114.6 (CH_2), 63.3 (CH), 55.7 (C), 41.7 (C), 26.3 (CH_3), 22.9 (CH_3), 19.7 (CH_3); GC t_R = 16.3 min; LRMS (EI) *m/z* (%) 249 (M^+, 2), 230 (10), 180 (10), 179 (95), 131 (14), 130 (100), 117 (13), 116 (98), 115 (41), 103 (12), 91 (12), 77 (17), 55(10); HRMS (EI) calcd for $C_{18}H_{27}NOS$ – C_4H_8 249.1109, found 249.1227.

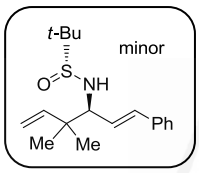


The minor compound ((S_S,1*E*,3*R*)-**30b**) was also isolated from the reaction described above as a white solid (106 mg, 7%): mp 45.1 – 46.8 °C; $[\alpha]^{20}_D$ + 4.0 (*c* 1.06, $CHCl_3$); R_f 0.34 (7:3 Hexane/EtOAc); IR ν 3288, 3057, 2957, 2925, 1637, 1366, 1337, 1183, 1059, 996, 985, 912 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 4H), 7.25 – 7.16 (m, 1H), 6.62 (d, *J* = 15.8 Hz, 1H), 6.20 (dd, *J* = 15.8, 8.3 Hz, 1H), 5.86 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.14 (dd, *J* = 10.8, 1.3 Hz, 1H), 5.08 (dd, *J* = 17.4, 1.3 Hz, 1H), 3.61 (t, *J* = 8.6 Hz, 1H), 3.30 (d, *J* = 9.0 Hz, 1H), 1.22 (s, 9H), 1.11 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4 (CH), 136.9 (C), 133.3 (CH), 128.8 (CH), 128.6 (CH), 127.8 (CH), 126.8 (CH), 114.2 (CH_2), 67.9 (CH), 56.8 (C), 41.9 (C), 24.6 (CH_3), 24.5 (CH_3), 22.9 (CH_3); GC t_R = 16.9 min; LRMS (EI) *m/z* (%) 249 (M^+, 2), 230 (10), 180 (10), 179 (95), 131 (14), 130 (100), 117 (13), 116 (98), 115 (35), 103 (12), 91 (13), 77 (17), 55(10); HRMS (EI) calcd for $C_{18}H_{27}NOS$ – C_4H_8 249.1109, found 249.1112

(R_S,1*E*,3*R*)-N-*tert*-Butylsulfinyl-4,4-dimethyl-1-phenylhexa-1,5-dien-3-amine (*ent*-30b)





Following the procedure described above for **30b**, but using (S_S)-*N*-*tert*-Butylsulfinyl amine, compound *ent*-**30b** was obtained in a similar yield with identical spectroscopic and physical data, except for $[\alpha]^{20}_D$ – 162.6 (*c* 1.01, $CHCl_3$).

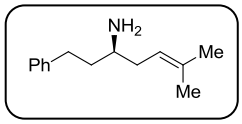
The minor compound ((R_S,1*E*,3*S*)-**30b**) was also isolated from the reaction described above as a white foam. The spectroscopic and physical data was identical to ((S_S,1*E*,3*R*)-**30b**), except for $[\alpha]^{20}_D$ – 4.5 (*c* 0.96, $CHCl_3$).

General procedure for the synthesis of the rearranged amines and lactams 32.

To a solution of (S_S,1*E*,3*S*)-**30b** (92 mg, 0.3 mmol) in dry MeOH (3.7 mL) at 0 °C was carefully added a solution of HCl in 1,4-dioxane (4M, 1.2 mmol, 300 μL). The reaction mixture was stirred for 1 h while reaching the room temperature. After removal of the solvent and volatiles under reduced pressure (*t*-$BuSO_2Me$), the corresponding hydrochloride **31b** was obtained as a white solid.

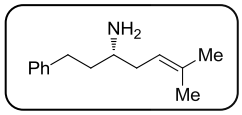
To a solution of crude hydrochloride **31b** in dry CH_2Cl_2 (2 mL) was added the corresponding aldehyde (0.36 mmol), and the reaction was stirred at 40 °C for 12 h. The reaction was quenched with a solution of $HONH_2 \cdot AcOH$ in MeOH (0.5 M, 1.4 mL).[36] The reaction mixture was diluted with EtOAc (5 mL) and NaOH (2 M, 5 mL), and after phase separation, the aqueous phase was extracted with EtOAc (3 x 5 mL). Organics were washed with NaOH (2 M, 5 mL) followed by brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (gradient from 97:3 CH_2Cl_2/MeOH to 90:10:0.05 CH_2Cl_2/MeOH/20% NH_4OH) to provide the desired amines **32a – 32l**, **32o** and **32p**. For lactams **32m** and **32n**, column chromatography was carried out with 1:3 Hexane/EtOAc. The enantiomers of some arranged products (*ent*-**32a**, *ent*-**32m**, *ent*-**32n**, *ent*-**32o** and *ent*-**32p**) were prepared following the same procedure but starting from donor *ent*-**30b**.

(*R*)-6-Methyl-1-phenyl-5-hepten-3-amine (32a)



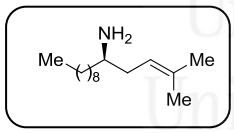
Following the general procedure from 3-Phenylpropanal, compound **32a** was obtained as a yellow oil after column chromatography (48 mg, 0.234 mmol, 78%): $[\alpha]^{20}_D$ - 6.2 (*c* 0.70, $CHCl_3$); $[\alpha]_D^{20}$ - 3.2 (*c* 0.80, CH_2Cl_2); R_f 0.28 (9:1 CH_2Cl_2/MeOH); IR ν 3360, 3292, 3026, 2963, 2915, 2855, 1496, 1453, 1376, 745, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.23 – 7.14 (m, 3H), 5.13 (ddd, *J* = 8.2, 2.7, 1.3 Hz, 1H), 2.84 (ddd, *J* = 12.8, 7.5, 5.3 Hz, 1H), 2.76 (ddd, *J* = 13.8, 10.3, 5.8 Hz, 2H), 2.65 (ddd, *J* = 13.7, 10.1, 6.2 Hz, 2H), 2.19 (dt, *J* = 12.3, 6.1 Hz, 1H), 2.15 – 2.05 (m, 1H), 1.85 – 1.75 (m, 1H), 1.72 (s, 3H), 1.70 – 1.65 (m, 1H), 1.63 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2 (C), 134.7 (C), 128.5 (CH), 128.5 (CH), 125.9 (CH), 120.7 (CH), 51.6 (CH), 38.6 (CH_2), 35.9 (CH_2), 32.7 (CH_2), 26.0 (CH_3), 18.2 (CH_3); GC t_R = 12.4 min; LRMS (EI) *m/z* (%) 203 (M^+, 0.1), 202 (0.3), 135 (10), 134 (100), 117 (33), 91 (89), 65 (10); HRMS (EI) calcd for $C_{14}H_{21}N$ 203.1674, found 203.1726.

(*S*)-6-Methyl-1-phenyl-5-hepten-3-amine (*ent*-32a)



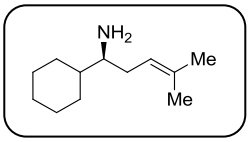
Following the general procedure from 3-Phenylpropanal and donor *ent*-**30b**, compound *ent*-**32a** was obtained with the same data as compound **32a** except for $[\alpha]^{20}_D$ + 6.5 (*c* 0.75, $CHCl_3$).

(*R*)-2-Methyl-2-tridecen-5-amine (32b)



Following the general procedure from *n*-decanal, compound **32b** was obtained as a yellow oil after column chromatography (47 mg, 0.210 mmol, 70%): $[\alpha]^{20}_D$ - 5.3 (*c* 0.95, $CHCl_3$); R_f 0.37 (9:1 CH_2Cl_2/MeOH); IR ν 3360, 3292, 2957, 2922, 2852, 1619, 1572, 815, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (ddd, *J* = 8.1, 2.6, 1.3 Hz, 1H), 2.75 (br s, 1H), 2.20 – 1.87 (m, 4H), 1.73 (s, 3H), 1.63 (s, 3H), 1.49 – 1.35 (m, 2H), 1.34 – 1.20 (m, 14H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.2 (C), 121.4 (CH), 51.9 (CH), 37.4 (CH_2), 36.4 (CH_2), 32.1 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 26.4 (CH_2), 26.1 (CH_3), 22.8 (CH_2), 18.2 (CH_3), 14.3 (CH_3); GC t_R = 12.5 min; LRMS (EI) *m/z* (%) 225 (M^+, 0.1), 224 (0.3), 157 (13), 156 (100), 81 (5), 69 (6), 56 (10); HRMS (EI) calcd for $C_{15}H_{31}N$ 225.2457, found 225.2469.

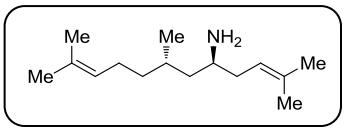
(*S*)-1-Cyclohexyl-4-methyl-3-penten-1-amine (32c)



Following the general procedure from Cyclohexylcarbaldehyde, compound **32c** was obtained as a yellow oil after column chromatography (35 mg, 0.195 mmol, 65%): $[\alpha]^{20}_D$ - 5.1 (*c* 0.85, CH_2Cl_2); R_f 0.20 (9:1 CH_2Cl_2/MeOH); IR ν 3370, 3292, 2921, 2851, 1448, 1376, 890, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (t, *J* = 7.3 Hz, 1H), 2.65 – 2.49 (m, 1H), 2.28 – 2.10 (m, 1H), 2.10 – 1.91 (m, 2H), 1.77 (br d, *J* = 11.3 Hz, 3H), 1.73 (s, 3H),

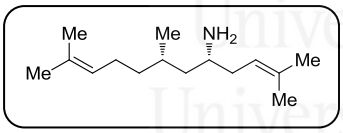
1.68 (br s, 2H), 1.63 (s, 3H), 1.38 – 0.91 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.1 (C), 121.9 (CH), 56.7 (CH), 43.1 (CH), 33.1 (CH_2), 29.9 (CH_2), 28.4 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 26.1 (CH_3), 18.2 (CH_3); GC t_R = 10.7 min; LRMS (EI) *m/z* (%) 181 (M^+, 0.1), 180 (0.3), 113 (8), 112 (100), 98 (9), 95 (37), 81 (12), 67 (6), 55 (6); HRMS (EI) calcd for $C_{12}H_{23}N$ 181.1830, found 181.1841.

(5*R*,7*S*)-2,7,11-Trimethyldodeca-2,10-dien-5-amine (32d)



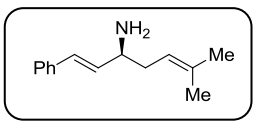
Following the general procedure from (*S*)-Citronellal, compound **32d** was obtained as a yellow oil after column chromatography (42 mg, 0.19 mmol, 63%): $[\alpha]^{20}_D$ + 5.0 (*c* 1.07, $CHCl_3$); R_f 0.29 (9:1 CH_2Cl_2/MeOH); IR ν 3350, 2963, 2913, 2859, 1727, 1668, 1450, 1376, 828, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 – 5.06 (m, 2H), 2.87 (tt, *J* = 9.6, 5.0 Hz, 1H), 2.35 – 1.90 (m, 6H), 1.73 (d, *J* = 0.6 Hz, 3H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.43 – 1.09 (m, 5H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4 (C), 131.3 (C), 124.9 (CH), 121.2 (CH), 49.4 (CH), 44.7 (CH_2), 37.9 (CH_2), 36.9 (CH_2), 29.4 (CH), 26.1 (CH_3), 25.9 (CH_3) , 25.6 (CH_2), 19.3 (CH_3), 18.2 (CH_3), 17.8 (CH_3); GC t_R = 12.0 min; LRMS (EI) *m/z* (%) 203 (M^+, 0.1), 155 (12), 154 (100), 137 (19), 112 (6), 98 (7), 96 (5), 95 (38), 82 (89), 70 (13), 69 (39), 67 (10); HRMS (EI) calcd for $C_{15}H_{29}N$ 223.2300, found 223.2279.

(5*S*,7*S*)-2,7,11-Trimethyldodeca-2,10-dien-5-amine (32e)



Following the general procedure from (*S*)-Citronellal, but using *ent*-**30b** as chiral donor, compound **32e** was obtained as a yellow oil after column chromatography (50 mg, 0.22 mmol, 75%): $[\alpha]^{20}_D$ + 10.6 (*c* 0.80, CH_2Cl_2); R_f 0.27 (9:1 CH_2Cl_2/MeOH); IR ν 3351, 2963, 2913, 2848, 1727, 1668, 1450, 1376, 829, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 – 5.06 (m, 2H), 2.88 (dt, *J* = 12.0, 7.4 Hz, 1H), 2.26 (br s, 2H), 2.19 – 2.09 (m, 1H), 2.06 –1.90 (m, 3H), 1.73 (d, *J* = 0.6 Hz, 3H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.58 – 1.51 (m, 1H), 1.44 – 1.30 (m, 2H), 1.27 – 1.07 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5 (C), 131.4 (C), 124.9 (CH), 121.1 (CH), 49.6 (CH), 44.9 (CH_2), 36.9 (CH_2), 36.0 (CH_2), 29.5 (CH), 26.1 (CH_3), 25.9 (CH_3), 25.4 (CH_2), 20.3 (CH_3), 18.2 (CH_3), 17.8 (CH_3); GC t_R = 12.2 min; LRMS (EI) *m/z* (%) 223 (M^+, 0.1), 155 (12), 154 (100), 137 (19), 112 (6), 98 (7), 95 (38), 82 (9), 81 (89), 70 (13), 69 (39), 67 (10); HRMS (EI) calcd for $C_{15}H_{29}N$ 223.2300, found 223.2283.

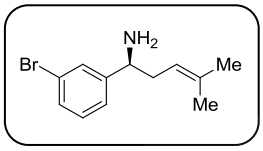
(*E*,*S*)-6-Methyl-1-phenylhepta-1,5-dien-3-amine (32f)



Following the general procedure from Cinnamaldehyde, compound **32f** was obtained as a yellow oil after column chromatography (48 mg, 0.240 mmol, 80%): $[\alpha]^{20}_D$ - 8.5 (*c* 0.92, CH_2Cl_2); R_f 0.15 (9:1 CH_2Cl_2/MeOH); IR ν 3370, 3301, 2917, 2859, 1448, 1376, 812 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 4H), 7.24 – 7.17 (m, 1H),

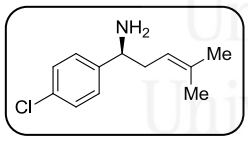
6.51 (d, *J* = 15.9 Hz, 1H), 6.21 (dd, *J* = 15.9, 6.8 Hz, 1H), 5.30 – 5.05 (m, 1H), 3.53 (q, *J* = 6.7 Hz, 1H), 2.24 (t, *J* = 7.0 Hz, 2H), 1.92 (br s, 2H), 1.73 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3 (C), 134.8 (CH), 134.3 (C), 129.1 (CH), 128.7 (CH), 127.4 (CH), 126.4 (CH), 120.5 (CH), 54.3 (CH), 36.6 (CH_2), 26.1 (CH_3), 18.2 (CH_3); GC t_R = 13.1 min; LRMS (EI) *m/z* (%) 201 (M^+, 0.1), 133 (11), 132 (100), 130 (9), 117 (8), 115 (31); HRMS (EI) calcd for $C_{14}H_{19}N$ 201.1517, found 201.1538.

(*S*)-1-(3-Bromophenyl)-4-methyl-3-penten-1-amine (32g)



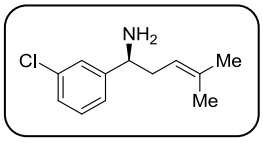
Following the general procedure from 3-Bromobenzaldehyde, compound **32g** was obtained as a yellow oil after column chromatography (37 mg, 0.146 mmol, 50%): $[\alpha]^{20}_D$ – 22.6 (*c* 1.20, $CHCl_3$); R_f 0.33 (9:1 CH_2Cl_2/MeOH); IR ν 3370, 3301, 2966, 2912, 1593, 1567, 1427, 1068, 782 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, *J* = 1.7 Hz, 1H), 7.39 – 7.33 (m, 1H), 7.29 – 7.23 (m, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 5.09 (tdd, *J* = 6.0, 2.8, 1.4 Hz, 1H), 3.91 (t, *J* = 6.7 Hz, 1H), 2.32 (t, *J* = 7.0 Hz, 2H), 1.72 (br s, 2H), 1.70 (d, *J* = 0.9 Hz, 3H), 1.58 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7 (C), 135.1 (C), 130.1 (C), 130.0 (CH), 129.7 (CH), 125.2 (CH), 122.6 (CH), 120.6 (CH), 55.9 (CH), 38.4 (CH_2), 26.0 (CH_3), 18.1 (CH_3); GC t_R = 12.9 min; LRMS (EI) *m/z* (%) 254 (0.1), 187 (12), 186 (98), 185 (13), 184 (100), 182 (2), 157 (7), 104 (9), 77 (13); HRMS (ES^+) calcd for $C_{12}H_{17}BrN$ 254.0544, found 254.0548.

(*S*)-1-(4-Chlorophenyl)-4-methyl-3-penten-1-amine (32h)



Following the general procedure from 4-Chlorobenzaldehyde, compound **32h** was obtained as a yellow oil after column chromatography (18 mg, 0.09 mmol, 30%): $[\alpha]^{20}_D$ – 25.5 (*c* 1.50, $CHCl_3$); R_f 0.33 (9:1 CH_2Cl_2/MeOH); IR ν 3375, 3286, 2968, 2912, 1859, 1668, 1489, 1089, 1013, 822 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 4H), 5.10 (tt, *J* = 7.3, 1.4 Hz, 1H), 3.95 (t, *J* = 7.0 Hz, 1H), 2.32 (t, *J* = 7.1 Hz, 2H), 1.72 (d, *J* = 0.9 Hz, 3H), 1.62 (br s, 2H), 1.60 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C), 135.0 (C), 132.5 (C), 128.5 (CH), 127.9 (CH), 120.7 (CH), 55.8 (CH), 38.5 (CH_2), 26.0 (CH_3), 18.1 (CH_3); GC t_R = 12.2 min; LRMS (EI) *m/z* (%) 143 (9), 142 (34), 141 (28), 140 (100), 138 (8), 115 (8), 113 (21), 78 (6), 77 (36); HRMS (EI) calcd for $C_{12}H_{16}ClN$ 209.0971, found 209.1251.

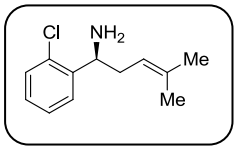
(*S*)-1-(3-Chlorophenyl)-4-methyl-3-penten-1-amine (32i)



Following the general procedure from 3-Chlorobenzaldehyde, compound **32i** was obtained as a yellow oil after column chromatography (27 mg, 0.129 mmol, 45%): $[\alpha]^{20}_D$ – 30.2 (*c* 0.87, $CHCl_3$); R_f 0.34 (9:1 CH_2Cl_2/MeOH); IR ν 3370, 3281, 2968, 2913, 1596, 1573, 1432, 784, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (t, *J* = 1.7 Hz, 1H), 7.26 – 7.16 (m, 3H), 5.19 – 4.97 (m, 1H), 3.92 (t, *J* = 6.7 Hz, 1H), 2.32

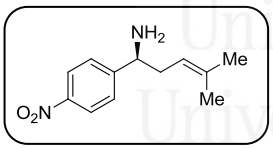
(t, *J* = 7.0 Hz, 2H), 1.88 (d, *J* = 3.6 Hz, 1H), 1.71 (d, *J* = 1.0 Hz, 3H), 1.64 (br s, 1H), 1.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5 (C), 135.1 (C), 134.3 (C), 129.7 (CH), 127.1 (CH), 126.8 (CH), 124.8 (CH), 120.6 (CH), 56.0 (CH), 38.5 (CH_2), 26.0 (CH_3), 18.1 (CH_3); GC t_R = 12.2 min; LRMS (EI) *m/z* (%) 206 (1), 142 (32), 141 (9), 140 (100), 138 (3), 77 (13); HRMS (ES^+) calcd for $C_{12}H_{17}ClN$ 210.1050, found 210.1044.

(*S*)-1-(2-Chlorophenyl)-4-methyl-3-penten-1-amine (32j)



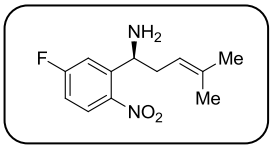
Following the general procedure from 2-Chlorobenzaldehyde, compound **32j** was obtained as a yellow oil after column chromatography (32 mg, 0.156 mmol, 52%): $[\alpha]^{20}_D$ – 69.8 (*c* 1.50, $CHCl_3$); R_f 0.50 (9:1 CH_2Cl_2/MeOH); IR ν 3370, 3282, 3060, 2967, 2913, 2853, 1668, 1439, 1035, 854, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.33 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.19 – 7.13 (m, 1H), 5.17 (tdd, *J* = 6.7, 2.8, 1.4 Hz, 1H), 4.42 (dd, *J* = 8.3, 4.8 Hz, 1H), 2.44 (dt, *J* = 11.6, 5.7 Hz, 1H), 2.36 – 2.19 (m, 1H), 1.72 (d, *J* = 0.7 Hz, 3H), 1.62 (br s, 2H), 1.61 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (C), 135.0 (C), 133.0 (C), 129.6 (CH), 127.9 (CH), 127.4 (CH), 127.1 (CH), 120.8 (CH), 52.4 (CH), 36.4 (CH_2), 26.0 (CH_3), 18.1 (CH_3); GC t_R = 11.9 min; LRMS (EI) *m/z* (%) 209 (0.1, M^+), 142 (34), 141 (9), 140 (100), 115 (8), 113 (5, 78 (3, 77 (13); Anal. Calc'd for $C_{12}H_{16}ClN$: C 68.73, H 7.69, N 6.68; Found: C 68.99, H 7.52, N 6.58.

(*S*)-1-(4-Nitrophenyl)-4-methyl-3-penten-1-amine (32k)



Following the general procedure from 4-Nitrobenzaldehyde, compound **32k** was obtained as a yellow oil after column chromatography (55 mg, 0.250 mmol, 83%): $[\alpha]^{20}_D$ – 21.7 (*c* 1.10, $CHCl_3$); R_f 0.36 (9:1 CH_2Cl_2/MeOH); IR ν 3376, 2971, 2911, 2848, 1597, 1507, 1342, 856, 751, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 8.8, 2.1 Hz, 2H), 7.54 (dd, *J* = 8.6, 2.1 Hz, 2H), 5.08 (tt, *J* = 7.4, 1.4 Hz, 1H), 4.08 (t, *J* = 6.7 Hz, 1H), 2.34 (t, *J* = 7.1 Hz, 2H), 1.71 (d, *J* = 0.7 Hz, 3H), 1.64 (br s, 2H), 1.57 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8 (C), 147.0 (C), 135.8 (C), 127.4 (CH), 127.4 (CH), 123.7 (CH), 123.7 (CH), 119.9 (CH), 55.9 (CH), 38.5 (CH_2), 26.0 (CH_3), 18.1 (CH_3); GC t_R = 14.4 min; LRMS (EI) *m/z* (%) 152 (9), 151 (100), 121 (4), 105 (31), 104 (13), 93 (5), 78 (5), 77 (6); HRMS (EI) calcd for $C_{12}H_{16}N_2O_2$ 220.1212, found 220.1202.

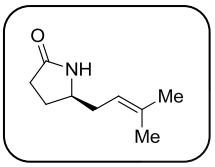
(*S*)-1-(5-Fluoro-2-nitrophenyl)-4-methyl-3-penten-1-amine (32l)



Following the general procedure from 5-Fluoro-2-nitrobenzaldehyde, compound **32l** was obtained as a yellow oil after column chromatography (42 mg, 0.176 mmol, 60%): $[\alpha]^{20}_D$ – 89.8 (*c* 0.75, $CHCl_3$); R_f 0.53 (9:1 CH_2Cl_2/MeOH); IR ν 3390, 3302, 2970, 2916, 2849, 1584, 1512, 1352, 851, 757, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.59 (dd, *J* = 9.9, 2.8 Hz, 1H),

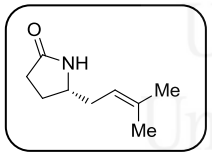
7.03 (ddd, *J* = 9.0, 7.1, 2.8 Hz, 1H), 5.13 (ttd, *J* = 6.6, 2.7, 1.3 Hz, 1H), 4.59 (ddd, *J* = 8.2, 4.8, 1.6 Hz, 1H), 2.47 – 2.36 (m, 1H), 2.34 – 2.23 (m, 1H), 1.72 (s, 3H), 1.60 (br s, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1 (d, *J* = 255.3 Hz, C), 145.3 (d, *J* = 8.0 Hz, C), 145.2 (C), 136.1 (C), 127.1 (d, *J* = 9.5 Hz, CH), 120.0 (CH), 115.5 (d, *J* = 24.4 Hz, CH), 114.7 (d, *J* = 24.4 Hz, CH), 50.7 (CH), 37.5 (CH_2), 26.0 (CH_3), 18.1 (CH_3); GC t_R = 13.0 min; LRMS (EI) *m/z* (%) 170 (9), 169 (100), 152 (3), 123 (17), 122 (17), 122 (23), 69 (4); HRMS (EI) calcd for $C_{12}H_{16}N_2O_2F$ 239.1196, found 239.1197.

(*R*)-5-Prenyl-2-pyrrolidinone (32m)



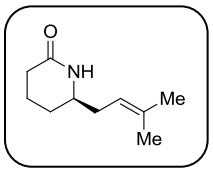
Following the general procedure from Methyl 4-oxobutanoate,[160] compound **32m** was obtained as a yellow oil after column chromatography (35 mg, 0.225 mmol, 75%): $[\alpha]^{20}_D$ – 14.5 (*c* 0.90, $CHCl_3$); R_f 0.20 (1:3 Hexane:EtOAc); IR ν 3210, 3100, 2969, 2915, 1689, 1440, 1424, 1343, 856 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (br s, 1H), 5.09 (tdd, *J* = 6.9, 2.8, 1.4 Hz, 1H), 3.65 (p, *J* = 6.6 Hz, 1H), 2.38 – 2.29 (m, 2H), 2.28 – 2.14 (m, 3H), 1.82 – 1.74 (m, 1H), 1.72 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1 (C), 135.5 (C), 119.3 (CH), 54.7 (CH), 35.3 (CH_2), 30.3 (CH_2), 26.9 (CH_2), 26.0 (CH_3), 18.1 (CH_3); GC t_R = 11.3 min; LRMS (EI) *m/z* (%) 153 (M^+, 2), 85 (5), 84 (100), 69 (2), 56 (6), 55 (3); HRMS (ES^+) calcd for $C_9H_{16}NO$ 154.1232, found 154.1231.

(*S*)-5-Prenyl-2-pyrrolidinone (*ent*-32m)



Compound *ent*-**32m** was obtained using *ent*-**30b** as chiral donor: The spectroscopical data was identical to **32m**, except for $[\alpha]^{20}_D$ + 14.1 (*c* 0.95, $CHCl_3$).

(*R*)-6-Prenyl-2-piperidinone (32n)

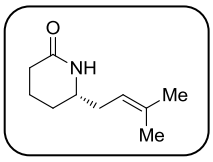


Following the general procedure from Methyl 5-oxopentanoate,[160] compound **32n** was obtained as a white solid after column chromatography (35 mg, 0.210 mmol, 70%): mp = 68.3 – 70.1 °C; $[\alpha]^{20}_D$ + 6.0 (*c* 1.10, $CHCl_3$); R_f 0.14 (1:3 Hexane:EtOAc); IR ν 3286, 3184, 3065, 2959, 2939, 2857, 1664, 1488, 1405, 834 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (br s, 1H), 5.06 (dddd, *J* = 7.3, 5.9, 2.8, 1.4 Hz, 1H), 3.41 – 3.25 (m, 1H), 2.40 (dddd, *J* = 17.8, 6.0, 3.1, 1.5 Hz, 1H), 2.28 (ddd, *J* = 14.6, 10.8, 5.9 Hz, 1H), 2.15 (t, *J* = 7.2 Hz, 2H), 1.98 – 1.84 (m, 2H), 1.73 (d, *J* = 0.8 Hz, 3H), 1.71 – 1.66 (m, 1H), 1.64 (s, 3H), 1.45 – 1.29 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (C), 136.5 (C), 119.2 (CH), 53.1 (CH), 35.8 (CH_2), 31.5 (CH_2), 28.9 (CH_2), 26.0 (CH_3), 20.2 (CH_2), 18.2 (CH_3); GC t_R = 12.1 min; LRMS

[160] Prepared as described in: Altendorfer, M.; Raja, A.; Sasse, F.; Irschik, H.; Menche, D. *Org. Biomol. Chem.* **2013**, *11*, 2116.

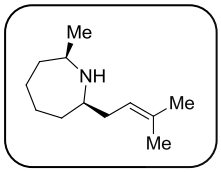
(EI) *m/z* (%) 167 (M^+, 0.5), 99 (6), 98 (100), 70 (7), 55 (28); Anal. Calc'd for $C_{10}H_{17}NO$: C 71.81, H 10.25, N 8.37; Found: C 71.93, H 10.04, N 8.15.

(*S*)-6-Prenyl-2-piperidinone (*ent*-32n)



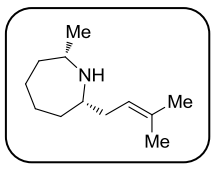
Compound *ent*-**32n** was obtained using *ent*-**30b** as chiral donor: The spectroscopical data was identical to **32n**, except for $[\alpha]^{20}_D$ – 6.5 (*c* 0.95, $CHCl_3$).

(2*R*,7*R*)-2-Methyl-7-prenylazepane (32o)



Following the general procedure from 6-Oxoheptanal,[161] However, instead of adding $HONH_2 \cdot AcOH$ to the arranged mixture, $NaBH_3CN$ (1.8 mmol, 114 mg) was added and the reaction was stirred for 12 h at room temperature. Then, the reaction mixture was diluted with EtOAc (5mL) and NaOH (2 M, 5 mL), and extracted with EtOAc (3 x 5mL), washed with NaOH (2 M, 5 mL) and brine (5 mL). Organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (gradient from 97:3 CH_2Cl_2/MeOH to 90:10:0.05 CH_2Cl_2/MeOH/20% NH_4OH) to provide the desired azepane **32o** as a yellow oil (20 mg, 0.110 mmol, 37%): $[\alpha]^{20}_D$ – 1.5 (*c* 1.10, $CHCl_3$); R_f 0.37 (9:1 CH_2Cl_2/MeOH); IR ν 3311, 2962, 2924, 2855, 1678, 1450, 1375, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 – 5.04 (m, 1H), 2.82 (dqd, *J* = 9.6, 6.4, 3.3 Hz, 1H), 2.67 (ddd, *J* = 10.0, 7.2, 3.2 Hz, 1H), 2.24 – 2.02 (m, 2H), 1.78 – 1.73 (m, 2H), 1.72 (d, *J* = 0.9 Hz, 3H), 1.71 – 1.64 (m, 3H), 1.62 (s, 3H), 1.61 – 1.50 (m, 2H), 1.49 – 1.36 (m, 2H), 1.14 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4 (C), 121.5 (CH), 59.7 (CH), 55.2 (CH), 38.0 (CH_2), 35.9 (CH_2), 35.7 (CH_2), 25.8 (CH_3), 25.3 (CH_2), 25.0 (CH_2), 23.6 (CH_3), 18.0 (CH_3); GC t_R = 9.2 min; LRMS (EI) *m/z* (%) 181 (M^+, 1), 113 (8), 112 (100), 95 (10), 82 (5), 69 (7), 56 (6); HRMS (ES^+) calcd for $C_{12}H_{24}N$ 182.1909, found 182.1906.

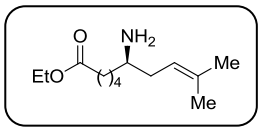
(2*S*,7*S*)-2-Methyl-7-prenylazepane (*ent*-32o)



Compound *ent*-**32o** was obtained using *ent*-**30b** as chiral donor: The spectroscopical data was identical to **32o**, except for $[\alpha]^{20}_D$ + 1.8 (*c* 0.95, $CHCl_3$).

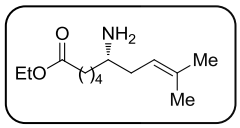
[161] Prepared as described in: Nicolaou, K. C.; Adsool, V. A.; Hale C. R. H. *Org. Lett.* **2010**, *12*, 1552.

(*R*)-Ethyl 6-amino-9-methyl-8-decenoate (32p)



Following the general procedure from Ethyl 6-oxohexanoate,[162] but in a larger scale (1.45 mmol of donor **30b**), compound **32p** was obtained as a yellow oil after column chromatography (286 mg, 1.261 mmol, 87%): $[\alpha]^{20}_D$ – 5.3 (*c* 1.20, $CHCl_3$); R_f 0.30 (1:3 Hexane:EtOAc); IR ν 3439, 3370, 2972, 2928, 2860, 1733, 1248, 1179, 851, 722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.13 (dd, *J* = 7.9, 6.9 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.77 (br s, 1H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.23 (br s, 2H), 2.18 – 1.94 (m, 2H), 1.73 (s, 3H), 1.70 – 1.65 (m, 1H), 1.63 (s, 3H), 1.62 – 1.54 (m, *J* = 13.0 Hz, 1H), 1.55 – 1.40 (m, 2H), 1.40 – 1.30 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8 (C), 134.5 (C), 121.1 (CH), 60.3 (CH_2), 51.7 (CH), 36.8 (CH_2), 36.3 (CH_2), 34.4 (CH_2), 26.03 (CH_3), 25.9 (CH_2), 25.1 (CH_2), 18.2 (CH_3), 14.4 (CH_3); GC t_R = 12.5 min; LRMS (EI) *m/z* (%) 227 (M^+, 0.1), 182 (9), 159 (9), 158 (100), 140 (13), 113 (8), 112 (72), 84 (17), 81 (12), 69 (27), 67 (17), 56 (23); Anal. Calc'd for $C_{13}H_{25}NO_2$: C 68.68, H 11.08, N 6.16; Found: C 68.30, H 10.71, N 5.79.

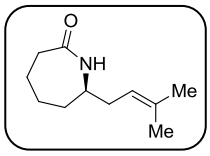
(*S*)-Ethyl 6-amino-9-methyl-8-decenoate (*ent*-32p)



Compound *ent*-**32p** was obtained using *ent*-**30b** as chiral donor: The spectroscopical data was identical to **32p**, except for $[\alpha]^{20}_D$ + 5.5 (*c* 0.95, $CHCl_3$).

Procedures for the synthesis of compounds 33, ent-33, 32a-Ns, 32p-Ns and pyrrolidines 34a and 34p.

(*R*)-7-Prenyl-2-azepanone (33)

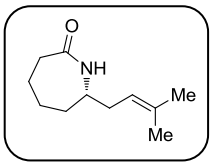


To a solution of aminoesther **32p** (59 mg, 0.261 mmol) in dry MeOH (3 mL) was added dropwise a freshly prepared 2M solution of NaOMe at 0 ºC. The reaction mixture was allowed to reach room temperature and stirred for 12 h, before being quenched with an ammonia buffer [NH_3(2M)/NH_4Cl (2M)]. The mixture was extracted with EtOAc (3 times), washed with water, dried over $MgSO_4$, filtered and concentrated under vacuum. After column chromatography, the desired product was isolated as a white solid (38 mg, 0.207 mmol, 71%): mp 75.2 – 78.5 ºC; $[\alpha]^{20}_D$ + 10.5 (*c* 1.10, $CHCl_3$); R_f 0.26 (1:3 Hexane:EtOAc); IR ν 3290, 3212, 3081, 2924, 2850, 1656, 1437, 1417, 1344, 1201, 856 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.46 (br s, 1H), 5.14 – 5.03 (m, 1H), 3.43 – 3.27 (m, 1H), 2.45 (dd, *J* = 8.5, 3.4 Hz, 2H), 2.18 (dd, *J* = 8.1, 7.0 Hz, 2H), 2.05 – 1.94 (m, 1H), 1.89 – 1.77 (m, 2H), 1.72 (d, *J* = 1.0 Hz, 3H), 1.63 (s, 3H), 1.59 – 1.48 (m, 2H), 1.44 – 1.28 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8 (C), 136.0 (C), 119.5 (CH), 53.8 (CH), 37.2 (CH_2), 35.7

[162] Prepared from Ethyl hept-6-enoate by oxidative cleavage of the double bond with OsO_4 cat./$NaIO_4$.

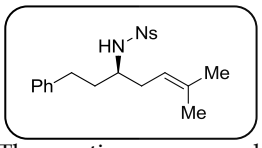
(CH_2), 35.0 (CH_2), 30.0 (CH_2), 26.0 (CH_3), 23.3 (CH_2), 18.1 (CH_3); GC t_R = 12.8 min; LRMS (EI) *m/z* (%) 181 (M^+, 0.6), 113 (7), 112 (100), 84 (19), 81 (9), 69 (32), 67 (20), 55 (10); Anal. Calc'd for $C_{11}H_{19}NO$: C 72.88, H 10.56, N 7.73; Found: C 72.65, H 10.69, N 8.04.

(*S*)-7-Prenyl-2-azepanone (*ent*-33)



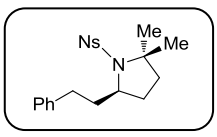
Compound *ent*-**33** was obtained from *ent*-**32p** following the same precedure described for compound **33**: The spectroscopical data was identical to **5**, except for $[\alpha]^{20}_D$ – 10.2 (*c* 0.95, $CHCl_3$).

(*R*)-*p*-Nosylate of 32a (32a-Ns)



To a solution of free amine **32a** (202 mg, 1.00 mmol) in CH_2Cl_2 (9 mL) at 0 °C, were added Et_3N (211 µL, 1.49 mmol) and *p*-nitrobenzenesulfonyl chloride (264 mg, 1.19 mmol). The solution was allowed to warm to 25 °C and stirred over 12 h. The reaction was quenched with HCl (1M), and after phase separation, the organic layer was washed with NaOH (1M), followed by water and brine. Evaporation of the solvent under vacuum gave crude **32a**-Ns, which was purified by column chromatography (9:1 Hexane/EtOAc) to provide the desired product as a white solid (360 mg, 86 %): mp 72.8 - 75.2 °C; $[\alpha]^{20}_D$ - 8.6 (*c* 1.03, $CHCl_3$); R_f 0.34 (8:2 Hexane/EtOAc); IR ν 3290, 3027, 2925, 1605, 1528, 1347, 1308, 1160, 1091, 852, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (dt, *J* = 9.0, 2.2 Hz, 2H), 7.98 (dt, *J* = 8.9, 2.2 Hz, 2H), 7.29 – 7.27 (m, 1H), 7.25 – 7.23 (m, 1H), 7.23 – 7.16 (m, 1H), 7.09 – 7.05 (m, 2H), 4.84 (ddd, *J* = 7.5, 4.4, 1.3 Hz, 1H), 4.56 (s, 1H), 3.41 – 3.26 (m, 1H), 2.67 – 2.50 (m, 2H), 2.18 (dt, *J* = 13.6, 6.7 Hz, 1H), 2.13 – 2.05 (m, 1H), 1.88 – 1.78 (m, 1H), 1.73 (ddt, *J* = 14.0, 9.3, 7.0 Hz, 1H), 1.61 (d, *J* = 0.6 Hz, 3H), 1.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2 (C), 147.0 (C), 141.0 (C), 136.5 (C), 128.7 (CH), 128.4 (CH), 128.4 (CH), 126.3 (CH), 124.4 (CH), 118.2 (CH), 54.4 (CH), 36.6 (CH_2), 33.4 (CH_2), 31.9 (CH_2), 26.1 (CH_3), 18.1 (CH_3); GC t_R = 24.3 min; LRMS (EI) *m/z* (%) 319 (22), 289 (4), 156 (10), 122 (5), 118 (10), 117 (100), 92 (12), 91 (93), 69 (6), 65 (5); HRMS (TOF) calcd for $C_{20}H_{24}N_2O_4S$ 389.1530, found 389.1535.

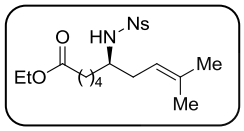
(*R*)- 1-(*p*-nosyl)-2,2-dimethyl-5-(3'-phenylethyl)pyrrolidine (34a)



Trifluoromethanesulfonic acid (10 µL, 0.1 mmol) was added to a solution of **32a**-Ns (179 mg, 0.5 mmol) in dry toluene (35 mL) and the reaction mixture was stirred at 0 °C for 1 h. After concentrate under reduced pressure, the residue was purified by column chromatography (9:1 Hexane/EtOAc) to provide the desired pyrrolidine **34a** as a white solid (164 mg, 0.46 mmol, 93%): mp 86.8 - 89.1 °C; $[\alpha]^{20}_D$ – 59.4 (*c* 1.05, $CHCl_3$); R_f 0.30 (9:1 Hexane/EtOAc); IR ν 2959, 2922, 1525, 1342, 1151, 855, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.36 – 7.30 (m, 2H), 7.30 – 7.26 (m,

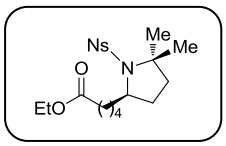
0.7), 7.25 – 7.23 (m, 0.3 H), 7.21 – 7.14 (m, 2H), 3.68 – 3.57 (m, 1H), 2.72 (ddd, *J* = 13.4, 8.5, 4.6 Hz, 1H), 2.50 (dt, *J* = 13.9, 8.4 Hz, 1H), 2.33 – 2.22 (m, 1H), 2.07 – 1.93 (m, 1H), 1.85 – 1.69 (m, 4H), 1.60 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6 (C), 147.6 (C), 141.0 (C), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.3 (CH), 124.1 (CH), 67.1 (C), 61.4 (CH), 40.6 (CH_2), 36.6 (CH_2), 32.9 (CH_2), 31.5 (CH_3), 27.1 (CH_2), 26.6 (CH_3); GC t_R = 24.0 min; LRMS (EI) *m/z* (%) 388 (M^+, 1), 373 (5), 284 (14), 283 (100), 253 (4), 186 (5), 156 (5), 122 (12), 117 (6), 105 (5), 98 (13), 92 (7), 91 (25), 82 (17), 81 (82), 79 (5); HRMS (ES^+) calcd for $C_{20}H_{24}N_2O_4S$ 389.1530, found 3890.1528.

(*R*)-*p*-Nosylate of 32p (32p-Ns)



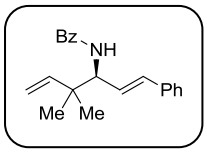
Compound **32p**-Ns was obtained from free amine **32p** (265 mg, 1.17 mmol) following the procedure described for **32a**-Ns, obtaining the desired product as a yellow wax (420 mg, 1.02 mmol, 88 %): $[\alpha]^{20}_D$ + 6.0 (*c* 0.95, $CHCl_3$); R_f 0.28 (8:2 Hexane/EtOAc); IR ν 3280, 2931, 2863, 1730, 1529, 1348, 1307, 1160, 1091, 853, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 9.0 Hz, 2H), 8.04 (d, *J* = 9.0 Hz, 2H), 4.83 (ddd, *J* = 7.5, 6.1, 1.4 Hz, 1H), 4.54 (d, *J* = 8.4 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.38 – 3.23 (m, 1H), 2.22 (t, *J* = 7.4 Hz, 2H), 2.18 – 1.94 (m, 2H), 1.60 (s, 3H), 1.55 (d, *J* = 7.5 Hz, 2H), 1.50 (s,3H), 1.49 – 1.28 (m, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.22 – 1.13 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C), 150.1 (C), 147.3 (C), 136.2 (C), 128.4 (CH), 124.4 (CH), 118.4 (CH), 60.5 (CH_2), 54.8 (CH), 34.8 (CH_2), 34.1 (CH_2), 33.6 (CH_2), 26.0 (CH_3), 25.2 (CH_2), 24.7 (CH_2), 18.1 (CH_3), 14.4 (CH_3); GC t_R = 25.9 min; LRMS (EI) *m/z* (%) 344 (6), 343 (36), 313 (8), 299 (9), 298 (16), 297 (100), 281 (9), 269 (11), 207 (24), 186 (6), 157 (5), 156 (17), 122 (13), 95 (28), 69 (71); HRMS (ES^+) calcd for $C_{19}H_{29}N_2O_6S$ 413.1746, found 413.1732.

(*R*)-Ethyl 5-(5,5-dimethyl-1-(*p*-nosyl)pyrrolidin-2-yl)pentanoate (34p)



Compound **34p** was obtained from compound **32p**-Ns (412 mg, 1.0 mmol) following the procedure described for **34a**, obtaining the desired product as a yellow oil (380 mg, 0.92 mmol, 93%): $[\alpha]^{20}_D$ – 29.3 (*c* 0.95, $CHCl_3$); R_f 0.40 (8:2 Hexane/EtOAc); IR ν 3110, 2970, 2939, 2869, 1731, 1528, 1462, 1347, 1305, 1152, 1092, 854, 736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 9.0 Hz, 2H), 8.05 (d, *J* = 9.1 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.80 (ddd, *J* = 9.4, 6.6, 2.9 Hz, 1H), 2.29 (t, *J* = 7.4 Hz, 2H), 2.07 – 1.59 (m, 7H), 1.58 (s, 3H), 1.57 – 1.42 (m, 2H), 1.36 – 1.32 (m, 1H), 1.31 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C), 149.7 (C), 148.7 (C), 128.5 (CH), 124.2 (CH), 66.7 (C), 62.9 (CH), 60.4 (CH_2), 40.7 (CH_2), 35.4 (CH_2), 34.2 (CH_2), 31.3 (CH_3), 27.3 (CH_2), 27.0 (CH_3), 26.2 (CH_2), 24.8 (CH_2), 14.4 (CH_3); GC t_R = 26.5 min; LRMS (EI) *m/z* (%) 367 (10), 285 (5), 284 (15), 283 (100), 253 (3), 226 (33), 97 (5), 82 (9), 81 (42); HRMS (ES^+) calcd for $C_{19}H_{29}N_2O_6S$ 413.1746, found 413.1740.

Determination of the enantiomeric ratio of donor 31b.



To a solution of *crude compound* **30b** (30 mg, 0.10 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise a solution of HCl in 1,4-dioxane (4 M, 0.40 mmol, 100µL) at 0 ºC under Ar atmosphere. After 1h the deprotection was finished (according TLC) and the solvent and volatiles (*t*-$BuSO_2Me$) were carefully removed under reduced pressure. To the obtained crude **31b** was added dry CH_2Cl_2 (0.2 mL) and the resulting solution was cooled to 0 ºC. A 2M solution of NaOH (150 µL) was added to the reaction mixture, followed by a dropwise addition of Benzoyl chloride (23 µL, 0.2 mmol). The reaction mixture was stirred for 12 h at room temperature before being quenched with an aqueous solution of NaOH (2M, 0.5 mL). Phase separation was followed by extraction of the aqueous layer with EtOAc (3 x 3 mL) and the combined organic layers were washed with NaOH (2M) followed by brine. Organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure giving the expected product (31 mg, 95 %, 93:7 er by chiral HPLC on a Chiracel ODH column, n-Hexane/i-PrOH 95:5, 1 mL/min, λ=220 nm).

Pure product **30b** was submitted to the same procedure described above for crude **30b**, obtaining Benzamide of **31b** (29 mg, 95 %, 99:1 er by chiral HPLC on a Chiracel ODH column, *n*-Hexane/*i*-PrOH 95:5, 1 mL/min, λ=220 nm): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.72 (m, 2H), 7.55 – 7.40 (m, 3H), 7.40 – 7.28 (m, 4H), 7.25 – 7.17 (m, 1H), 6.59 (d, *J* = 15.8 Hz, 1H), 6.25 (d, *J* = 7.1 Hz, 1H), 6.20 (d, *J* = 7.0 Hz, 1H), 5.97 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.28 – 5.09 (m, *J* = 29.4 Hz, 2H), 4.77 – 4.66 (m, 1H), 1.17 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (C), 144.0 (CH), 136.7 (C), 134.8 (C), 132.4 (CH), 131.5 (CH), 128.7 (CH), 128.5 (CH), 127.6 (CH), 126.8 (CH), 126.6 (CH), 126.5 (CH), 114.5 (CH_2), 58.8 (C), 41.3 (CH), 25.0 (CH_3), 23.7 (CH_3).

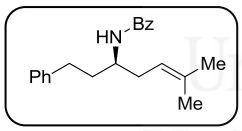
Determination of the enantiomeric ratio of amines 32a, 32c, 32f – 32l, 32o and 32p: *General procedure for benzoylation.*

A solution of the corresponding free amine **30** (0.10 mmol) in CH_2Cl_2 (0.2 mL) was cooled to 0 ºC and a solution of NaOH (100 µL, 2 M) was added to the reaction mixture, followed by the dropwise addition of Benzoyl chloride (23 µL, 0.2 mmol). After being stirred for 12 h at room temperature, an aqueous solution of NaOH (0.5 mL, 2 M) was added and the aqueous layer was extracted with EtOAc (3 x 3 mL) and the combined organic layers were washed with NaOH (2 M) and brine. Organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the expected product quantitatively, which was directly submitted to HPLC analysis.

This table summarizes the HPLC results obtained for the obtained benzamides, using a Chiracel ODH column (detection at λ=220 nm) with a flow of 1.0 mL/min (except for benzamide of 32c, 0.5 mL/min).

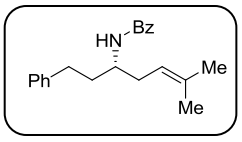
Benzamide	Solvent system *n*-Hexane/*i*-PrOH	t_R major (min)	t_R minor (min)	er (**32**/*ent*-**32**)
Benzamide of **32a**	95:5	30.4	23.9	88(*R*):12(*S*)
Benzamide of **32c**	95:5	20.8	18.5	82(*R*):18(*R*)
Benzamide of **32f**	95:5	37.7	42.0	89(*E*,*S*):11(*E*,*R*)
Benzamide of **32g**	95:5	31.8	20.8	89(*S*):11(*R*)
Benzamide of **32h**	95:5	32.8	21.4	89(*S*):11(*R*)
Benzamide of **32i**	95:5	29.5	18.9	89(*S*):11(*R*)
Benzamide of **32j**	95:5	18.4	14.9	92(*S*):8(*R*)
Benzamide of **32k**	90:10	36.5	30.1	90(*S*):10(*R*)
Benzamide of **32l**	95:5	37.8	28.0	94(*S*):6(*R*)
Benzamide of **32o**	98:2	17.0	20.8	86(2*R*,7*R*):14(2*S*,7*S*)
Benzamide of **32p**	95:5	20.5	30.1	85(*R*):15(*S*)

Benzamide of (*R*)-32a.



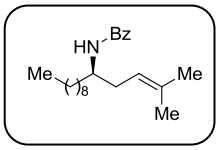
Following the general procedure for benzoylation from compound (*R*)-**32a**, Benzamide of (*R*)-**32a** was obtained as a white solid; R_f 0.61 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 – 8.13 (m, 1H), 7.74 – 7.64 (m, 2H), 7.60 – 7.38 (m, 3H), 7.33 – 7.27 (m, 1H), 7.25 – 7.13 (m, 3H), 5.90 (d, *J* = 8.8 Hz, 1H), 5.19 (t, *J* = 7.4 Hz, 1H), 4.35 – 4.17 (m, 1H), 2.73 (t, *J* = 8.0 Hz, 2H), 2.49 – 2.20 (m, 2H), 2.09 – 1.75 (m, 2H), 1.72 (s, 3H), 1.63 (s, 3H); GC t_R = 18.5 min; LRMS (EI) *m/z* (%) 307 (M^+, 0.1), 238 (41), 186 (10), 122 (33), 117 (16), 105 (100), 95 (14), 77 (29).

Benzamide of (*S*)-32a.



Following the general procedure for benzoylation from compound (*S*)-**32a**, Benzamide of (*S*)-**32a** was obtained as a white solid showing spectroscopical data identical to the one described for Benzamide of (*R*)-**32a**.

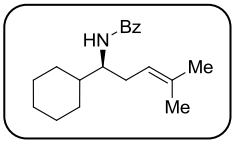
Benzamide of (*R*)-32b.



Following the general procedure for benzoylation from compound (*R*)-**32b**, Benzamide of (*R*)-**32b** was obtained as a yellow oil. In this case the HPLC analysis was unsuccessful and the ratio was determined by ^{1}H-NMR analysis of the MPA derivative (MPA-**32b**):

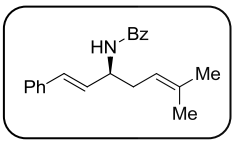
R_f 0.37 (9:1 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2H), 7.53 – 7.39 (m, 3H), 5.86 (d, *J* = 9.1 Hz, 1H), 5.18 (t, *J* = 7.4 Hz, 1H), 4.14 (dt, *J* = 14.3, 7.0 Hz, 1H), 2.35 (dt, *J* = 13.6, 6.7 Hz, 1H), 2.28 – 2.15 (m, 1H), 1.72 (s, 3H), 1.62 (s, 3H), 1.44 – 1.35 (m, *J* = 4.9 Hz, 2H), 1.35 – 1.14 (m, 14H), 0.87 (t, *J* = 6.7 Hz, 3H); GC t_R = 18.3 min; LRMS (EI) *m/z* (%) 328 (M^+, 0.1), 261 (10), 260 (48), 208 (6), 122 (6), 106 (10), 105 (100), 77(14).

Benzamide of (*S*)-32c.



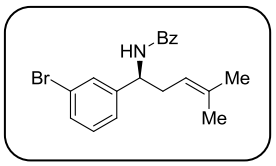
Following the general procedure for benzoylation from compound (*S*)-**32c**, Benzamide of (*S*)-**32c** was obtained as a white solid; R_f 0.61 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.33 (m, 5H), 5.88 (d, *J* = 9.1 Hz, 1H), 5.16 (t, *J* = 7.2 Hz, 1H), 4.14 – 3.94 (m, 1H), 2.48 – 2.29 (m, 1H), 2.29 – 2.11 (m, 1H), 1.76 (d, *J* = 10.2 Hz, 4H), 1.70 (s, 3H), 1.61 (s, 3H), 1.51 (ddd, *J* = 14.7, 9.9, 3.2 Hz, 1H), 1.35 – 0.95 (m, 6H); GC t_R = 17.2 min; LRMS (EI) *m/z* (%) 285 (M^+, 0.1), 217 (15), 216 (95), 134 (3), 122 (11), 106 (8), 105 (100), 77 (25).

Benzamide of (*E, S*)-32f.



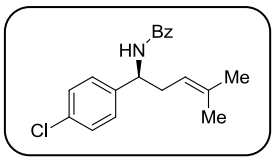
Following the general procedure for benzoylation from compound (*E,S*)-**32f**, Benzamide of (*E,S*)-**32f** was obtained as a white solid; R_f 0.56 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.1 Hz, 2H), 7.57 – 7.41 (m, 4H), 7.41 – 7.28 (m, 4H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.24 (dd, *J* = 16.0, 5.9 Hz, 1H), 6.17 (d, *J* = 7.9 Hz, 1H), 5.23 (t, *J* = 7.5 Hz, 1H), 4.99 – 4.85 (m, 1H), 2.49 (qt, *J* = 15.1, 7.4 Hz, 2H), 1.74 (s, 3H), 1.68 (s, 3H); GC t_R = 19.3 min; LRMS (EI) *m/z* (%) 305 (M^+, 0.6), 237 (13), 236 (71), 169 (3), 115 (7), 106 (8), 105 (100), 77 (27).

Benzamide of (*S*)-32g.



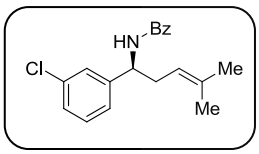
Following the general procedure for benzoylation from compound (*S*)-**32g**, Benzamide of (*S*)-**32g** was obtained as a white solid; R_f 0.55 (8:2 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.71 (m, 2H), 7.62 – 7.34 (m, 6H), 7.20 (t, *J* = 7.7 Hz, 1H), 6.37 (d, *J* = 7.4 Hz, 1H), 5.15 (dd, *J* = 14.2, 7.0 Hz, 1H), 5.12 – 5.02 (m, 1H), 2.60 (d, *J* = 6.5 Hz, 2H), 1.71 (d, *J* = 0.9 Hz, 3H), 1.63 (s, 3H); GC t_R = 18.9 min; LRMS (EI) *m/z* (%) 291 (3), 290 (16), 289 (3), 288 (16), 238 (4), 236 (4), 184 (2), 182 (2), 142 (4), 106 (8), 105 (100), 77 (29).

Benzamide of (*S*)-32h.



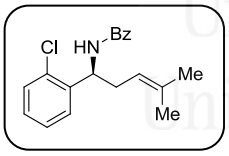
Following the general procedure for benzoylation from compound (*S*)-**32h**, Benzamide of (*S*)-**32h** was obtained as a white solid; R_f 0.60 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.70 (m, 2H), 7.62 – 7.36 (m, 3H), 7.36 – 7.27 (m, 4H), 6.38 (d, *J* = 7.5 Hz, 1H), 5.16 (q, *J* = 6.9 Hz, 1H), 5.07 (dddd, *J* = 7.2, 5.9, 2.7, 1.3 Hz, 2H), 2.59 (t, *J* = 7.0 Hz, 3H), 1.70 (d, *J* = 1.0 Hz, 1H), 1.63 (s,3H); GC t_R = 18.4 min; LRMS (EI) *m/z* (%) 314 (M^+, 0.3), 246 (11), 245 (7), 244 (31), 192 (7), 177 (5), 106 (8), 105 (100), 77 (30).

Benzamide of (*S*)-32i.



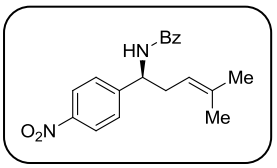
Following the general procedure for benzoylation from compound (*S*)-**32i**, Benzamide of (*S*)-**32i** was obtained as a white solid; R_f 0.60 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 – 7.73 (m, 2H), 7.56 – 7.40 (m, 3H), 7.35 – 7.30 (m, 1H), 7.26 – 7.17 (m, 2H), 6.38 (br d, *J* = 7.1 Hz, 1H), 5.16 (dd, *J* = 14.0, 6.9 Hz, 1H), 5.08 (t, *J* = 7.2 Hz, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.71 (d, *J* = 0.9 Hz, 3H), 1.64 (br s, 5H); GC t_R = 18.2 min; LRMS (EI) *m/z* (%) 314 (M^+, 0.3), 246 (11), 245 (5), 244 (33), 192 (7), 177 (4), 106 (8), 105 (100), 77 (29).

Benzamide of (*S*)-32j.



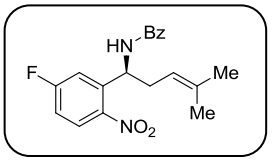
Following the general procedure for benzoylation from compound (*S*)-**32j**, Benzamide of (*S*)-**32j** was obtained as a white solid; R_f 0.51 (8:2 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.03 (m, 2H), 7.84 – 7.33 (m, 8H), 6.67 (d, *J* = 7.4 Hz, 1H), 5.48 (dd, *J* = 14.0, 7.4 Hz, 1H), 5.18 – 5.05 (m, 1H), 2.78 – 2.54 (m, 5H), 1.70 (d, *J* = 1.0 Hz, 3H), 1.62 (s, 3H); GC t_R = 18.4 min; LRMS (EI) *m/z* (%) 314 (M^+, 0.3), 246 (12), 245 (5), 244 (30), 192 (7), 177 (4), 106 (9), 105 (100), 77 (29).

Benzamide of (*S*)-32k.



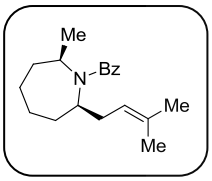
Following the general procedure for benzoylation from compound (*S*)-**32k**, Benzamide of (*S*)-**32k** was obtained as a white solid; R_f 0.47 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 8.15 (m, 2H), 7.80 – 7.74 (m, 2H), 7.57 – 7.42 (m, 5H), 6.52 (d, *J* = 6.6 Hz, 1H), 5.22 (q, *J* = 6.8 Hz, 1H), 5.07 (t, *J* = 7.3 Hz, 1H), 2.62 (tq, *J* = 14.5, 7.2 Hz, 2H), 1.72 (d, *J* = 0.7 Hz, 3H), 1.64 (s, 3H); GC t_R = 22.9 min; LRMS (EI) *m/z* (%) 256 (9), 255 (43), 204 (2), 203 (13), 156 (2), 142 (4), 106 (8), 105 (100), 78 (3), 77 (27).

Benzamide of (*S*)-32l.



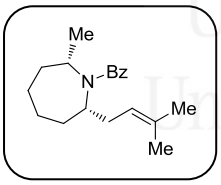
Following the general procedure for benzoylation from compound (*S*)-**32l**, Benzamide of (*S*)-**32l** was obtained as a white solid; R_f 0.49 (7:3 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.53 – 7.40 (m, 3H), 7.22 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.07 (ddd, *J* = 9.1, 7.1, 2.8 Hz, 1H), 6.75 (d, *J* = 6.0 Hz, 1H), 5.63 (dd, *J* = 13.9, 6.1 Hz, 1H), 5.15 (dddd, *J* = 7.4, 6.1, 2.7, 1.4 Hz, 1H), 2.83 – 2.70 (m, 1H), 2.68 – 2.51 (m, 1H), 1.74 (d, *J* = 0.9 Hz, 3H), 1.66 (s, 3H); GC t_R = 19.0 min; LRMS (EI) *m/z* (%) 342 (M^+, 0.08), 274 (3), 273 (15), 188 (3), 148 (3), 137 (3), 122 (6), 106 (8), 105 (100), 77 (27).

Benzamide of (2*R*, 7*R*)-32o.



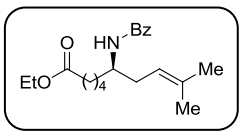
Following the general procedure for benzoylation from compound (2*R*, 7*R*)-**32o**, Benzamide of (2*R*, 7*R*)-**32o** was obtained as a white solid: R_f 0.33 (8:2 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.36 (m, 5H), 5.23 (br s, 0.5H), 5.03 – 4.85 (m, 1H), 4.85 – 4.74 (m, 0.5H), 4.18 – 4.04 (m, 0.5H), 3.97 – 3.82 (m, 0.5H), 2.60 – 2.20 (m, 2H), 2.17 – 1.88 (m, 2H), 1.85 – 1.24 (m, 14H); GC t_R = 16.8 min; LRMS (EI) *m/z* (%) 285 (M^+, 0.2), 217 (11), 216 (75), 105 (100), 77 (19).

Benzamide of (2*S*, 7*S*)-32o.



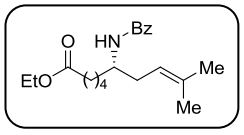
Following the general procedure for benzoylation from compound (2*S*, 7*S*)-**32o**, Benzamide of (2*S*, 7*S*)-**32o** was obtained with identical spectroscopical data as the one described for Benzamide of (2*R*, 7*R*)-**32o.**

Benzamide of (*R*)-32p.



Following the general procedure for benzoylation from compound (*R*)-**32p**, Benzamide of (*R*)-**32p** was obtained as a yellow oil; R_f 0.50 (8:2 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.64 (m, 2H), 7.54 – 7.39 (m, 3H), 5.89 (br d, *J* = 8.9 Hz, 1H), 5.17 (t, *J* = 7.4 Hz, 1H), 4.27 – 3.94 (m, 3H), 2.44 – 2.12 (m, 4H), 1.72 (s, 3H), 1.66 (d, *J* = 5.1 Hz, 1H), 1.62 (s, 3H), 1.53 – 1.33 (m, 2H), 1.27 – 1.18 (m, 6H); GC t_R = 18.7 min; LRMS (EI) *m/z* (%) 331 (M^+, 0.2), 263 (8), 262 (47), 216 (16), 164 (8), 122 (6), 106 (8), 105 (100), 77 (18).

Benzamide of (*S*)-32p.



Following the general procedure for benzoylation from compound (*S*)-**32p**, Benzamide of (*S*)-**32p** was obtained with identical spectroscopical data as the one described for Benzamide of (*R*)-**32p**.

Determination of the enantiomeric ratio of lactams 32m, 32n and 33.

Lactams **32m**, **32n** and **33** were directly submitted to HPLC analysis without further derivatization. This table summarizes the HPLC results obtained for the obtained benzamides, using a Chiracel ODH column (UV detection at λ=220 nm) with a flow of 1.0 mL/min.

Lactam	Solvent system *n*-Hexane/*i*-PrOH	t_R (*R*) (min)	t_R (*S*) (min)	er (*R*)/(*S*)
32m	90:10	8.1	9.5	88:12
32n	90:10	8.6	10.2	71:29
33	97:3	17.7	20.7	85:15

Determination of the diastereomeric ratio of amines 32d and 32e.

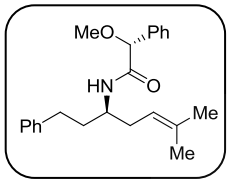
For these two compounds the diastereomeric ratio was estimated by comparing the ^{13}C-NMR spectra of both diastereoisomers. The relative height was measured for each pair of signals corresponding to the same carbon and the average of well resolved pair of signals was taken as diastereomeric ratio of amines **32d** (81:19 dr) and **32e** (93:7 dr).

Determination of the absolute configuration of amines 32a, 32b and 32k:
General procedure for the formation of MPA amides.

To a solution of (*R*)-α-Methoxyphenylacetic acid (83 mg, 0.5 mmol) in dry CH_2Cl_2 (2 mL) were added the corresponding free amine (0.5 mmol), DMPA (61 mg, 0.5 mmol) and EDC (115 mg, 0.6 mmol). The reaction mixture was stirred for 2 h at 23 ºC. The organic layer was washed sequentially with water, HCl (1 M), water, saturated $NaHCO_3$ aqueous solution and brine. The residue was dried over $MgSO_4$, filtered and concentrated at reduced pressure without further purification.

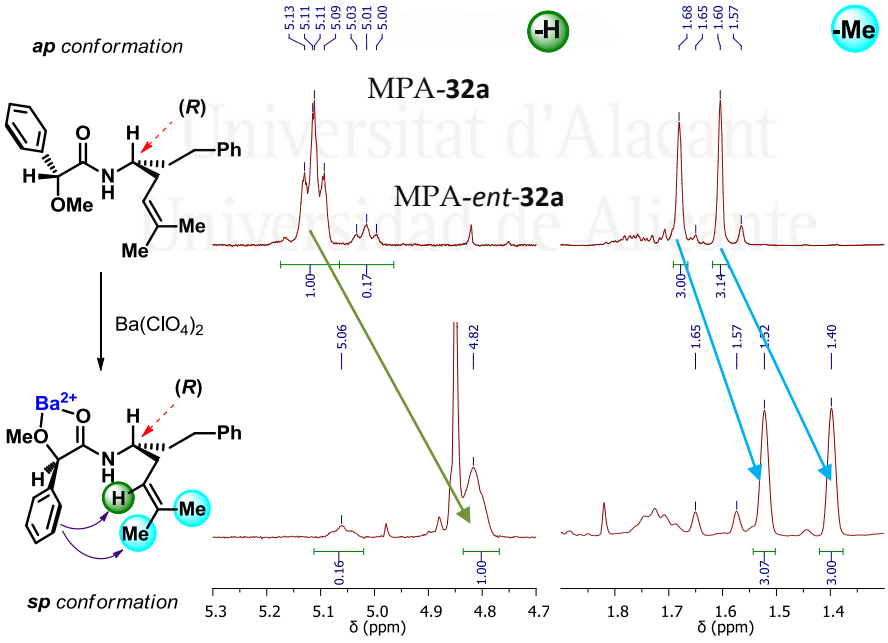
As described by the group of Riguera,[158] the addition of Ba^{2+} to the NMR sample of MPA amides *should shift the equilibrium from an antiperiplanar to a synperiplanar conformation*, which lead to an increase shielding of the vinylic signals by the phenyl group of the MPA auxiliary. Following this protocol, two experiments of ^1H NMR in CD_3CN were performed for each amide, before and after the addition of $Ba(ClO_4)_2$. The most relevant signals for the determination of absolute configuration of the selected amides are shown below.

(*R*)-MPA-32a.

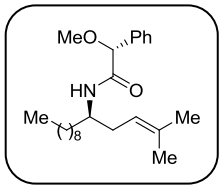


Following the general procedure of formation of MPA amides from amine **32a**, compound MPA-**32a** was obtained as a colorless oil:

^1H NMR (400 MHz, CD_3CN) δ 7.46 – 7.02 (m, 10H), 6.89 (d, *J* = 9.1 Hz, 1H), 5.11 (dd, *J* = 8.0, 6.7 Hz, 1H), 4.57 (s, 1H), 3.89 – 3.72 (m, 1H), 3.34 (s, 3H), 2.55 – 2.36 (m, 2H), 2.30 – 2.13 (m, 4H), 1.68 (s, 3H), 1.60 (s, 3H); *after the addition of 100 mg of* $Ba(ClO_4)_2$: ^1H NMR (400 MHz, CD_3CN) δ 7.54 – 7.07 (m, 10H), 6.84 (d, *J* = 9.3 Hz, 1H), 4.81 (s, 1H), 4.76 (br s, 1H), 3.86 – 3.76 (m, 1H), 3.31 – 3.23 (m, 3H), 2.59 – 2.39 (m, 2H), 2.18 – 1.96 (m, 4H), 1.47 (s, 3H), 1.35 (s, 3H).



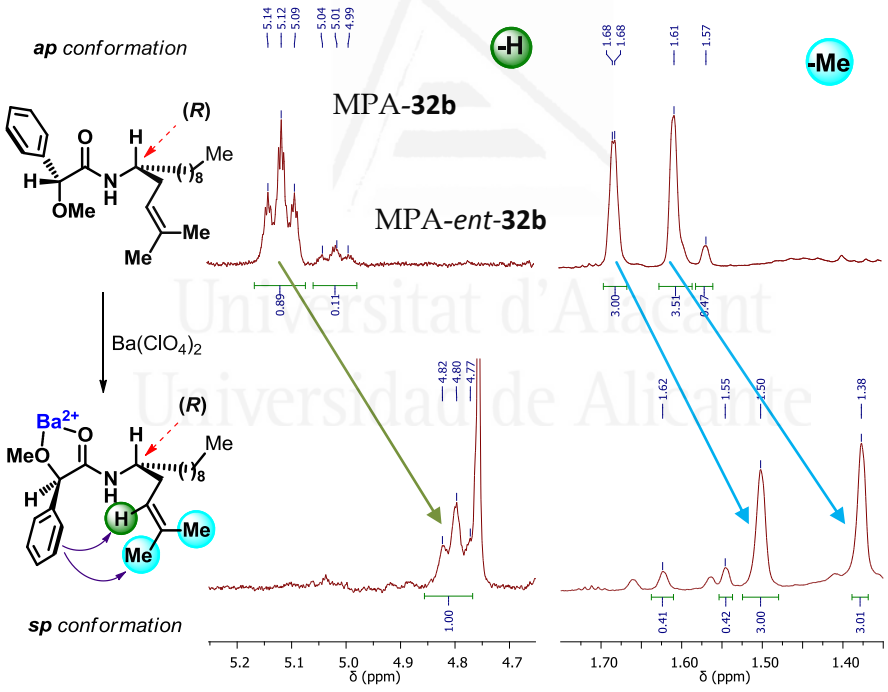
(*R*)-MPA-32b.



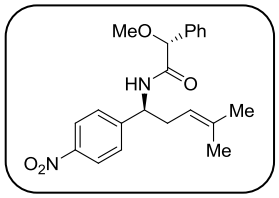
Following the general procedure of formation of MPA amides from amine **32b**, compound MPA-**32b** was obtained as a colorless oil:

^{1}H NMR (400 MHz, CD_3CN) δ 7.42 – 7.30 (m, 5H), 6.76 (d, *J* = 8.9 Hz, 1H), 5.19 – 5.04 (m, 1H), 4.53 (s, 1H), 3.85 – 3.69 (m, 1H), 3.32 (s, 3H), 1.68 (d, *J* = 0.9 Hz, 3H), 1.61 (s, 3H), 1.33 – 1.07 (m, 18H), 0.88 (t, *J* = 6.8 Hz, 3H); *after the addition of 100 mg of* $Ba(ClO_4)_2$: ^{1}H NMR (400 MHz, CD_3CN) δ 7.48 – 7.31 (m, 5H), 6.78 (d, *J* = 9.2 Hz, 1H), 4.80 (t, *J* = 7.7 Hz, 1H), 4.76 (s, 1H), 3.85 – 3.66 (m, 1H), 1.50 (s, 3H), 1.38 (s, 3H), 1.31 – 1.07 (m, 18H), 0.85 (t, *J* = 6.7 Hz, 3H).

In this case, the enantiomeric ratio of the free amine **32b** was taken directly from the diastereomeric ratio of the corresponding (*R*)-MPA derivatives-**32b** (89:11 dr).

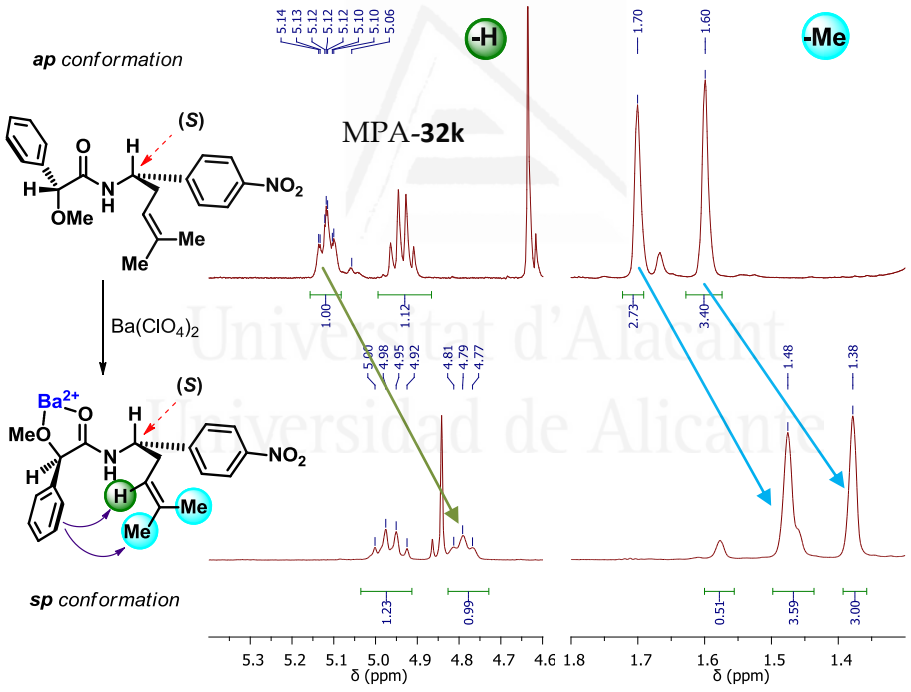


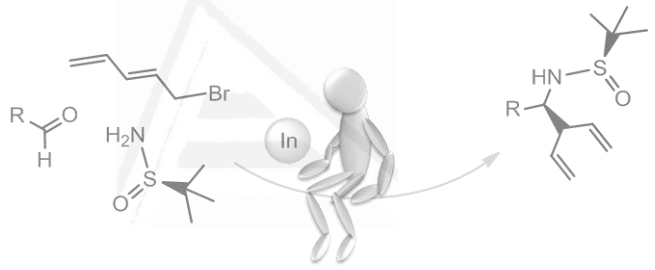
(*R*)-MPA derivative of 32k.



Following the general procedure of formation of MPA amides from amine **32k**, compound MPA-**32k** was obtained as a colorless oil:

^{1}H NMR (400 MHz, CD_3CN) δ 8.12 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.43 – 7.23 (m, 6H), 5.12 (ddd, *J* = 7.2, 5.9, 1.4 Hz, 1H), 4.94 (q, *J* = 7.4 Hz, 1H), 4.64 (s, 1H), 3.39 (s, 3H), 2.54 (t, *J* = 7.2 Hz, 2H), 1.70 (s, 3H), 1.60 (s, 3H); *after the addition of 100 mg of* $Ba(ClO_4)_2$: ^{1}H NMR (400 MHz, CD_3CN) δ 8.12 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.50 – 7.28 (m, 6H), 4.96 (dd, *J* = 15.2, 7.8 Hz, 1H), 4.84 (s, 1H), 4.79 (t, *J* = 6.8 Hz, 1H), 3.27 (s, 3H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.48 (s, 3H), 1.38 (s, 3H).





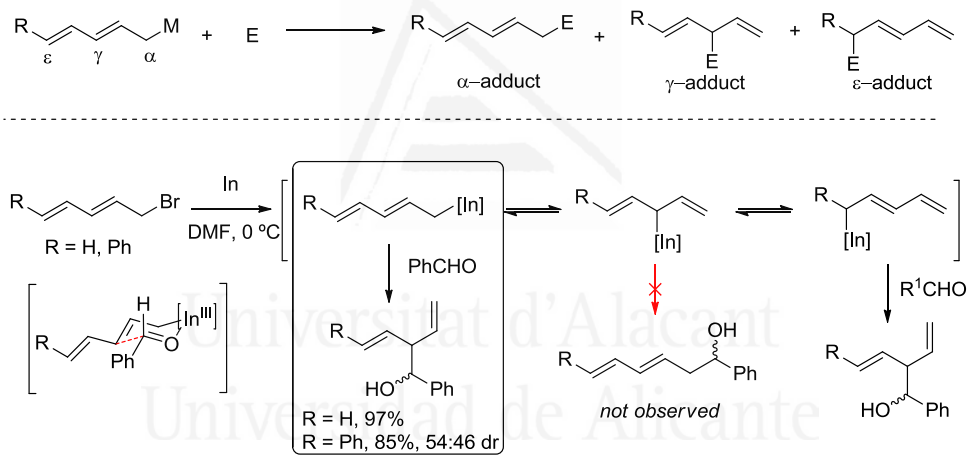
Chapter IV:

Aminopentadienylation of carbonyl compounds

PART OF THE CONTENT OF THIS CHAPTER WILL BE PUBLISHED IN DUE COURSE.

IV.1. INTRODUCTION

Pentadienylmetals can suffer from metallotropic 1,3-or 1,5-rearranganments and upon reaction with electrophiles can give rise to three possible regioisomers: the α-, γ- and ε- adducts (**Scheme 23**). Pentadienyl reagents of Mg,[163] Be,[164] Zn,[165] Sn,[166], Si,[167] and B[168] have been examined in the addition to aldehydes or ketones, obtaining different levels of selectivity. Interestingly, in the vast majority of these studies the γ-adduct was obtained as the main product. In some of the cases a Lewis acid was necessary to activate the electrophile and some protocols are clearly limited by the manipulation of hazardous reagents. Another major drawback for all these reagents is their sensitivity to moisture which complicates their manipulation making these procedures poorly reliable.

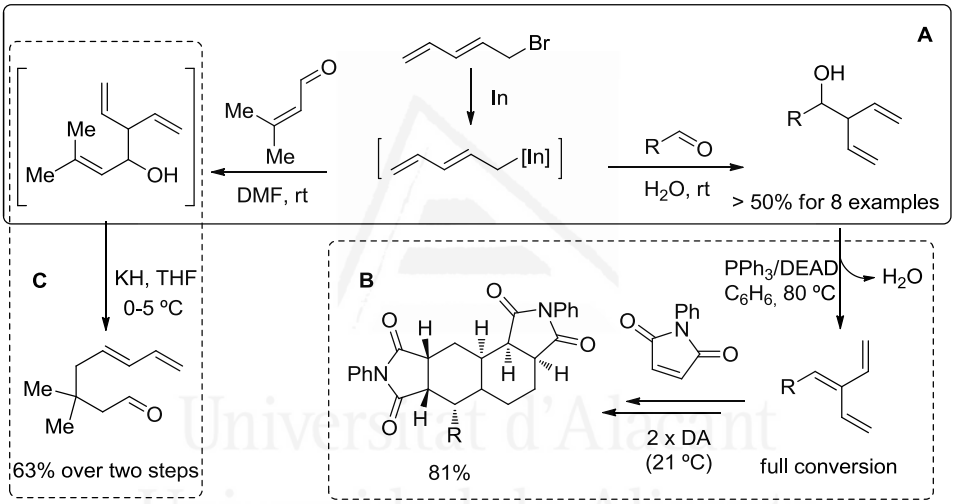


Scheme 23

The indium mediated Barbier-type reaction are superior protocols to the above mentioned substrates due to their experimental simplicity and because toxic reagents are avoided. In this context Araki and co-workers examined the

[163] Yasuda, H.; Yamauchi, M.; Nakamura, A.; Sei, T.; Kai, Y.; Yasuoka, N.; Kasai, N. *Bull, Chem. Soc. Jpn.* **1980**, *53*, 1089.
[164] Yasuda, H.; Ohnuma, Y.; Nakamura, A.; Sei, T.; Kai, Y.; Yasuoka, N., Kasai, N. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1101.
[165] (a) Ghosez, L.; Marko, I.; Hesbain-Frisque, A.-M. *Tetrahedron Lett.* **1986**, *27*, 5211. (b) Jung, M. E.; Nichols, C. *Tetrahedron Lett.* **1996**, *37*, 7667.
[166] Nishigaichi, Y.; Fujimoto, M.; Takuwa, A. *Synlett* **1994**, *731*.
[167] Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 3783.
[168] (a) Fujita, K.; Schlosser, M. *Helv. Chim. Acta* **1982**, *65*, 1258. (b) Suginome, M.; Yamamoto, Y., Fujii, K.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9608.

addition of penta-2,4-dienylindium derivatives, under Barbier conditions, observing the exclusive formation of γ-adducts in the addition to carbonyl compounds (**Scheme 23**).[169] It is supposed that metallotropic rearrangement takes place rapidly at the assayed reaction conditions, and the addition of the In(III) specie to the aldehyde takes place at γ-position through a cyclic chair-like transition state. Presumably, the addition occurs preferentially from the fully conjugated linear pentadienyl indium, but it is not clear if the dominant cause is the greater stability of this specie (thermodynamic control) or its greater reactivity (Curtin-Hammet conditions).



Scheme 24

Soon after Araki's work, the group of Fall observed that *in-situ* formed 2,4-pentadienyl indium reacts smoothly with a range of carbonyl compounds, including α,β-unsaturated aldehydes and ketones, in DMF or aqueous media with excellent γ-selectivity (**Scheme 24, A**).[170] Interestingly, dehydration of the diene alcohol gave cross-conjugated trienes, which are appropriately functionalized to participate in two consecutive Diels-Alder reactions to generate multicyclic systems commonly found in triterpenoid skeletons (**Scheme 24, B**). Furthermore, taking advantage of the very high 1,2-chemoselective addition to α,β-unsaturated aldehydes, the anionic oxy-Cope rearrangement was examined.

[169] Hirashita, T.; Inoue, S.; Yamamura, H.; Kawai, M.; Araki, S. *J. Organomet. Chem.* **1997**, *549*, 305.
[170] Woo, S.; Squires, N.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 573.

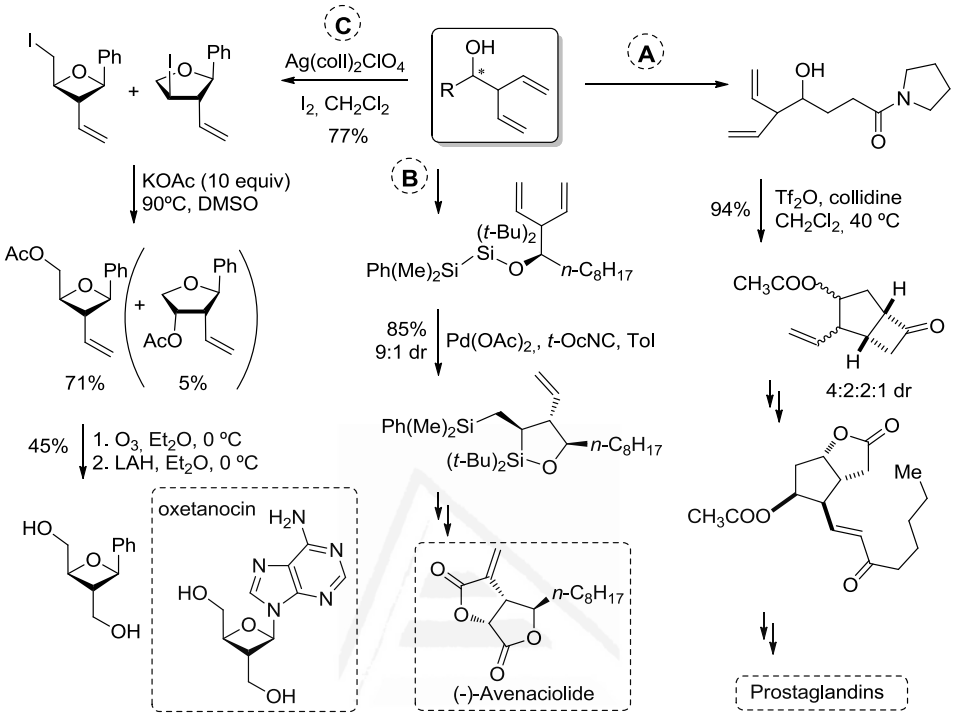
The reaction proceeded smoothly in THF (5 ºC or 21 ºC) to furnish the desired linear isomers in good yields (**Scheme 24, C**).[171] It was also found that in the case of aromatic conjugated ketones or cyclohexenones, the addition of pentadienylindium is followed by an spontaneous oxy-Cope rearrangement to afford the 1,4-aduct product.[172] Importantly, the second double bond is required for this [3,3]-sigmatropic rearrangement since standard homoallyl alkoxy indiums fail to undergo this transformation.

The alcohols obtained in the γ-pentadienylation of carbonyl compounds have proven to be valuable building blocks in the synthesis of more complex molecules. In 1986, the group of Ghosez developed a short synthetic route towards prostaglandins where a key intermediate was prepared by γ-pentadienylation of an aldehyde and was submitted to an intramolecular [2+2] cycloaddition with a ketiminium salt (**Scheme 25, A**).[165a]

An interesting intramolecular bis-silylation of α-substituted homoallylic alcohols to give 5-exo ring closure products was developed by the group of Ito. [173] When this palladium catalyzed reaction was applied to dienols, using bulky substituents on the silicon atom adjacent to the ether oxygen, the reaction took place with excellent diasterofacial (100:0) and high diasterotopic group selectivity (9:1) (**Scheme 25, B**).[174] The major diastereoisomer was isolated pure after column chromatography (85% yield) and was carried forward to complete the synthesis of (-)-Avenaciolide,[168b] a *bis*-γ-lactone isolated from *Aspergillus avenaceus* that posseses antifungal activity.

Preparation of oxetanocin analogues was also possible by using this building block in a cationic intramolecular iodoetherification,[165b] which allowed the selective preparation of trisubstituted oxetanes with the same spatial substitution than natural oxetanocin (**Scheme 25, C**).

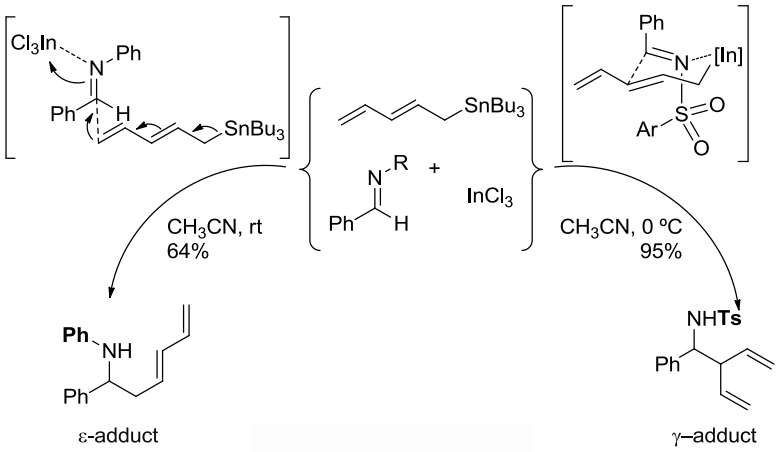
[171] Melekhov, A.; Fallis, A. G. *Tetrahedron Lett.* **1999**, *40*, 7867.
[172] Villalva-Servín, N. P.; Melekov, A.; Fallis, A. G. *Synthesis* **2003**, *5*, 790.
[173] Murakami, M., Anderson, P. G.; Suginome, M.; Ito, Y. *J. Am. Chem. Soc*. **1991**, *113*, 3987.
[174] Castelo-Branco, P. A.; Rubinger, M. M.; Alves, L. de-C.; de Barros, P. M.; Pereira, S. G.; de Melo, V. J.; Pilo-Veloso, D.; Zambolim, L. *Chem. Biodivers.* **2007**, *4*, 2745.



Scheme 25

To our best knowledge there is only one report on the pentadienylation of imines, using tributylpentadienyltin and Lewis acids (i. e. $InCl_3$) as additives.[175] In their work, the authors have found that *N*-phenyl imines afford the ε-adduct as the only regioisomer, presumably by Lewis acid activation of the imine and nucleophilic attack of the pentadienyltin specie through an acyclic transition state. Remarkably, with less basic *N*-tosyl imines the only regioisomer isolated was the corresponding γ-adduct. The formation of this compound could be explained by considering that after transmetallation, the resulting allylindium intermediate is coordinated to the iminic nitrogen and reacts through a cyclic transition state (**Scheme 26**).

[175] Nishigaichi, Y.; Ishihara, M.; Fushitani, S.; Uenaga, K.; Takuwa, A. *Chemistry Lett.* **2004**, *33*, 108.



Scheme 26

IV.2. OBJECTIVES

Based on the above commented precedents and in our research experience, we anticipated that the reaction of *tert*-butylsulfinylimines and of pentadienylindium reagent, both generated *in situ*, would allows the regio- and stereoselective formation of bis-homoallylic amines. In this chapter we describe our studies in this area. To demonstrate the utility of these molecules as building blocks, some synthetic transformations were explored.

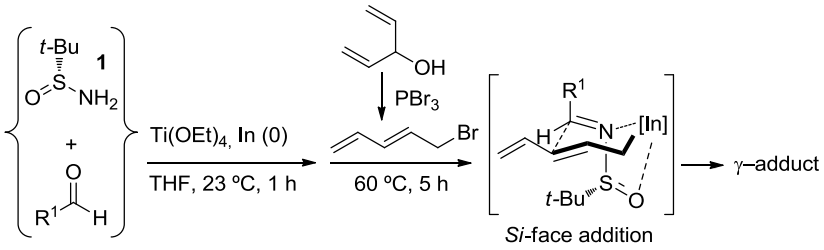
IV.3. RESULTS AND DISCUSSION

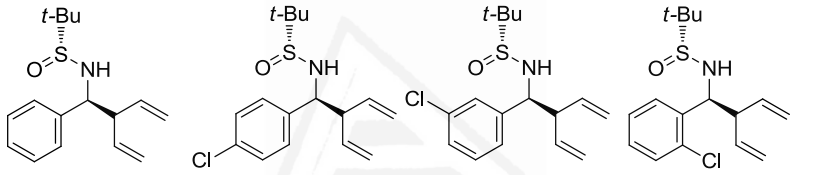
Aminopentadienylation of Aldehydes.

The one-pot protocol developed in our research group for the α-aminoallylation of aldehydes was implemented to prepare several α-pentadienyl substituted amines. In this case, the required pentadienyl bromide was prepared by reaction of commercially available penta-1,4-dien-3-ol with PBr_3 in diethyl ether at 0 ºC for 1 h. The methodology involves the formation of the corresponding imine by condensation of an aldehyde with chiral *N*-*tert*-butylsulfinamide in the presence of $Ti(OEt)_4$ and indium powder at room temperature. After 1 h, the prepared pentadienyl bromide was added to the reaction mixture and the temperature was

increased to 60 °C. Under these conditions, a range of aldehydes was examined (**Table 6**).

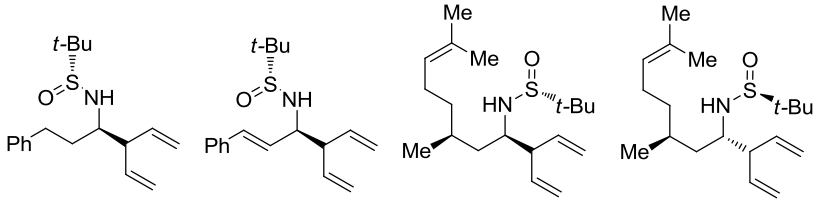
Table 6.





35a: 14%, 90:10 dr **35b**: 66%, >98:2 dr **35c**: 83%, 90:10 dr **35d**: 21%, >98:2 dr

35e: 55%,[a] >98:2 dr **35f**: 90%, 98:2 dr **35g**: 73%, >98:2 dr **35h**:[b] 70%, 98:2 dr



35i:[b] 85%, 97:3 dr **35j**: 72%, 97:3 dr **35k**: 86%, >97:3 dr[c] **35l**:[d] 84%, >97:3 dr[c]

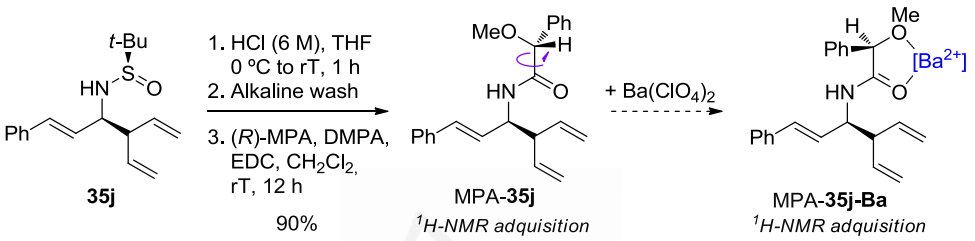
Isolated yields and diastereomeric ratios (^{1}H-NMR) after column chromatography are shown. [a]The crude reaction showed a 74:26 ratio between γ- and α-allylation products. [b]*ent*-**35h** and *ent*-**35i** were also synthesized using *ent*-**1** [c] Diasteromeric ratio measured by using ^{13}C NMR. [d]In this case *ent*-**1** was used.

Preliminary results with benzaldehyde were a bit disappointed since the corresponding γ-adduct **35a** was isolated in a poor 14% yield with modest diastereoselection (90:10 dr). Better yields and good diastereoselectivities were achieved with 3-, or 4-chlorobenzaldehyde (compounds **35b** to **35c**) where chloride enhances the electrophilic character of the carbonylic carbon by inductive effect. In the case of 2-chlorobenzaldehyde, the steric hindrance around the carbonylic carbon is reflected in a low reaction yield (**35d**, 21%). The α-branched cyclohexilcarbaldehyde gave a 74:26 mixture of γ/α adducts, being the major regioisomer **35e** isolated in 55% yield after column chromatography. We were pleased to observe that less sterically hindered aldehydes showed a better performance under the same conditions (**35f**). As in the aminoallylation case, enolizable aliphatic aldehydes, which are challenger substrates with other allylic organometallic species, were well tolerated (**35h**). Importantly for all α-unsubstituted aldehydes examined, including the presence of a bromine atom (**35g**) or a phenyl ring in a more remote position (**35i**), only γ-adducts were isolated in good yields and excellent diasteroselectivity. Interestingly, in the case of cinnamaldehyde, the 1,2-addition product was exclusively observed (**35j**). Moreover, in order to examine the influence of a chiral aldehyde in the diastereoselection, the (*S*)-citronellal was examined with both enantiomeric forms of the *N*-*tert*-butylsulfinamides. It is worth noting that products **35k** and **35l** were obtained in very good yields and diastereoselectivities, with no remarkable match or mismatched cases.

To assign the stereochemistry of the major diastereoisomer we assumed that the pentadienyl indium is coordinated by the sulfinylimine and reacts through a cyclic transition state, like we have previously proposed in the addition of allylindium species (see Bibliographic Background, **Scheme XXVIb**). Our working model is also consistent with the proposal of Nishigaichi for the addition of pentadienyl indium reagents to *N*-sulfonyl imines and predicts the addition to the *si*-face of the (R_S)-*N*-sulfinyl imine.

The assignment of the absolute configuration of product **35j** was performed by using ^{1}H-NMR analysis of its (*R*)-MPA derivative.[158] This amide was synthesized by condensation of the free amine of **35j** with (*R*)-MPA, after removal of the sulfinyl group (**Scheme 27**). As described in Chapter III, the MPA amide derivatives are more stable in its *antiperiplanar* conformation. However, the addition of $Ba(ClO_4)_2$ facilitates the formation of a chelate where the *synperiplanar* conformer is locked. This conformational equilibrium shift for compound MPA-**35j**-Ba leads to an increase shielding of the hydrogens contained in the

pentadienyl moiety, as well as a down shift displacement of signal corresponding to the double bond's hydrogen closer to the phenyl group (**Figure 9**). The same analysis was performed for product **35i** (from 3-phenylpropanal) observing identical stereochemistry. These results are in agreement with the configuration of the stereogenic center predicted by our working model for the pentadienylation reaction (described before).



Scheme 27

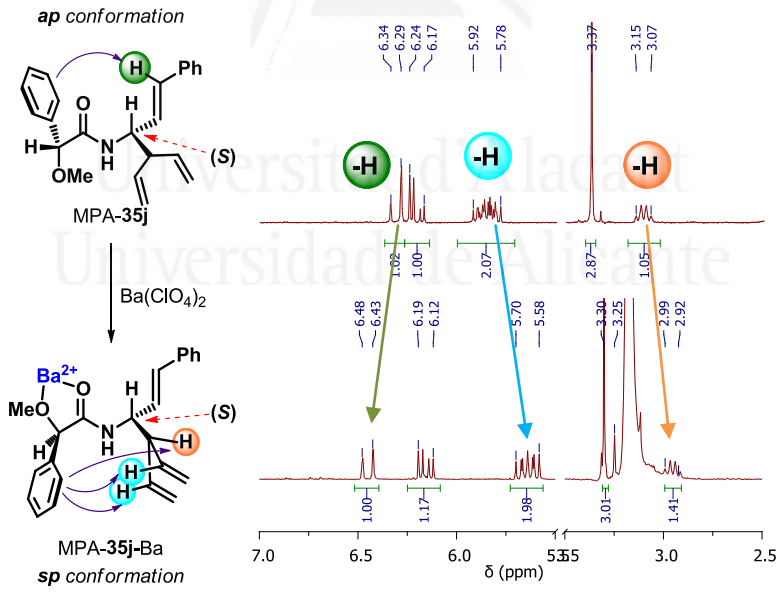
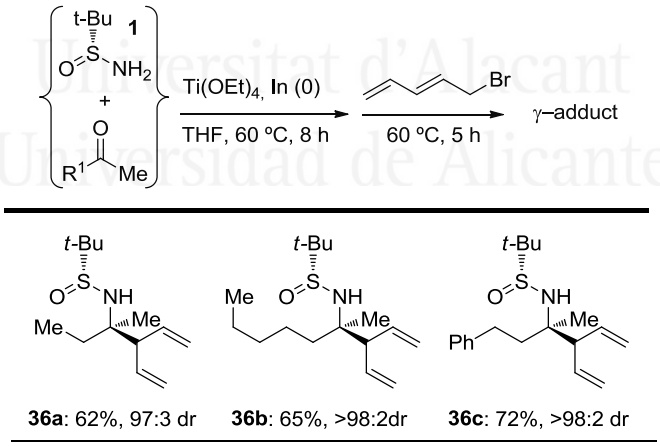


Figure 9

Aminopentadienylation of Ketones.

For further exploration of the potential of this methodology, some methyl ketones were submitted to the same reaction conditions (**Table 7**). However, the formation of the corresponding ketoimines required an increase of the temperature to 60 °C and 8 h of reaction, whereupon 5-bromo-1,3-pentadiene was added. It is remarkable to say that indium powder was still active after the imine formation, which confirms the stability of indium in the presence of moisture and/or ethanol at 60 °C. Due to the steric hindrance of ketones compared to aldehydes, and the congested products that the γ-addition would give, we thought that a partial α-addition may occur. However, when aliphatic methyl ketones were submitted to the reaction conditions, γ-adducts were exclusively obtained in good overall yields with excellent diastereoselectivities indeed (**36a** to **36c**). Unfortunately, methylphenyl ketone and α,β-unsaturated ketones- like 4-phenyl-3-buten-2-one and 2-cyclohexenone – failed to give the expected adduct, affording either the corresponding ketimine or complex mixtures of products.

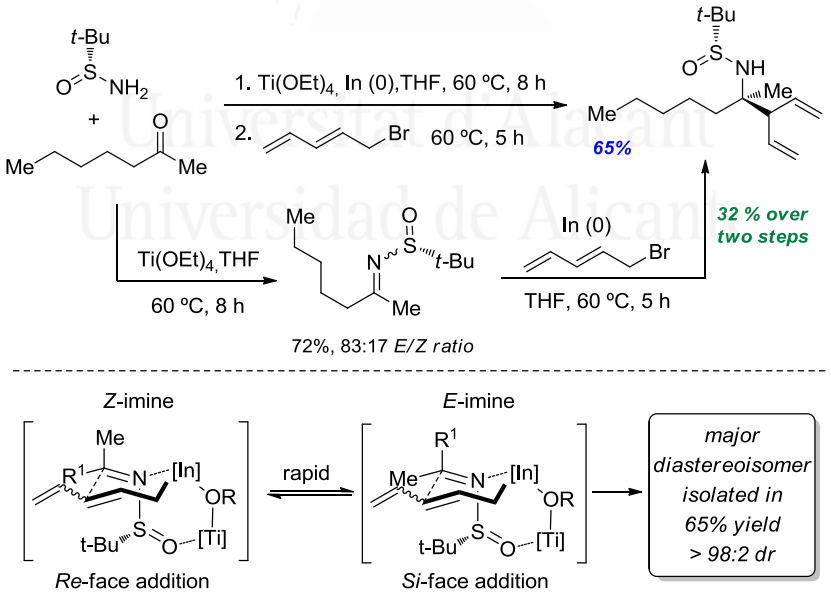
Table 7.



Isolated yields and diastereomeric ratios (^{1}H-NMR) after column chromatography are shown.

Since the protocol seems to be limited to methyl-α-unsubstituted aliphatic ketones, we decided to evaluate its efficiency compared to the two-steps protocol recently reported by our research group for the allylation of *tert*-butylsulfinylketimines.[57] The selected substrate was 2-heptanone and we have found that the one pot protocol was twice more efficient than the two steps

protocol (65% vs 32% yield, **Scheme 28**). To account for this difference we speculated that Ti(IV) could enhanced the electrophilicity of the sulfinimine through indium coordination to an alkoxy ligand that serve as bridge in a more stable [4.0.4] bicyclic transition state, thereby accelerating the addition of the pentadienyl indium reagent. This hypothetical transition state was also proposed for the simple aminoallylation of aldehydes; however, lower reaction rate differences were observed for the less sterically demanding allylindium reagent.[176] More importantly, regardless the poor *E*/*Z* selectivity in the formation all methyl alkyl ketoimines examined,[177] excellent diasteroselectivites were observed for the final products. To explain the excellent dynamic kinetic resolution observed in the allylation of *tert*-butylsulfinylimines it has been suggested by the Ellman group[54] and our group[57] that Lewis acids accelerate the equilibration of the *E*/*Z* imines and that final diastereoselection is related to the difference of activation energies of both possible transition states (Curtin-Hammet control). We think this explanation is also reasonable in our case and we proposed that the major diastereoisomer is formed in the addition to the *si*-face of the (R_S, *E*)-imine, as previously observed in the two-steps protocol.

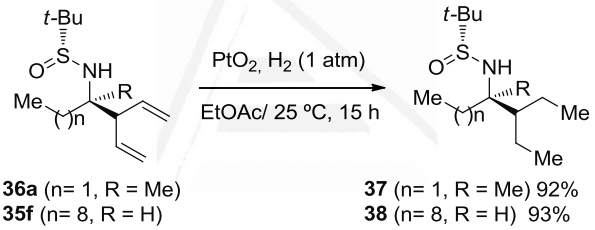


Scheme 28

[176] PhD Thesis of Sidi Mohamed-El Habib Medjahdi- University of Alicante, May 2011.
[177] 85:15 or 83:17 *E*/*Z* ratio for ketoimines derived from 2-butanone or 2-heptanone respectively.

Synthetic Applications.

At this point we decided to explore some synthetic applications of the enantioenriched obtained pentadienyl amines. Hydrogenation of both double bonds was accomplished for substrates **36a** and **35f** using PtO_2 as catalyst, which has proven to tolerate the presence of the sulfinyl group thereby avoiding the deprotection of the amine functionality.[178] The corresponding amines **37** and **38** were obtained in excellent yields without any detectable epimerization (**Scheme 29**). To the best of our knowledge, chiral amines α-substituted with a 3-pentyl moiety have not been reported so far. It is worth noting that a direct addition of 3-pentyl organometallic reagents to imines would be sterically disfavored and reduction or other processes related to single electron transfers are more reasonable in these cases.

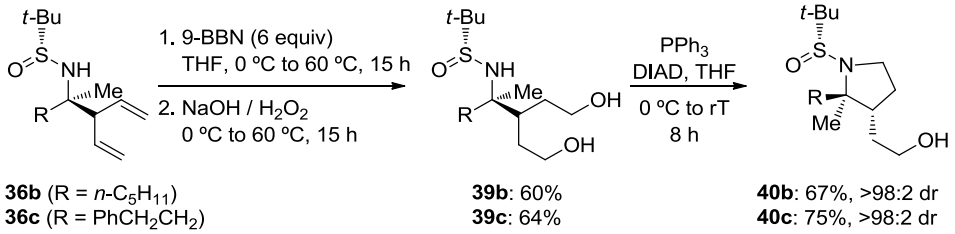


Scheme 29

Given the occurrence of pyrrolidines in natural or synthetic bioactive compounds we consider of interest to develop a new entry to 2,3-disubstituted pyrrolidines. To achieve this goal we submitted α-substituted pentadienyl amines **36b** and **36c** to a hydroboration/oxidation sequence using 1.2 equivalents of 9-borabicyclenonane (9-BBN). We explored these conditions in order to differentiate the diastereotopic vinylic groups, but low conversion into a complex mixture of alcohols was observed. However, when an excess of 9-BBN (6 equiv.) was used, the corresponding diols were achieved with moderate yields and excellent regioselectivities (**Scheme 30**). We were pleased to observe that cyclization of the chiral amino-diols under Mitsunobu conditions afforded the corresponding pyrrolidines in good yields and, more importantly, excellent diasteroselectivities (96:4 dr by ^{1}H-NMR in the crude of **40b** and **40c**). After

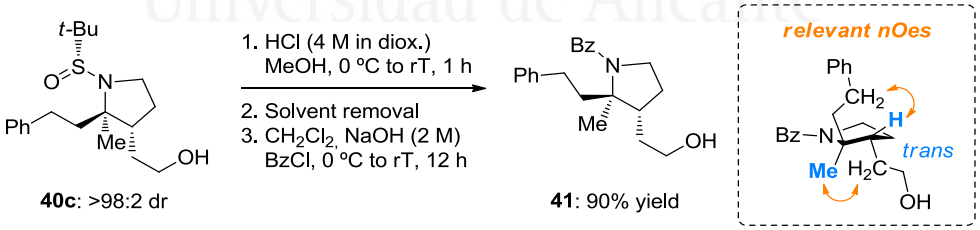
[178] Procupiou, G.;Lewis, W.;Harbottle, G.; Stockman, R. A. *Org. Lett.* **2013**, *15*, 2030.

column chromatography,[179] only one diastereoisomer with the same pattern of signals was observed by ^{1}H-NMR of compounds **40b** and **40c**.



Scheme 30

In order to elucidate the configuration of the new formed chiral center in compounds **40**, relevant ^{1}H NMR signals were assigned by using bidimensional experiments (COSY and HSQC), but no clear nOe signals were observed in any of the cases. However, amine deprotection and benzoylation of compound **40c** gave the amide **41** with a more rigid structure which permitted an easier identification of all ^{1}H NMR signals of the molecule. Enhancement of the signal of the methylene adjacent to phenyl group was observed upon irradiation of the methyne proton signal (next to the quaternary center). Moreover, irradiation of the methyl group caused an enhancement of the β-methylene group of the hydroxiethyl chain. These nOes clearly indicated the *trans*-relationship between the methyne proton and the methyl group (**Scheme 31**).

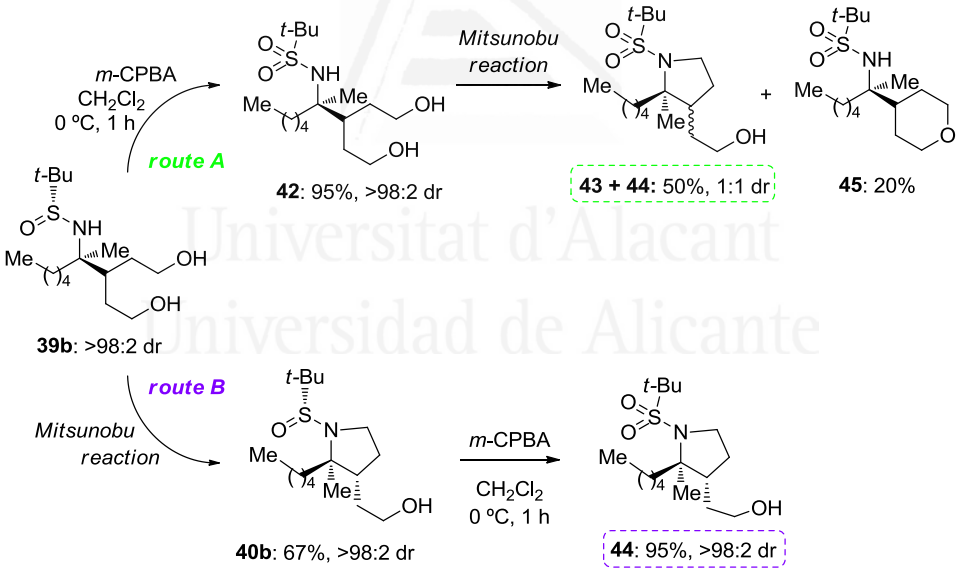


Scheme 31

This excellent diastereoselectivity is noteworthy since both alkyl groups attached to the quaternary center exhibit similar steric bulkiness (similar A values). We reasoned that this unexpectedly high diastereoselection should be supported on kinetic grounds. For a better understanding of this diastereoselective Mitsunobu reaction, we removed the chirality of the sulfinyl group before the cyclization.

[179] After the column, a mixed fraction of the minor isomer and the major one facilitated the identification of the ^{1}H-NMR signals of the minor diasteroisomer to calculate the diastereoselectivity.

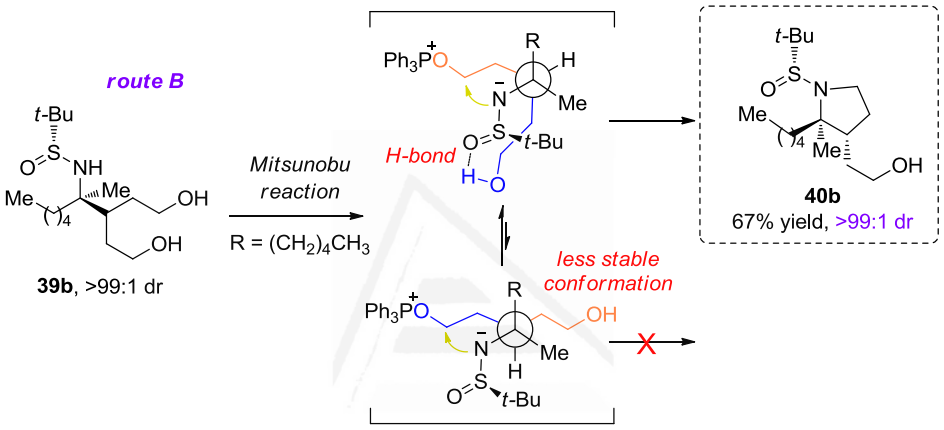
Sulfinyl oxidation of compound **39b** by using *m*-CPBA gave, after only one hour at 0 ºC, full conversion into the sulfonyl compound **42**. Mitsunobu cyclization of this compound afforded a 1:1 diastereomeric mixture of pyrrolidines **43** and **44** in 50% yield, accompanied by tetrahydropyran **45** (20%) byproduct (**Scheme 32**, route A). On the other hand, sulfinyl oxidation of compound **40b** took place smoothly to afford pyrrolidine **44** with excellent yield and diastereoselection (**Scheme 32**, route B). Comparison of the ^{1}H NMR spectra of the pyrrolidines obtained using both routes clearly demonstrate that cyclization of compound **42** led to a 1:1 mixture of diasteroisomers, whilst cyclization of **39b** led to a single diasteroisomer. Therefore, this experiment set clear that *the chirality of the sulfinyl group is essential to achieve a good diastereoselection in this Mitsunobu reaction*. In addition, the chemoselectivity was higher in the ciclyzation of the sulfinamine **39b** (route B), where formation of a tetrahydropyran byproduct was not observed.



Scheme 32

The importance of the chiral sulfinyl group in the diastereoselection suggests its active participation in the cyclization. We thought that a possible hydrogen bond between one of the hydroxiethyl groups and the oxygen of the sulfinyl group might appear, leaving only the other hydroxyl group susceptible of suffering the nitrogen attacks. As depicted in **Scheme 33**, the oxygen of the sulfinyl group of

compound **39b** could form a hydrogen bond with one of the hydroxyl groups, stabilazing the reactive conformation that give rise to the observed diastereoisomer, whilst in the alternative approach no hydrogen bond could be formed. This model is consistent with the lack of diastereoselection observed when sulfonyl compound **42** was submitted to Mitsunobu reaction conditions, where two reactive conformations with hydrogen bonds involving one of the sulfonyl oxygen atoms are equally accessible.



Scheme 33

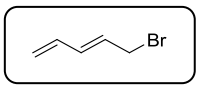
The synthesis of enantiomerically pure pyrrolidines containing two consecutive stereocenters highlights the potential of α-substituted pentadienyl amines as building blocks in organic synthesis. We have also demonstrated that the chiral sulfinyl moiety plays a crucial role in the preparation of these optically pure pyrrolidines under Mitsunobu reaction conditions. We are currently exploring other synthetic applications.

IV.4. EXPERIMENTAL SECTION

General Remarks.

(R_s)-*N*-*tert*-Butylsulfinyl amine and its enantiomer were a gift of Medalchemy (> 99% ee by chiral HPLC on a Chiracel AS column, *n*-Hexane/*i*-PrOH 90:10, 1 mL/min, λ=222 nm). TLCs were performed on silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) or ninhydrine stain. Flash chromatographies were carried out on handpacked columns of silica gel 60 (230- 400 mesh). Melting points are uncorrected. Optical rotations were measured using a polarimeter with a thermally jacketted 5 cm cell at approximately 20 ºC and concentrations (c) are given in g/100 mL. Infrared analyses were performed with a spectrophotometer equipped with an ATR component; wavenumbers are given in cm^{-1}. GC analyses were obtained with an HP-5 column (30 m × 0.25 mm, i.d. × 0.25 µm) and an EI (70 EV) detector; the temperature program was as follows: hold at 60 °C for 3 min, ramp from 60 to 270 °C at 15 °C/min, hold at 270 °C for 10 min. Mass spectra (EI) were obtained at 70 eV; and fragment ions in m/z with relative intensities (%) in parentheses. HRMS analyses were also carried out in the electron impact mode (EI) at 70 eV using a quadrupole mass analyzer or in the electrospray ionization mode (ES^+) using a TOF analyzer. ^{1}H NMR spectra were recorded at 300 or 400 MHz, using $CDCl_3$ or CD_3CN as the solvent and TMS as internal Standard (0.00 ppm); the data is being reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded with ^{1}H-decoupling at 101 MHz using the solvent signal as reference (77.16 ppm for $CDCl_3$). DEPT-135 experiments were performed to assign CH, CH_2 and CH_3.

2,4-pentadienyl bromide[180]



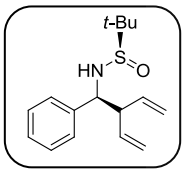
To a stirring solution of PBr_3 (190 µL, 2 mmol) in dry EtO_2 (2.5 mL) under Ar atmosphere, was added 1,4-pentadien-3-ol (485 µL, 5 mmol) dropwise at 0 ºC. The resulting solution was stirred at 0 ºC until the starting material disappeared (followed by GC, starting alcohol: t_R = 2.2 min, product: t_R = 4.0 min). The reaction was carefully quenched by the addition of brine (1 mL). The layers were separated and organics were washed three times with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$ and filtered. The volatiles were carefully removed at 40 ºC at atmospheric pressure. The product was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 – 6.22 (m, 2H), 5.90 (dt, *J* = 13.0, 7.8 Hz, 1H), 5.28 (d, *J* = 14.9 Hz, 1H), 5.17 (d, *J* = 10.2 Hz, 1H), 4.03 (d, *J* = 7.6 Hz, 1H).

[180] 2,4-pentadienyl bromide was prepared as described in: Tekavec, T. N.; Louie, J. *Tetrahedron* **2008**, *64*, 6870.

General procedure for the synthesis of sulfinamides 35.

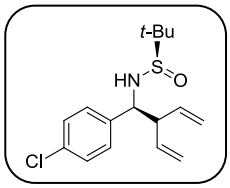
To a dry flask was added (R_S)-*N*-*tert*-butylsulfinamide (**1**, 61 mg, 0.5 mmol) followed by indium powder (71 mg, 0.63 mmol), and the mixture was evacuated and put under Ar atmosphere. Then a solution of the corresponding aldehyde (0.55 mmol) in dry THF (1 mL) and $Ti(OEt)_4$ (225 μL, 1 mmol) were added successively and the reaction mixture was stirred under Ar for 1 h at 23 ºC. At this time 2,4-pentadienyl bromide (110 mg, 0.75 mmol) was added to the mixture and it was heated to 60 ºC for 3 h. The mixture was allowed to reach room temperature and was carefully added over a stirring mixture of 4:1 EtOAc/brine (50 mL). The resulted white suspension was filtered through a short pad of Celite, washed with EtOAc and organics were concentrated *in vacuo*. The resulted suspension was diluted in 4:1 EtOAc/Hexane (50 mL), filtered again through Celite and the organics were concentrated under reduced pressure.

(R_S, *S*)-N-*tert*-Butylsulfinyl-1-phenyl-2-vinylbut-3-en-1-amine (35a)



The crude product prepared from benzaldehyde following the general procedure was purified by column chromatography (7:3 Hexane/EtOAc). The expected product was obtained as a yellow oil (19 mg, 14%, 90:10 dr according ^{1}H NMR): $[\alpha]_D^{20}$ – 121.5 (*c* 1.3, $CHCl_3$); R_f 0.12 (8:2 Hexane/EtOAc); IR ν 3280, 3079, 2958, 1634, 1455, 1056, 917 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 5.81 (ddd, *J* = 17.0, 10.2, 9.0 Hz, 1H), 5.57 (ddd, *J* = 17.3, 10.5, 7.1 Hz, 1H), 5.33 – 5.20 (m, 2H), 5.03 – 4.88 (m, 2H), 4.28 (dd, *J* = 8.7, 1.5 Hz, 1H), 3.92 (br s, 1H), 3.07 (dd, *J* = 16.2, 8.4 Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (C), 137.7 (CH), 136.4 (CH), 128.9 (CH), 128.3 (CH), 127.9 (CH), 119.0 (CH_2), 117.5 (CH_2), 60.2 (CH), 56.0 (CH), 55.8 (C), 22.8 (CH_3); CG t_R = 14.6 min.; LRMS (EI) *m/z* (%) 154 (13), 153 (100), 137 (7), 136 (25), 129 (8), 105 (21), 104 (25), 77 (11); HRMS (EI) calcd for $C_{16}H_{23}NOS$ – C_4H_8 221.0874, found 221.0888.

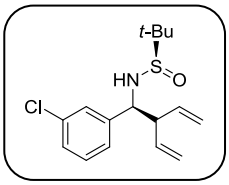
(R_S,1*S*)-N-*tert*-Butylsulfinyl-1-(4-chlorophenyl)-2-vinylbut-3-en-1-amine (35b)



Compound **35b** was prepared from *p*-Chlorobenzaldehyde following the general procedure and purified by column chromatography (7:3 Hexane/EtOAc). The expected product was obtained as a yellow oil (102 mg, 66%, single diastereoisomer according to ^{1}H NMR): $[\alpha]_D^{20}$ - 150.7 (*c* 0.69, $CHCl_3$); R_f 0.20 (7:3 Hexane/EtOAc); IR ν 3277, 3080, 2979, 2959, 1737, 1635, 1597, 1490, 1062, 1013, 919, 828 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.18 (m, 2H), 5.78 (ddd, *J* = 17.0, 10.2, 9.0 Hz, 1H), 5.54 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.30 (dd, *J* = 10.3, 1.6 Hz, 1H), 5.24 (ddd, *J* = 17.1, 1.6, 0.7 Hz, 1H), 5.00 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.93 (dt, *J* = 17.2, 1.3 Hz, 1H), 4.26 (dd, *J* = 8.6, 1.3 Hz, 1H), 3.91 (s, 1H), 3.02 (dd, *J* = 16.4, 8.6 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3 (C), 137.4 (CH), 136.1 (CH), 133.7 (C), 130.2 (CH), 128.6 (CH), 119.3 (CH_2), 117.9 (CH_2), 59.5 (CH), 56.1 (CH), 55.9 (C), 22.7 (CH_3);

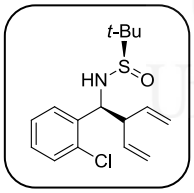
CG t_R = 16.0 min.; LRMS (EI) *m/z* (%) 189 (33), 187 (100), 170 (5), 157 (3), 142 (5), 141 (14), 140 (10), 139 (33), 138 (21), 128 (4), 67 (5); HRMS (TOF) calcd for $C_{16}H_{23}NOSCl$ 312.1189, found 312.1185.

(*R*S,1*S*)-N-*tert*-Butylsulfinyl-1-(3-chlorophenyl)-2-vinylbut-3-en-1-amine (35c)



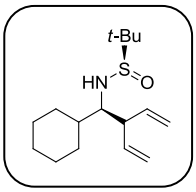
Compound **35c** was prepared from *m*-Chlorobenzaldehyde following the general procedure and purified by column chromatography (7:3 Hexane/EtOAc). The expected product was obtained as a colorless oil (129 mg, 83%, 90:10 dr according to ^{1}H NMR): $[\alpha]_D^{20}$ – 105.8 (*c* 0.72, $CHCl_3$); R_f 0.30 (7:3 Hexane/EtOAc); IR ν 3276, 3217, 2978, 2960, 1634, 1597, 1574, 1474, 1316, 1056, 920, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.27 (m, 1H), 7.27 – 7.24 (m, 2H), 7.19 – 7.14 (m, 1H), 5.78 (ddd, *J* = 17.1, 10.2, 9.0 Hz, 1H), 5.56 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.30 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.25 (dd, *J* = 17.1, 0.7 Hz, 1H), 5.04 – 4.99 (m, 1H), 4.95 (dt, *J* = 17.2, 1.3 Hz, 1H), 4.26 (dd, *J* = 8.6, 1.2 Hz, 1H), 3.91 (s, 1H), 3.03 (q, *J* = 8.4 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0 (C), 137.3 (CH), 136.0 (CH), 134.3 (C), 129.5 (CH), 128.7 (CH), 128.1 (CH), 127.2 (CH), 119.4 (CH_2), 118.0 (CH_2), 59.7 (CH), 56.0 (CH), 55.9 (C), 22.7 (CH_3); CG t_R = 15.8 min.; LRMS (EI) *m/z* (%) 189 (38), 188 (10), 187 (100), 170 (12), 157 (4), 142 (6), 141 (13), 140 (10), 139 (28), 138 (20), 128 (5), 67 (5); HRMS (TOF) calcd for $C_{16}H_{23}NOSCl$ 312.1189, found 312.1186.

(*R*S, 1*S*)-N-*tert*-Butylsulfinyl-1-(2-chlorophenyl)-2-vinylbut-3-en-1-amine (35d)



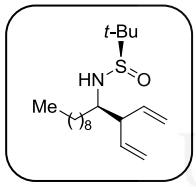
Compound **35d** was prepared from *o*-Chlorobenzaldehyde following the general procedure and purified by column chromatography (7:3 Hexane/EtOAc). The expected product was obtained as a colorless oil (33 mg, 21%, single diastereoisomer according to ^{1}H NMR): $[\alpha]_D^{20}$ – 113.8 (*c* 0.60, $CHCl_3$); R_f 0.29 (7:3 Hexane/EtOAc); IR ν 3281, 3079, 2978, 2959, 1634, 1573, 1473, 1363, 1062, 919, 730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.25 (td, *J* = 7.5, 1.5 Hz, 1H), 7.22 – 7.17 (m, 1H), 5.84 (ddd, *J* = 17.1, 10.2, 8.7 Hz, 1H), 5.74 (ddd, *J* = 17.4, 10.4, 7.3 Hz, 1H), 5.28 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.21 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.4 Hz, 1H), 4.97 (dt, *J* = 17.1, 1.4 Hz, 1H), 4.94 (s, 1H), 3.86 (s, 1H), 3.18 (dd, *J* = 15.1, 7.4 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (C), 136.9 (CH), 136.1 (CH), 134.4 (C), 129.8 (CH), 129.7 (CH), 128.7 (CH), 126.7 (CH), 119.3 (CH_2), 117.7 (CH_2), 56.1 (CH), 55.9 (C), 55.1 (CH), 22.7 (CH_3); CG t_R = 15.5 min.; LRMS (EI) *m/z* (%) 189 (30), 187 (100), 170 (7), 142 (6), 141 (13), 140 (10), 139 (30), 138 (21), 128 (6), 67 (5); HRMS (TOF) calcd for $C_{16}H_{23}NOSCl$ 312.1189, found 312.1187.

(R_S,1*R*)-N-*tert*-Butylsulfinyl-1-cyclohexyl-2-vinylbut-3-en-1-amine (35e)



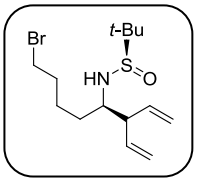
The crude product prepared from cyclohexilcarbaldehyde following the general procedure was obtained as a mixture of α- and γ- allylic products (26:74 according ^{1}H NMR). The desired γ- product was purified by column chromatography (9:1 Hexane/ EtOAc) giving a colorless wax (78 mg, 55%, single diastereoisomer according to ^{1}H NMR): $[\alpha]_D^{20}$ – 72.8 (*c* 0.73, $CHCl_3$); R_f 0.20 (8:2 Hexane/EtOAc); IR ν 3292, 3232, 3075, 2978, 2924, 2852, 1638, 1449, 1363, 1059, 995, 912, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 – 5.81 (m, 2H), 5.21 – 5.07 (m, 4H), 3.32 (d, *J* = 5.3 Hz, 1H), 3.15 – 3.05 (m, 2H), 1.79 – 1.48 (m, 6H), 1.23 (s, 9H), 1.21 – 0.97 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6 (CH), 138.1 (CH), 117.4 (CH_2), 117.3 (CH_2), 62.7 (CH), 56.5 (C), 52.0 (CH), 40.7 (CH), 31.5 (CH_2), 27.8 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 23.1 (CH_3); CG t_R = 14.7 min.; LRMS (EI) *m/z* (%) 227 (7), 160 (24), 159 (100), 144 (59), 96 (31), 95 (53), 94 (11), 81 (32), 79 (11), 77 (28), 68 (13), 67 (22), 55 (18); HRMS (EI) calcd for $C_{16}H_{29}NOS$ – C_4H_8 227.1344, found 227.1339.

(R_S,4*R*)-N-*tert*-Butylsulfinyl-3-vinyltridec-1-en-4-amine (35f)



The crude product (93:7 dr according ^{1}H NMR) prepared from decanal following the general procedure was purified by column chromatography (9:1 Hexane/EtOAc). The expected product was obtained as a yellow oil (150 mg, 90%, 98:2 dr according to ^{1}H NMR): $[\alpha]_D^{20}$ – 50.3 (*c* 1.01, $CHCl_3$); R_f 0.23 (8:2 Hexane/EtOAc); IR ν 3290, 3209, 3077, 2954, 2924, 2854, 1635, 1466, 1362, 1065, 999, 914, 721 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 – 5.80 (m, 1H), 5.80 – 5.74 (m, 1H), 5.27 – 5.07 (m, 4H), 3.42 (d, *J* = 7.0 Hz, 1H), 3.32 – 3.23 (m, 1H), 3.16 (dd, *J* = 13.5, 7.3 Hz, 1H), 1.56 – 1.50 (m, 1H), 1.32 – 1.23 (m, 15H), 1.21 (s, 9H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (CH), 136.4 (CH), 119.1 (CH_2), 117.2 (CH_2), 58.8 (CH), 56.2 (C), 53.3 (CH), 32.0 (CH_2), 31.5 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 25.6 (CH_2), 22.9 (CH_3), 22.8 (CH_2), 14.3 (CH_3); CG t_R = 16.3 min.; LRMS (EI) *m/z* (%) 271 (7), 270 (1), 222 (11), 204 (16), 203 (100), 156 (7), 95 (14), 84 (30), 70 (48), 55 (20); HRMS (EI) calcd for $C_{19}H_{37}NOS$ – C_4H_8 270.1892, found 270.1880.

(R_S,4*R*)-N-*tert*-Butylsulfinyl-8-bromo-3-vinyloct-1-en-4-amine (35g)

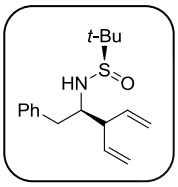


The crude product (94:6 dr according to ^{1}H NMR) prepared from 5-bromopentanal[181] following the general procedure was purified by column chromatography (8:2 Hexane/EtOAc). The expected product was obtained as a yellow oil (122 mg, 73%, single diastereoisomer according to ^{1}H NMR): $[\alpha]_D^{20}$ – 52.4 (*c* 1.13, $CHCl_3$); R_f 0.27 (7:3

[181] 5-bromopentanal was prepared from Ethyl 5-bromovaleronate by DIBAL-H reduction at – 78ºC.

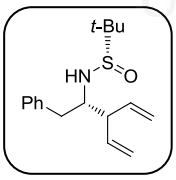
Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 – 5.69 (m, 2H), 5.36 – 5.05 (m, 4H), 3.45 (dd, *J* = 6.8, 5.1 Hz, 1H), 3.40 (t, *J* = 6.6 Hz, 2H), 3.32 – 3.22 (m, 1H), 3.16 (dd, *J* = 14.2, 6.9 Hz, 1H), 1.96 – 1.76 (m, 2H), 1.68 – 1.54 (m, 2H), 1.49 – 1.29 (m, 2H), 1.22 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6 (CH), 136.1 (CH), 119.4 (CH_2), 117.5 (CH_2), 58.4 (CH), 56.2 (C), 53.2 (CH), 33.8 (CH_2), 32.6 (CH_2), 30.6 (CH_2), 24.2 (CH_2), 22.9 (CH_3); CG t_R = 15.4 min.; LRMS (EI) *m/z* (%) 281 (4), 279 (4), 214 (9), 213 (100), 212 (10), 211 (97), 200 (7), 144 (10), 104 (8), 95 (11), 85 (5), 84 (38), 83 (4), 81 (22), 79 (9), 77 (17), 69 (14), 68 (24), 67 (45), 56 (12), 55 (18), 53 (12); HRMS (EI) calcd for $C_{14}H_{26}BrNOS$ – C_4H_8 279.0292, found 279.0290.

(*R*S,2*R*)-N-*tert*-Butylsulfinyl-1-phenyl-3-vinylpent-4-en-2-amine (35h)



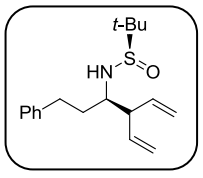
The crude product (97:3 dr according ^{1}H NMR) prepared from phenylethanal following the general procedure was purified by column chromatography (8:2 Hexane/EtOAc). The expected product was obtained as a yellow oil (102 mg, 70%, 98:2 dr according to ^{1}H NMR): $[\alpha]_D^{20}$ + 20.4 (*c* 0.73, $CHCl_3$); R_f 0.29 (7:3 Hexane/EtOAc); IR ν 3291, 3074, 2981, 1495, 1455, 1216, 1057, 921, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.13 (m, 5H), 5.99 – 5.79 (m, 2H), 5.36 – 5.12 (m, 4H), 3.59 (ddd, *J* = 13.6, 8.2, 4.7 Hz, 1H), 3.44 (d, *J* = 7.2 Hz, 1H), 3.22 (dd, *J* = 12.2, 7.3 Hz, 1H), 2.91 (dd, *J* = 14.0, 4.9 Hz, 1H), 2.60 (dd, *J* = 13.9, 9.0 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9 (C), 136.9 (CH), 136.2 (CH), 129.5 (CH), 128.2 (CH), 126.2 (CH), 119.5 (CH_2), 117.8 (CH_2), 60.8 (CH), 56.0 (C), 52.4 (CH), 38.2 (CH_2), 22.5 (CH_3); CG t_R = 16.4 min.; LRMS (EI) *m/z* (%) 235 (5), 167 (5), 146 (5), 145 (8), 144 (100), 128 (6), 104 (24), 92 (7), 91 (35), 81 (19), 68 (4); HRMS (EI) calcd for $C_{17}H_{25}NOS$ – C_4H_8 235.1031, found 235.1032.

(*S*S,2*S*)-N-*tert*-Butylsulfinyl-1-phenyl-3-vinylpent-4-en-2-amine (*ent*-35h)



It was prepared from (*S*S)-*N*-*tert*-butylsulfinamide (*ent*-**1**) following the same general procedure obtaining a yellow oil (100 mg, 69%). Physical and spectroscopy data were found to be the same than for **35h**, except for the optical rotation: $[\alpha]_D^{20}$ – 21.1 (*c* 1.2, $CHCl_3$).

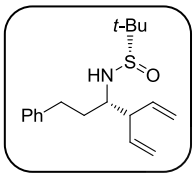
(*R*S,3*R*)-N-*tert*-Butylsulfinyl-1-phenyl-4-vinylhex-5-en-3-amine (35i)



Compound **35i** was prepared from 3-phenylpropanal following the general procedure. After purification by column chromatography (8:2 Hexane/EtOAc), the expected product was obtained as a yellow oil (130 mg, 85%, 97:3 dr according to ^{1}H NMR): $[\alpha]_D^{20}$ – 61.5 (*c* 0.85, $CHCl_3$); R_f 0.17 (8:2 Hexane/EtOAc); IR ν 3286, 3079, 2977, 2950, 1635, 1602, 1455, 1057, 917 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.27 – 7.14 (m, 3H), 5.88 – 5.71 (m, 2H), 5.34 – 5.23 (m, 2H), 5.23 – 5.11 (m, 2H), 3.56 (d, *J* = 7.1 Hz, 1H), 3.35 (tdd, *J* = 7.2, 5.3, 3.6 Hz, 1H), 3.24 (dd, *J* = 13.9, 6.9 Hz, 1H),

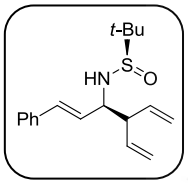
2.82 – 2.73 (m, 1H), 2.61 (ddd, *J* = 13.7, 10.4, 6.3 Hz, 1H), 1.99 – 1.89 (m, 1H), 1.72 – 1.60 (m, 1H), 1.28 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0 (C), 137.7 (CH), 136.0 (CH), 128.6 (CH), 128.5 (CH), 126.1 (CH), 119.6 (CH_2), 117.4 (CH_2), 58.3 (CH), 56.3 (C), 53.3 (CH), 33.6 (CH_2), 32.0 (CH_2), 23.0 (CH_3).; CG t_R = 16.3 min.; LRMS (EI) *m/z* (%) 249 (M^+–C_4H_8, 8), 181 (18), 145 (8), 133 (11), 132 (10), 118 (12), 117 (81), 96 (24), 92 (10), 91 (100), 81 (5), 77 (8), 67 (9), 65 (10); HRMS (EI) calcd for $C_{18}H_{27}NOS$ – C_4H_8 249.1187, found 249.1176.

(S_S,3*S*)-N-*tert*-Butylsulfinyl-1-phenyl-4-vinylhex-5-en-3-amine (*ent*-35i)



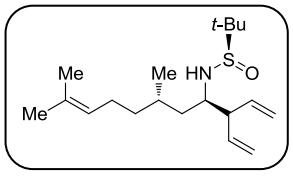
It was prepared from (S_S)-*N*-*tert*-butylsulfinamide (*ent*-**1**) following the same general procedure obtaining a colorless oil (122 mg, 80%, 97:3 dr according to ^{1}H NMR). Physical and spectroscopy data were found to be the same than for **35i**, except for the optical rotation: $[\alpha]_D^{20}$ + 56.4 (*c* 1.7, $CHCl_3$).

(R_S,1*E*,3*R*)-N-*tert*-Butylsulfinyl-1-phenyl-4-vinylhexa-1,5-dien-3-amine (35j)



Compound **35j** was prepared from cinnamaldehyde following the general procedure. After purification by column chromatography (9:1 Hexane/EtOAc), the expected product was obtained as a white solid (109 mg, 72%, 97:3 dr according to ^{1}H NMR): mp 47.9 – 50.0 °C; $[\alpha]_D^{20}$ + 133.5 (*c* 1.01, $CHCl_3$); R_f 0.30 (7:3 Hexane/EtOAc); IR ν 3281, 3079, 2977, 1635, 1363, 1059, 966, 918, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 4H), 7.27 – 7.22 (m, 1H), 6.61 (d, *J* = 15.8 Hz, 1H), 5.98 (dd, *J* = 15.9, 8.0 Hz, 1H), 5.95 – 5.75 (m, 2H), 5.32 – 5.12 (m, 4H), 3.99 (td, *J* = 7.2, 2.6 Hz, 1H), 3.67 (d, *J* = 2.7 Hz, 1H), 3.05 (q, *J* = 7.3 Hz, 1H), 1.23 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2 (CH), 136.7 (C), 136.5 (CH), 133.9 (CH), 128.7 (CH), 128.0 (CH), 127.9 (CH), 126.7 (CH), 118.5 (CH_2), 118.3 (CH_2), 59.1 (CH), 55.8 (C), 54.3 (CH), 22.8 (CH_3); CG t_R = 16.7 min.; LRMS (EI) *m/z* (%) 228 (5), 181 (6), 180 (11), 179 (97), 162 (5), 141 (5), 131 (13), 130 (100), 129 (8), 117 (12), 116 (88), 115 (39), 103 (11), 91 (14), 78 (5), 77 (17), 67 (6); HRMS (EI) calcd for $C_{18}H_{25}NOS$ – C_4H_8 247.1031, found 247.1040.

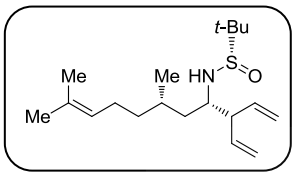
(R_S,4*R*,6*S*)-N-*tert*-Butylsulfinyl-6,10-dimethyl-3-vinylundeca-1,9-dien-4-amine (35k)



The crude prepared from (*S*)-citronellal following the general procedure was purified by column chromatography (8:2 Hexane/EtOAc). The expected product was obtained as a yellow oil (139 mg, 86%, >97:3 dr according to ^{13}C NMR): $[\alpha]_D^{20}$ – 31.5 (*c* 0.93, $CHCl_3$); R_f 0.32 (7:3 Hexane/EtOAc); IR ν 3288, 3080, 2958, 2928, 1635, 1457, 1363, 1059, 1001, 917, 798 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 – 5.70 (m, 2H), 5.31 – 5.20 (m, 2H), 5.15 (dt, *J* = 4.5, 1.6 Hz, 1H), 5.11 (dt, *J* = 11.0, 1.6 Hz, 1H), 5.08 – 5.02 (m, 1H), 3.44 – 3.31 (m, 2H), 3.26 (t, *J* = 6.9 Hz, 1H), 1.96 (q, *J* = 7.3 Hz, 2H), 1.66 (d, *J* = 1.0 Hz, 3H), 1.59 (s, 3H), 1.57 – 1.52 (m,

1H), 1.35 – 1.23 (m, 4H), 1.21 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (CH), 135.7 (CH), 131.2 (C), 124.7 (CH), 119.8 (CH_2), 116.7 (CH_2), 57.9 (CH), 56.2 (C), 53.9 (CH), 38.9 (CH_2), 37.8 (CH_2), 28.5 (CH), 25.7 (CH_3), 25.4 (CH_2), 22.7 (CH_3), 18.7 (CH_3), 17.7 (CH_3); CG t_R = 15.5 min.; LRMS (EI) *m/z* (%) 220 (33), 201 (12), 193 (23), 178 (45), 168 (5), 152 (76), 137 (49), 121 (38), 109 (100), 96 (44), 81 (97), 69 (89), 55 (35); HRMS (EI) calcd for $C_{19}H_{35}NOS$ – C_4H_8 269.1813, found 269.1808.

(S_S,4*S*,6*S*)-N-*tert*-Butylsulfinyl-6,10-dimethyl-3-vinylundeca-1,9-dien-4-amine (35l)

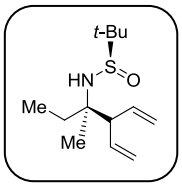


The crude product prepared from (*S*)-citronellal and *ent*-**1** following the general procedure was purified by column chromatography (8:2 Hexane/EtOAc). The expected product was obtained as a yellow oil (137 mg, 84%, >97:3 dr according to ^{13}C NMR): $[\alpha]_D^{20}$ + 30.5 (*c* 1.02, $CHCl_3$); R_f 0.28 (7:3 Hexane/EtOAc); IR ν 3290, 3077, 2958, 2924, 1635, 1456, 1362, 1059, 1001, 916, 794 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 – 5.74 (m, 2H), 5.32 – 5.21 (m, 2H), 5.18 – 5.05 (m, 3H), 3.43 – 3.34 (m, 2H), 3.24 (t, *J* = 8.2 Hz, 1H), 2.00 (td, *J* = 15.0, 6.8 Hz, 1H), 1.94 – 1.83 (m, 1H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.60 (s,3H), 1.45 – 1.35 (m, 3H), 1.21 (s, 9H), 1.19 – 1.13 (m, 1H), 1.13 – 1.01 (m, 1H), 0.89 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4 (CH), 136.0 (CH), 131.2 (C), 124.7 (CH), 119.6 (CH_2), 117.0 (CH_2), 57.6 (CH), 56.1 (C), 53.3 (CH), 39.3 (CH_2), 35.6 (CH_2), 28.7 (CH), 25.7 (CH_3), 25.1 (CH_2), 22.7 (CH_3), 20.4 (CH_3), 17.7 (CH_3); CG t_R = 15.6 min.; LRMS (EI) *m/z* (%)220 (33), 201 (12), 193 (25), 178 (47), 168 (5), 152 (77), 137 (47), 121 (35), 109 (100), 96 (44), 81 (92), 69 (86), 55 (35); HRMS (EI) calcd for $C_{19}H_{35}NOS$ – C_4H_8 269.1813, found 269.1819.

General procedure for the synthesis of sulfinamides 36.

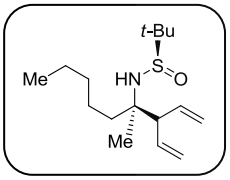
To a dry flask were added (R_S)-*N*-*tert*-butylsulfinamide (**1**, 61 mg, 0.5 mmol) followed by indium powder (71 mg, 0.63 mmol), and the mixture was evacuated and put under Ar atmosphere. Then a solution of the corresponding ketone (0.55 mmol) in dry THF (1 mL) and $Ti(OEt)_4$ (281 μL, 1.25 mmol) were added successively and the reaction mixture was stirred under Ar for 12 h at 65 ºC. At this time 2,4-pentadienyl bromide (154 mg, 1.05 mmol) was added to the mixture and it was heated to 65 ºC for 7 h. The mixture was allowed to reach room temperature and was carefully added over a stirring mixture of 4:1 EtOAc/brine (20 mL). The resulted white suspension was filtered through a short pad of Celite, washed with EtOAc and organics were concentrated *in vacuo*. The resulted suspension was diluted in 4:1 EtOAc/Hexane (20 mL), filtered again through Celite and the organics were concentrated under reduced pressure.

(R_S, 3*R*)-N-*tert*-Butylsulfinyl-3-methyl-4-vinylhex-5-en-3-amine (36a)



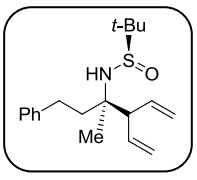
From 2-butanone, the expected product was obtained following the general procedure as a colorless crystal (75 mg, 62%, 97:3 dr according ^{1}H NMR) after column chromatography (9:1 Hexane/EtOAc): mp 35.2 – 36.8 °C; $[\alpha]_D^{20}$ – 66.6 (*c* 0.72, $CHCl_3$); R_f 0.37 (7:3 Hexane/EtOAc); IR ν 3292, 3075, 2976, 2940, 1632, 1457, 1380, 1176, 1059, 1001, 919, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 – 5.75 (m, 2H), 5.24 – 5.10 (m, 4H), 3.49 (s, 1H), 2.98 (t, *J* = 8.6 Hz, 1H), 1.66 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.56 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.29 (s, 3H), 1.21 (s, 9H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (CH), 136.2 (CH), 118.8 (CH_2), 118.1 (CH_2), 59.2 (C), 57.5 (CH), 56.2 (C), 30.6 (CH_2), 24.1 (CH_3), 23.0 (CH_3), 7.5 (CH_3); GC t_R = 12.2 min.; LRMS (EI) *m/z* (%) 176 (16), 122 (5), 121 (6), 120 (100), 102 (21), 81 (10), 71 (5), 67 (10), 57 (17); HRMS (TOF) calcd for $C_{13}H_{26}NOS$ (M^++1) 244.1735, found 244.1728.

(R_S, 4*R*)-N-*tert*-Butylsulfinyl-4-methyl-3-vinylnon-1-en-4-amine (36b)



From 2-heptenone, the expected product was obtained following the general procedure as a colorless oil (93 mg, 65%, single diastereoisomer according to ^{1}H NMR) after column chromatography (9:1 Hexane/EtOAc): $[\alpha]_D^{20}$ – 63.8 (*c* 0.98, $CHCl_3$); R_f 0.33 (7:3 Hexane/EtOAc); IR ν 3297, 3075, 2954, 2935, 1632, 1456, 1380, 1178, 1064, 1002, 914, 731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 – 5.78 (m, 2H), 5.27 – 5.17 (m, 2H), 5.16 – 5.10 (m, 2H), 3.50 (s, 1H), 2.97 (t, *J* = 8.5 Hz, 1H), 1.67 – 1.43 (m, 2H), 1.40 – 1.30 (m, 2H), 1.30 (s, 3H), 1.28 – 1.20 (m, 4H), 1.20 (s, 9H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (CH), 136.1 (CH), 118.7 (CH_2), 118.1 (CH_2), 59.0 (C), 57.7 (CH), 56.1 (C), 38.0 (CH_2), 32.2 (CH_2), 24.5 (CH_3), 22.9 (CH_3), 22.6 (CH_2), 22.5 (CH_2), 14.1 (CH_3); GC t_R = 13.9 min.; LRMS (EI) *m/z* (%) 229 (4), 163 (6), 162 (13), 161 (100), 159 (5), 158 (49), 144 (5), 118 (9), 110 (6), 105 (23), 97 (15), 95 (10), 91 (7), 67 (12), 57 (12), 55 (12); HRMS (TOF) calcd for $C_{16}H_{32}NOS$ (M^++1) 285.2126, found 286.2201.

(R_S, 3*R*)-N-*tert*-Butylsulfinyl-3-methyl-1-phenyl-4-vinylhex-5-en-3-amine (36c)



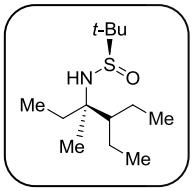
From 4-phenyl-2-butanone, the expected product was obtained following the general procedure as a colorless oil (115 mg, 72%, single diastereoisomer according to ^{1}H NMR) after column chromatography (9:1 Hexane/EtOAc): $[\alpha]_D^{20}$ – 74.2 (*c* 0.73, $CHCl_3$); R_f 0.34 (7:3 Hexane/EtOAc); IR ν 3076, 3025, 2977, 2953, 2867, 1632, 1603, 1455, 1381, 1063, 1063, 1002, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.12 (m, 5H), 5.99 – 5.79 (m, 2H), 5.34 – 5.11 (m, 4H), 3.62 (br s, 1H), 3.07 (t, *J* = 8.6 Hz, 1H), 2.73 – 2.54 (m, 2H), 1.93 (ddd, *J* = 14.2, 10.9, 6.4 Hz, 1H), 1.80 (ddd, *J* = 14.2, 11.2, 7.0 Hz, 1H), 1.39 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4 (C), 136.6

(CH), 135.9 (CH), 128.6 (CH), 128.5 (CH), 126.1 (CH), 119.3 (CH_2), 118.4 (CH_2), 58.9 (C), 58.0 (CH), 56.4 (C), 40.5 (CH_2), 29.5 (CH_2), 24.5 (CH_3), 23.1 (CH_3); GC t_R = 16.6 min.; LRMS (EI) *m/z* (%) 263 (8), 196 (7), 195 (56), 178 (5), 159 (14), 158 (38), 147 (47), 146 (21), 132 (15), 131 (25), 110 (29), 95 (6), 92 (9), 9 (100), 83 (18), 87 (11), 65 (11); HRMS (TOF) calcd for $C_{19}H_{30}NOS$ (M^++1) 320.2048, found 320.2039.

General procedure of hydrogenation to obtain compounds 37 and 38.

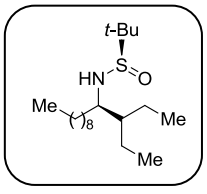
To a solution of the corresponding compound **35** or **36** (0.2 mmol) in EtOAc (6 mL) was added PtO_2 (6 mg, 10 mol %) and flushed with hydrogen atmosphere. The mixture was vigorously stirred at room temperature for 15 h. The catalysis was removed by filtration through a pad of Celite, eluting with more EtOAc. The solvent was removed under vacuum and the residue was purified by column chromatography (9:1 Hexane:EtOAc).

(R_S, 3*R*)-N-*tert*-Butylsulfinyl-4-ethyl-3-methylhexan-3-amine (37)



Compound **37** was obtained from compound **36a**, following the general procedure, as a colorless oil (45 mg, 92%, >98:2 dr according to ^{1}H NMR): $[\alpha]_D^{20}$ – 55.7 (*c* 0.79, $CHCl_3$); R_f 0.34 (7:3 Hexane/EtOAc); IR ν 3237, 2961, 2875, 1464, 1379, 1362, 1178, 1052, 937, 920 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16 (br s, 1H), 1.67 – 1.51 (m, 4H), 1.35 – 1.26 (m, 1H), 1.22 (s, 3H), 1.20 (s, 9H), 1.19 – 1.08 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 61.7 (C), 55.9 (C), 50.4 (CH), 31.4 (CH_2), 23.9 (CH_3), 23.1 (CH_2), 23.0 (CH_2), 22.9 (CH_3), 14.6 (CH_3), 14.0 (CH_3), 8.2 (CH_3); GC t_R = 12.6 min.; LRMS (EI) *m/z* (%) 191 (36), 176 (19), 162 (8), 127 (98), 126 (28), 120 (64), 119 (9), 102 (16), 97 (10), 85 (68), 72 (13), 71 (100), 57 (74), 55 (10); HRMS (TOF) calcd for $C_{13}H_{30}NOS$ (M^++1) 248.2048, found 248.2037.

(R_S, 4*R*)-N-*tert*-Butylsulfinyl-3-ethyltridecan-4-amine (38)

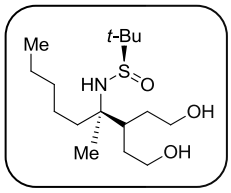


Compound **38** was obtained from compound **35f**, following the general procedure, as a colorless oil (62 mg, 93%): $[\alpha]_D^{20}$ – 38.6 (*c* 0.79, $CHCl_3$); R_f 0.54 (7:3 Hexane/EtOAc); IR ν 3243, 2957, 2923, 2871, 2854, 1462, 1362, 1056, 753 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.20 (dt, *J* = 7.4, 4.4 Hz, 1H), 3.02 (d, *J* = 7.6 Hz, 1H), 1.43 – 1.30 (m, 5H), 1.30 – 1.17 (m, 16H), 1.14 (s, 9H), 0.87 (t, *J* = 7.3 Hz, 6H), 0.81 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 58.4 (CH), 56.0 (C), 46.2 (CH), 32.4 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 26.6 (CH_2), 22.9 (CH_3), 22.8 (CH_2), 22.5 (CH_2), 22.1 (CH_2), 14.2 (CH_3), 12.4 (CH_3), 12.3 (CH_3); GC t_R = 13.4 min.; LRMS (EI) *m/z* (%) 203 (16), 186 (17), 157 (12), 156 (100), 154 (6), 100 (12), 97 (7), 91 (33), 84 (11), 83 (19), 71 (11), 70 (14), 69 (12), 56 (15), 55 (19); HRMS (TOF) calcd for $C_{19}H_{42}NOS$ (M^++1) 332.2987, found 332.2993.

General procedure of dihydroboration/dioxidation to obtain compounds 39b and 39c.

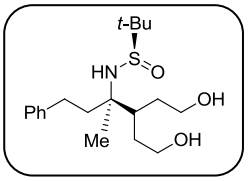
The corresponding homoallylamine **36b** or **36c** (0.6 mmol) was dissolved in dry THF (0.2 mL) under Ar atmosphere and cooled to 0 ºC. A solution of 9-BBN (0.5 M in THF, 7.2 mL, 3.6 mmol), was dropwised into the stirring mixture and allowed to react for 15 h at 60 ºC. After cooling again to 0 ºC, 2M solution of NaOH (1.6 mL) was carefully added and, after 5 min, H_2O_2 solution (30% wt/v, 1 mL) was added. The mixture was stirred for 15 h at 60 ºC and then allowed to reach room temperature. The organic phase was collected and the aqueous phase was extracted 3 times with EtOAc. Organics were dried over $MgSO_4$, filtered and concentrated to obtain the crude diol. After column chromatography (98:2 EtOAc/MeOH) the pure products **39b** or **39c** were obtained.

(*R*S, 4*R*)-N-*tert*-Butylsulfinyl-1-hydroxyl-3-(2'-hydroxyethyl)-4-methylnonan-4-amine (39b)



From **36b**, the expected product was obtained following the general procedure as a colorless oil (115 mg, 60%, single diastereoisomer according to ^{1}H NMR): $[\alpha]_D^{20}$ – 30.5 (*c* 0.95, $CHCl_3$); R_f 0.16 (98:2 EtOAc/MeOH); IR ν 3301, 2953, 2933, 2870, 1457, 1363, 1098, 1012, 935, 753 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 – 3.71 (m, 3H), 3.71 – 3.53 (m, 2H), 3.42 (br s, 1H), 3.12 (br s, 1H), 2.00 – 1.82 (m, 4H), 1.54 – 1.31 (m, 6H), 1.28 (s, 3H), 1.27 – 1.23 (m, 3H), 1.21 (s, 9H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 62.3 (CH_2), 61.3 (C), 61.0 (CH_2), 56.1 (C), 41.5 (CH), 38.5 (CH_2), 34.0 (CH_2), 33.4 (CH_2), 32.4 (CH_2), 23.3 (CH_3), 22.9 (CH_3), 22.8 (CH_2), 22.6 (CH_2), 14.0 (CH_3); GC t_R = 15.8 min.; LRMS (EI) *m/z* (%) 163 (5), 161 (83), 160 (11), 134 (10), 129 (44), 128 (69), 115 (11), 114 (100), 112 (10), 111 (21), 110 (14), 105 (30), 91 (20), 85 (11), 84 (14), 83 (21), 82 (15), 81 (21), 71 (18), 70 (20), 69 (28), 67 (24), 57 (32), 55 (60); HRMS (TOF) calcd for $C_{16}H_{36}NO_3S$ (M^++1) 322.2416, found 322.2418.

(*R*S, 3*R*)-N-*tert*-Butylsulfinyl-1-hydroxyl-3-(2'-hydroxyethyl)-4-methyl-6-phenylhex-4-amine (39c)



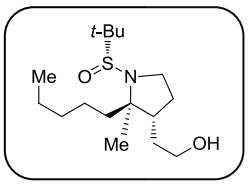
From **36c**, the expected product was obtained following the general procedure as a colorless wax (136 mg, 64%, single diastereoisomer according to ^{1}H NMR): $[\alpha]_D^{20}$ – 39.9 (*c* 0.80, $CHCl_3$); R_f 0.15 (98:2 EtOAc/MeOH); IR ν 3271, 2949, 1454, 1363, 1031, 730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 1H), 7.27 – 7.22 (m, 1H), 7.22 – 7.09 (m, 3H), 4.09 (s, 1H), 4.02 – 3.81 (m, 1H), 3.81 – 3.72 (m, 2H), 3.69 – 3.49 (m, 2H), 2.74 – 2.54 (m, 2H), 2.03 – 1.84 (m, 3H), 1.81 – 1.72 (m, 2H), 1.49 – 1.39 (m, 2H), 1.38 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3 (C), 128.6 (CH), 128.4 (CH), 126.1 (CH), 62.1 (CH_2), 61.3 (C), 61.0 (CH_2), 56.3 (C), 41.4 (CH), 41.1 (CH_2), 34.0 (CH_2), 33.6 (CH_2), 29.9 (CH_2), 23.4 (CH_3), 23.0 (CH_3); GC t_R = 17.22 min.; LRMS (EI) *m/z* (%) 323 (12), 289 (10), 275 (20), 249 (13), 207 (8), 202 (14), 201

(82), 176 (11), 159 (41), 157 (11), 153 (17), 148 (12), 146 (15), 131 (34), 129 (100), 105 (32), 103 (11), 101 (54), 91 (72), 77 (14).

General procedure of Mitsunobu reaction to obtain compounds 40b, 40c and 43+44 (1:1 mixture).

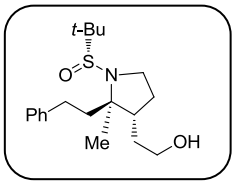
The corresponding diol **39b**, **39c** or **42** (1 equiv) was dissolved in dry THF (0.3 M) under Ar atmosphere and cooled to 0 ºC. PPh_3 (1.2 equiv) was added to the reaction mixture followed by a DIAD solution in THF (0.6 M, 1.2 equiv). The reaction was stirred for 15 h at 25 ºC. All volatiles were removed *in vacuo* before purification by column chromatography (99:1, EtOAc/MeOH) to obtain the corresponding pure products **40b**, **40c** or **43+44**.

(*R*S,2*R*,3*R*)-N-*tert*-Butylsulfinyl-2-methyl-2-pentyl-3-(2'-hydroxyethyl)pyrrolidine (40b)



From compound **39b** (160 mg, 0.5 mmol), the expected product was obtained following the general procedure as a colorless oil (101 mg, 67%, 96:4 dr crude, single stereoisomer after purification according ^{1}H NMR): $[\alpha]_D^{20}$ – 62.5 (*c* 1.05, $CHCl_3$); R_f 0.29 (98:2 EtOAc/MeOH); IR ν 3385, 2954, 2932, 2871, 1458, 1377, 1361, 1035, 1017, 955 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (m, 2H), 3.65 (dd, *J* = 16.0, 8.2 Hz, 1H), 2.78 (dd, *J* = 16.6, 9.7 Hz, 1H), 2.10 – 1.95 (m, 2H), 1.91 – 1.45 (m, 6H), 1.44 – 1.25 (m, 6H), 1.22 (s, 9H), 1.17 (s, 3H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 69.3 (C), 61.9 (CH_2), 57.4 (C), 41.2 (CH), 39.9 (CH_2), 39.8 (CH_2), 32.8 (CH_2), 32.6 (CH_2), 29.5 (CH_2), 24.7 (CH_3), 23.3 (CH_2), 22.8 (CH_2), 21.7 (CH_3), 14.2 (CH_3); GC t_R = 14.83 min.; LRMS (EI) *m/z* (%) 184 (11), 166 (10), 129 (9), 128 (100), 126 (11), 111 (16), 110 (14), 97 (10), 96 (14), 84 (11), 82 (13), 71 (12), 55 (15); HRMS (TOF) calcd for $C_{16}H_{34}NO_2S$ (M^++1) 304.2310, found 304.2302.

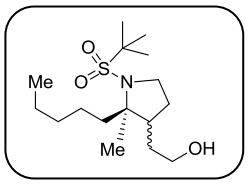
(*R*S,2*R*,3*R*)-N-*tert*-Butylsulfinyl-2-methyl-2-(2'phenylethyl)-3-(2''-hydroxyethyl)pyrrolidine (40c)



From compound **39c** (106 mg, 0.3 mmol), the expected product was obtained following the general procedure as a colorless oil (75 mg, 75%, 96:4 dr crude, single diastereoisomer after purification according to ^{1}H NMR): $[\alpha]_D^{20}$ – 40.4 (*c* 1.10, $CHCl_3$); R_f 0.21 (98:2 EtOAc/MeOH); IR ν 3370, 3025, 2960, 1602, 1455, 1362, 1031, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 2H), 7.24 – 7.12 (m, 3H), 3.82 (t, *J* = 9.5 Hz, 1H), 3.79 – 3.68 (m, 1H), 3.62 (dd, *J* = 15.8, 8.5 Hz, 1H), 2.83 (dd, *J* = 17.1, 9.7 Hz, 1H), 2.67 (t, *J* = 8.5 Hz, 2H), 2.14 (s, 1H), 2.08 – 1.94 (m, 2H), 1.91 – 1.78 (m, 2H), 1.78 – 1.58 (m, 1H), 1.58 – 1.48 (m, 1H), 1.47 – 1.35 (m, 1H), 1.26 (s, 9H), 1.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4 (C), 128.6 (CH), 128.4 (CH), 126.0 (CH), 69.3 (C), 61.6 (CH_2), 57.8 (C), 41.2 (CH), 41.2 (CH_2), 40.0 (CH_2), 32.7 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 24.9 (CH_3), 21.8 (CH_3); GC t_R = 17.3 min.; LRMS (EI) *m/z* (%) 230 (9), 207 (17), 202 (25), 200 (21),

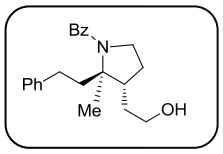
186 (24), 172 (12), 159 (36), 158 (32), 131 (24), 127 (43), 126 (41), 118 (16), 117 (25), 108 (11), 105 (10), 92 (11), 91 (100), 33 (65), 32 (71),l 77 (11), 68 (17), 56 (17), 55 (24).

(2*R*, 3*S*)- and (2*R*,3*R*)-N-*tert*-Butylsulfonyl-2-methyl-2-pentyl-3-(2'-hydroxyethyl)pyrrolidine (43+44)



A 1:1 mixture of compounds **43** and **44** was obtained from compound **42** (100 mg, 0.15 mmol) following the general procedure of the Mitsunobu reaction (47 mg, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 – 3.72 (m, 2H), 3.71 – 3.53 (m, 4H), 3.44 (dd, *J* = 16.4, 8.1 Hz, 1H, **43**), 3.24 (dd, *J* = 16.3, 9.8 Hz, 1H, **44**), 2.25 – 2.10 (m, 1H), 2.10 – 1.94 (m, 4H), 1.93 – 1.46 (m, 10H), 1.45 (s, 3H, **43**), 1.40 (s, 18H), 1.32 (s, 3H, **44**), 1.32 – 1.01 (m, 11H), 0.88 (t, *J* = 6.5 Hz, 6H).

Procedure of benzoylation to obtain compound: (2R,3R)-N-benzoyl-2-methyl-2-pentyl-3-(2'-hydroxyethyl)pyrrolidine (41).

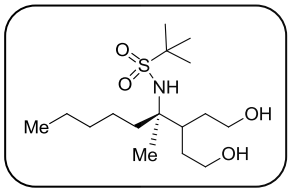


Pyrrolidine **40c** (20 mg, 0.05 mmol) was dissolved in dry MeOH (0.5 mL) at 0 °C and a 4 M solution of HCl in dioxane (50 µL) was dropwised. After stirring for 1 h, the solvent was removed under vacuum and the hydrochloride was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C. A solution of NaOH (2M, 1 mL) was added followed by benzoylchloride (7 µL, 0.06 mmol) and the reaction mixture was stirred at 25 °C. during 15 h. The product was extracted with CH_2Cl_2 and washed with NaOH (2M) and brine. Organics were dried over $MgSO_4$, filtered and concentrated under vacuum. After column chromatography (7:3 Hexane/EtOAc), the expected product **41** was obtained as a colorless oil (15 mg, 90%, single diastereoisomer according to ^{1}H NMR after purification): $[\alpha]_D^{20}$ – 61.5 (*c* 1.00, $CHCl_3$); R_f 0.31 (1:1 Hexane/EtOAc); IR ν 3406, 3025, 2930, 1612, 1415, 1265 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 5H), 7.31 – 7.27 (m, 1H), 7.26 – 7.21 (m, 3H), 7.20 – 7.12 (m, 1H), 3.79 (dt, *J* = 15.6, 6.1 Hz, 1H), 3.68 (dt, *J* = 10.1, 7.5 Hz, 1H), 3.46 – 3.29 (m, 2H), 2.97 – 2.81 (m, 1H), 2.72 – 2.60 (m, 2H), 2.37 (dddd, *J* = 13.9, 11.1, 5.8, 3.1 Hz, 1H), 2.01 – 1.90 (m, 1H), 1.85 – 1.42 (m, 5H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8 (C), 142.6 (C), 139.0 (C), 129.4 (CH_2), 128.7 (CH_2), 128.5 (CH_2), 128.5 (CH_2), 126.4 (CH_2), 125.9 (CH_2), 66.8 (C), 61.8 (CH_2), 50.9 (CH_2), 41.7 (CH), 37.8 (CH_2), 32.0 (CH_2), 30.5 (CH_2), 28.6 (CH_2), 19.6 (CH_3); GC t_R = 22.5 min.; LRMS (EI) *m/z* (%) 244 (01), 231 (23), 230 (39), 207 (28), 188 (14), 187 (12), 106 (9), 105 (100), 91 (9), 77 (25).

General procedure for the oxidation of the sulfinyl group to obtain compounds 42 and 44.

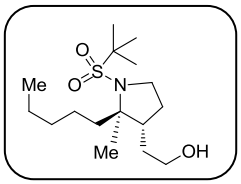
The corresponding sulfinyl compound (**39b** or **40b**) was dissolved in dry CH_2Cl_2 (0.05 M) and placed under Ar atmosphere. The solution was cooled at 0 ºC and *m*-CPBA (1.20 equiv) was added. The reaction was stirred 1 h at 0 ºC, observing full conversion by TLC. Quenched by adding a saturated aqueous solution of $NaHSO_3$ and saturated aqueous solution of $NaHCO_3$, the layers were separated and the aqueous phase was extracted with CH_2Cl_2. Combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure.

(4*R*)-N-*tert*-Butylsulfonyl-1-hydroxyl-3-(2'-hydroxyethyl)-4-methylnonan-4-amine (42)



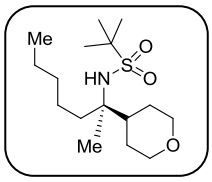
Compound **42** was obtained following the general procedure from compound **39b** (0.35 mmol). After column chromatography (1:1 Hexane/EtOAc) the expected product was obtained as a colorless oil (112 mg, 95%, single diastereoisomer according to ^{1}H NMR): $[\alpha]_D^{20}$ – 5 (*c* 0.60, $CHCl_3$); R_f 0.14 (1:1 Hexane/EtOAc); IR ν 3443, 2953, 2872, 1468, 1287, 1117, 1049, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (s, 1H), 3.84 – 3.60 (m, 4H), 2.01 – 1.74 (m, 4H), 1.63 – 1.39 (m, 4H), 1.38 (s, 9H), 1.34 (s, 3H), 1.31 – 1.16 (m, 5H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 64.3 (C), 62.1 (CH_2), 61.3 (CH_2), 60.1 (C), 39.7 (CH), 38.9 (CH_2), 33.2 (CH_2), 32.5 (CH_2), 32.3 (CH_2), 24.6 (CH_3), 23.1 (CH_2), 22.8 (CH_2), 21.5 (CH_3), 14.3 (CH_3); GC t_R = 17.6 min.; LRMS (EI) *m/z* (%) 338 (M^++1, 1), 322 (13), 241 (7), 234 (29), 202 (35), 115 (9), 114 (100), 57 (28).

(2*R*,3*R*)-N-*tert*-Butylsulfonyl-2-methyl-2-pentyl-3-(2'-hydroxyethyl)pyrrolidine (44)



Compound **44** was obtained from compound **40b** (90 mg, 0.13 mmol) following the general procedure of sulfinyl oxidation. In this case a single diastereoisomer was obtained as a colorless wax (40 mg, 95%, 96:4 dr crude, single diastereoisomer according to ^{1}H NMR after purification): $[\alpha]_D^{20}$ – 5 (*c* 070, $CHCl_3$); R_f 0.16 (7:3 Hexane/EtOAc); IR ν 3489, 2956, 2930, 2871, 1465, 1298, 1116, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 – 3.73 (m, 1H), 3.72 – 3.65 (m, 1H), 3.64 – 3.54 (m, 1H), 3.24 (td, *J* = 9.9, 6.5 Hz, 1H), 2.99 (br s, 1H), 2.25 – 2.10 (m, 1H), 2.10 – 1.89 (m, 2H), 1.78 – 1.61 (m, 2H), 1.61 – 1.50 (m, 1H), 1.50 – 1.42 (m, 1H), 1.40 (s, 9H), 1.37 – 1.34 (m, 1H), 1.32 (s, 3H), 1.31 – 1.15 (m, 5H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.1 (C), 61.9 (C), 67.8 (CH_2), 49.8 (CH_2), 42.5 (CH), 39.5 (CH_2), 33.0 (CH_2), 32.4 (CH_2), 28.9 (CH_2), 25.6 (CH_3), 24.33 (CH_2), 22.8 (CH_2), 22.6 (CH_3), 14.2 (CH_3); GC t_R = 18.0 min.; LRMS (EI) *m/z* (%) 248 (13), 184 (7), 129 (8), 128 (100), 111 (6), 57 (22).

(4R)-N-tert-Butylsulfonyl-1-(4'-oxacyclohexyl) heptan-2-amine (45).



Compound **45** (20%) was obtained as byproduct in the reaction to obtain compound **43+44**. R_f 0.50 (7:3 Hexane/EtOAc); IR ν 3289, 2952, 2928, 1457, 1299, 1121, 952 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.11 – 3.98 (m, 2H), 3.48 – 3.29 (m, 3H), 1.88 (tt, *J* = 12.1, 3.2 Hz, 1H), 1.78 – 1.44 (m, 7H), 1.40 (s, 9H), 1.35 (s, 3H), 1.33 – 1.16 (m, 7H), 0.90 (t, *J* = 6.8 Hz, 3H); GC t_R = 16.6 min.; LRMS (EI) *m/z* (%) 248 (15), 234 (30), 178 (7), 128 (43), 114 (100), 57 (39); ^{13}C NMR (101 MHz, $CDCl_3$) δ 68.4 (C), 63.5 (CH_2), 60.3 (CH_2), 53.6 (C), 44.9 (CH), 38.4 (CH_2), 32.3 (CH_2), 27.8 (CH_2), 27.3 (CH_2), 24.7 (CH_3), 23.2 (CH_2), 22.8 (CH_2), 21.2 (CH_3), 14.2 (CH_3).

Conclusions

From **Chapter I** we can conclude that 2-allylpiperidine derivatives can be prepared in an enantioenriched way by using a two steps protocol based on the indium-mediated aminoallylation methodology developed in our research group.

- The chemoselectivity of both steps has permitted the synthesis of both enantiomeric forms of this interesting building block in an excellent overall yield (90%) in a 4g-scale.
- The synthetic utility of this building block has been illustrated in the synthesis of some natural and unnatural products, by taking advantage of straightforward modifications of the allyl moiety and functionalizations on the nitrogen atom.

In **Chapter II**, a general synthesis of all known natural tetraponerines, from **T1** to **T8**, has been described. The synthesis was inspired on biosynthetic and degradation studies as well as supported by a configurational analysis of **T3** and **T4** by DFT calculations.

- The divergence of the procedure has made possible the access to all tetraponerines from simple materials such us 4-bromobutanal, 5-bromopentanal, allylbromide, *cis*-hexene and both enantiomeric forms of *N*-*tert*-butylsulfinamide.
- The prevalence of the stereocontrol by the chiral sulfinyl group in the second aminoallylation step, and the thermodynamic control at the aminal center in the last cyclization, have been key steps in the preparation of all enantioenriched tetraponerines.

Chapter III gathers all chiral linear prenylamines synthesized by using a 2-azonia-Cope rearrangement.

- An enantioenriched branched homoallylamine has been used as a chiral amino-prenyl donor to a variety of aldehydes, obtaining the corresponding linear homoallylic amines in good yields and enantioselectivities. The mild reaction conditions chosen have demonstrated to be compatible with some functional groups, including an ester functionality that served as a convenient handle to form lactams *in situ*.
- A substoichiometric amount of an acid has been shown to be essential in the rearrangement process.

- The absolute configuration of some linear homoallylic amines was unequivocally determined by analyzing the ^{1}H NMR spectra of their (*R*)-MPA-derivatives.
- The singular reactivity of these trisubstituted double bonds compared to monosubstituted homologues has been illustrated in the preparation of pyrrolidines by acid catalyzed hydroamination.

Lastly, in **Chapter IV**, the use of 2,4-pentadienyl bromide as diallyl reagent was explored in our indium-mediated protocol, giving access to a new family of homoallylic amines.

- The protocol accomodates a wide range of aromatic and aliphatic aldehydes, obtaining excellent to good diastereo- and excellent γ-regioselectivities. Noteworthy, the methodology has also been adapted to ketones with excellent results.
- The dihydroboration/dioxidation of selected compounds was followed by a Mitsunobu ciclyzation to afford enantioenriched 2,2,3-trisubstituted pyrrolidines. Interesting, it was demonstrated that the chiral sulfinyl group is crucial in the differentiation of the diastereotopic hydroxyethyl groups upon cyclization.

Biography

I was born in Alicante on September 28th, 1987.

I took my Primary studies at the Santa Teresa first School in Alicante. From here I continued to I.E.S. Enric Valor High School in El Campello, Alicante, where I graduated in 2005 with honors level.

I took my ungraduate degree in Chemistry at Faculty of Science, University of Alicante, graduating in 2010. Upon finishing the degree I was presented with the Special Mention Award for achieving the highest mark in the year.

During the last year of my degree, I was granted a research fellowship for students from the *Ministerio de Educación y Ciencia*, which I used working in the Department of Organic Chemistry at the University of Alicante.

From September 2010 to February 2011, thanks to a postgraduate grant co-funded by *FICYT* and *Ministerio de Educación y Ciencia*, I moved to Stockholm, Sweden. I was involved in research at the Institute of Environmental Medicine at the *Karolinska Institutet* under the supervision of Dr. Rachel Heimeier and Prof. Helen Håkanson.

In September 2010 I started my Master's programme entitled *Máster en Química Médica* at the Faculty of Sciences of the University of Alicante. I presented my master's thesis in September 2012 obtaining the maximum score (10).

Since then, thanks to a doctoral grant from the *Generalitat Valenciana* (VALi+d, ACIF/2011/159) I have been working on my PhD at the Organic Synthesis Institute of the University of Alicante.

Resumen en castellano

Esta memoria describe el uso del protocolo de aminoalilación mediada por indio metálico, desarrollado en nuestro grupo de investigación, para la síntesis de homoalilaminas enantioméricamente enriquecidas, de las cuales se conoce que poseen un gran potencial actuando como productos de partida en la síntesis de compuestos naturales. En este caso se ha explorado la utilización de diversos derivados de bromuro de alilo en la reacción de aminoalilación, así como el potencial sintético de los productos obtenidos.

La tesis está dividida en cuatro capítulos, cada uno de los cuales posee un resumen que contiene una pequeña introducción al contenido del capítulo y los resultados más relevantes del mismo. Los capítulos han sido organizados de forma cronológica conforme se han ido obteniendo los resultados.

Al final de este libro se ha adjuntado un CD con la Información Complementaria de la tesis (Supporting Information), el cual incluye la totalidad de los espectros de RMN ^{1}H y de RMN ^{13}C para todos los compuestos preparados, así como los cromatogramas de gases (GC) y espectros de masas (MS) de todas las tetraponerinas sintetizadas (Capítulo II) y los HPLC de algunos de los compuestos obtenidos de forma enantioméricamente pura. También se han adjuntado las geometrías optimizadas y las energías del punto cero, así como los datos termodinámicos de todas las estructuras calculadas de las tetraponerinas **T3** y **T4** (Capítulo II). Así mismo, se han incluído los datos cristalográficos en formato CIF de las estructuras cristalinas mostradas en la tesis.

Una parte del trabajo recogido en esta memoria, ha sido publicado en los siguientes artículos:

- Bosque, I.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2012**, *77*, 780.
- Bosque, I.; González-Gómez, J. C.; Guijarro, A.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2012**, *77*, 10340.
- Bosque, I.; Foubelo, F.; González-Gómez, J. C. *Org. Biomol. Chem.* **2013**, *11*, 7507.

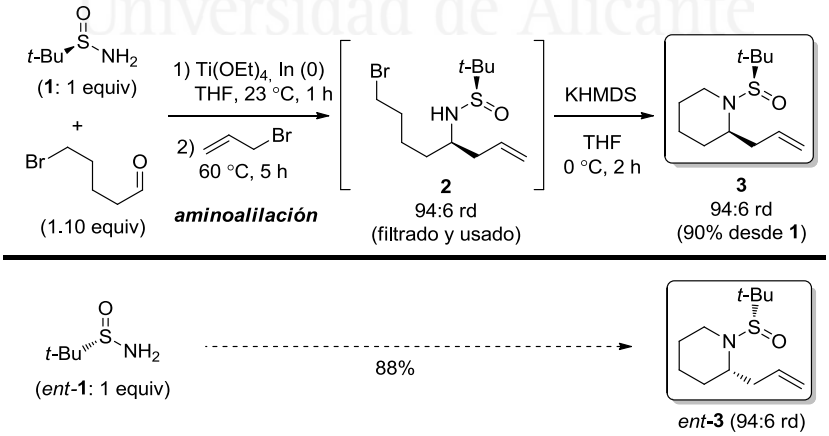
Capítulo I:

2-Alilpiperidina Enantioméricamente Enriquecida: Un Precursor muy Útil en la Síntesis de Alcaloides.

En este capítulo se describe la preparación estereocontrolada de la (2*R*,R_s)-2-alil-*N*-(*terc*-butilsulfinil)piperidina y de su enantiómero de forma muy eficiente y en una escala de hasta 4 gramos. El potencial de este compuesto como producto de partida ha quedado demostrado con la síntesis de varios productos naturales y no naturales como son la (+)-coniina, la (-)-pelletierina o la 5-*epi*-cermicina C.

Síntesis de la 2-Alilpiperidina.

El proceso de aminoalilación desarrollado en nuestro grupo de investigación se empleó sobre el 5-bromopentanal utilizando el enantiómero (*R*) de la *N*-*terc*-butilsulfinamida. El producto, el cual se obtuvo con buena diastereoselectividad (94:6 rd), se utilizó sin necesidad de purificación en la posterior ciclación. Esta reacción se llevó a cabo utilizando KHMDS en THF a 0 ºC, ya que estas condiciones fueron las que mejores resultados ofrecieron. Así, el producto **3** se obtuvo con un excelente rendimiento global (90% a partir de la sulfinamida de partida) y una diasteroselectividad de 94:6 rd (**Esquema 1**). De la misma forma se sintetizó el correspondiente enantiómero partiendo, en este caso, de la (*S*)-*N*-*terc*-butilsulfinamida, con iguales resultados.



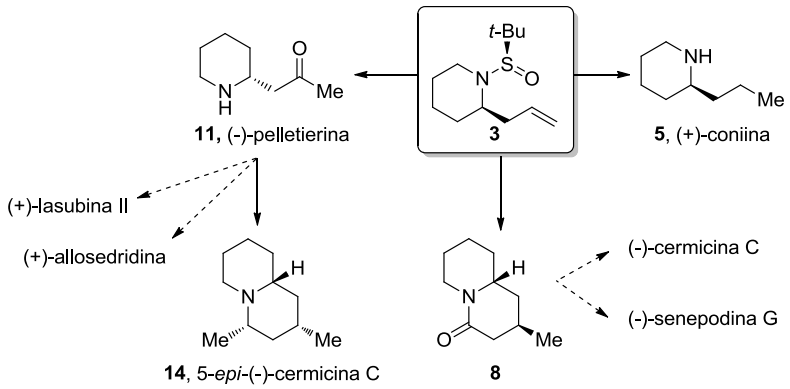
Esquema 1

Síntesis de Otros Alcaloides Relacionados.

A partir de este compuesto **3**, se sintetizó el alcaloide natural (+)-coniina, mediante dos sencillos pasos de desprotección del grupo sulfinilo en medio ácido, e hidrogenación del doble enlace alílico utilizando Pd/C como catalizador. La comparación de la rotación óptica del producto obtenido con la de la encontrada en la bibliografía para la (+)-coniina, confirmó la estereoquímica de la misma, la cual resultó ser la configuración absoluta predicha según el modelo de trabajo usado en nuestro protocolo de aminoalilación.

La síntesis formal de la (-)-cermicina C y la (-)-senepodina G se llevó a cabo a partir del mismo compuesto **3** (**Esquema 2**). En este caso, se cambió en grupo sulfinilo del nitrógeno por el grupo acriloílo utilizando las condiciones de Schotten-Bauman. Tras ello, se llevó a cabo la metátesis de cierre de anillo (RCM) obteniendo el correspondiente bicilo [4.4.0], el cual, tras adición-1,4 de metilo, dió lugar al compuesto **8**, reconocido precursor de los alcaloides como los dos mencionados anteriormente.

Otro alcaloide más simple, la (-)-pelletierina, se obtuvo, al igual que en el caso anterior, mediante un cambio en el grupo protector del nitrógeno en el compuesto **3** (en este caso al grupo *terc*-butoxicarbonil o Boc), y ruptura oxidativa del doble enlace alílico, utilizando para ello cantidades catalíticas de tetraetóxido de osmio. Finalmente, la desprotección del nitrógeno en condiciones ácidas dió lugar a la (-)-pelletierina, la cual es a su vez precursora de otros alcaloides como son la (+)-allosedridina o la (+)-lasubina II, y de otros productos no naturales como la 5-*epi*-(+)-cermicina C. La síntesis de esta última se llevó a cabo en tres pasos partiendo de la pelletierina sintetizada.



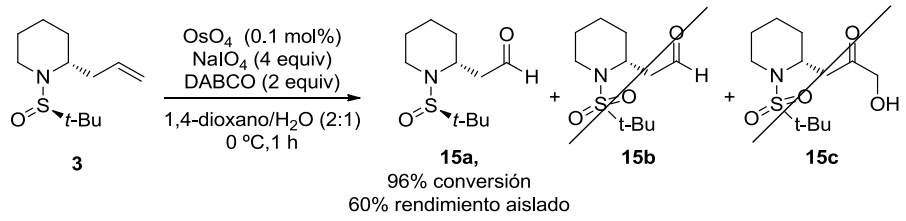
Esquema 2

Cabe destacar que, puesto que la síntesis de los compuestos **3** y *ent*-**3** mediante la metodología propuesta resultó ser muy efectiva, formalmente se podría acceder a los cuatro diasteroisómeros tanto de la senepodina G como de la cermicina C, siguiendo los caminos de reacción descritos.

Síntesis de N-terc-Butilsulfinil-2-(2'-piperidil)acetaldehído.

Como se recoge en la bibliografía, la adición de reactivos organometálicos a *N*-carbamatos derivados del 2-(2'-piperidil)acetaldehído dan acceso a alcaloides del género *Sedum*. Por ello, consideramos de interés la preparación del *N-terc*-butilsulfinil-2-(2'-piperidil)acetaldehído, de manera que la quelación por parte del grupo sulfinilo y el carbonilo, proporcionaran un entorno adecuado para la adición estereoselectiva en el aldehído, pudiendo así acceder a la síntesis de compuestos pertenecientes a esta familia de alcaloides.

La ruptura oxidativa del doble enlace alílico del compuesto **3** se llevó a cabo bajo las condiciones de Jonhson-Lemieux, pero no se obtuvo el compuesto deseado, sino una mezcla de los compuestos derivados de sulfonilo, **15b** y **15c**. Tras una exhaustiva optimización de las condiciones de reacción usando diferentes aditivos, diferente carga del aditivo así como diferentes tiempos de reacción y temperaturas, la utilización de DABCO como aditivo a 0 ºC proporcionó el entorno idóneo para provocar la ruptura oxidativa del alilo del compuesto **2** y, al mismo tiempo, evitar la oxidación del sulfinilo obteniendo así el compuesto deseado **15a**. Sin embargo, a pesar de la buena conversión obtenida, el rendimiento aislado no superó el 60% (tres réplicas, **Esquema 3**).



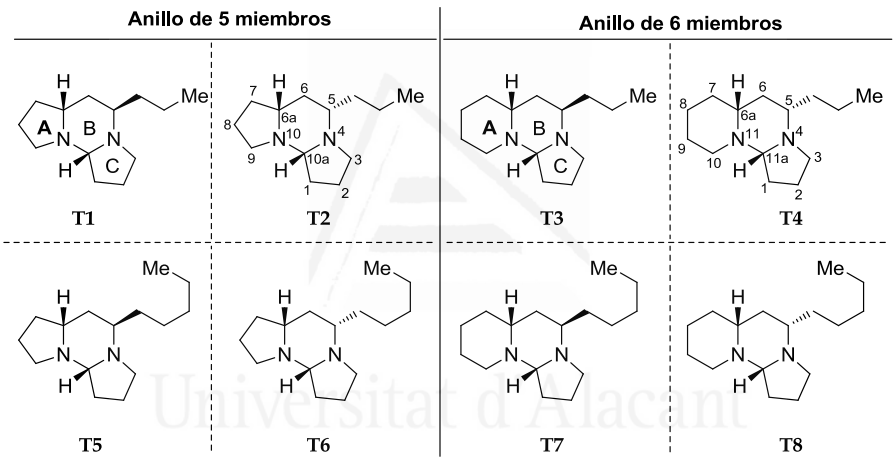
Esquema 3

Aún así, la adición de alilindio se realizó a 25 ºC y a -60 ºC, obteniendo, tras posterior hidrogenación del doble enlace, mezclas de la 2-*epi*-(-)-halosalina y su homólogo natural, que resultó ser minoritario en ambos casos.

Capítulo II:

Tetraponerinas: Singular Familia de Alcaloides.

Las tetraponerinas son unos alcaloides muy particulares que poseen un esqueleto tricíclico doblemente nitrogenado, y una cadena lateral en una de sus posiciones. Existen ocho tetraponerinas naturales, llamadas **T1** a **T8**, y entre ellas se diferencian en el tamaño del anillo A (de 5 o 6 átomos), en la longitud de la cadena lateral (propilo o pentilo) posicionada en el carbono 5, y en la estereoquímica de este carbono (**Esquema 4**).



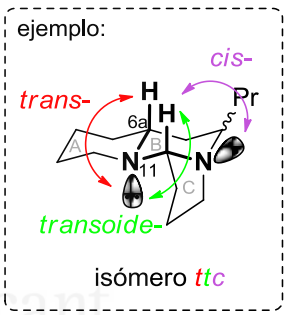
Esquema 4

Hasta la fecha, según lo encontrado en la bibliografía, sólo se ha descrito un procedimiento general que permita el acceso a todas las tetraponerinas naturales. Sin embargo, se conoce muy poco sobre su modo de actuación a nivel biológico, aunque si se han encontrado propiedades muy interesantes. Es por ello que nos planteamos la búsqueda de una ruta sintética que permitiera acceder a todas las tetraponerinas. Además, consideramos que un estudio teórico del espectro configuracional de las mismas, podría ayudar a entender en un futuro su modo de actuación.

Análisis Estereoquímico de T3 y T4 Mediante Estudios Computacionales.

Se realizó un exhaustivo estudio de todas las posibles configuraciones de las tetraponerinas **T3** y **T4**, optimizando las geometrías de cada uno de los 12 isómeros posibles en cada una de ellas.

La nomenclatura usada para describir cada una de estos posibles isómeros configuracionales se centró en la fusión de los fragmentos de indolizidina y quinolicidina de estas tetraponerinas, así como en la fusión entre ambos fragmentos. Así pues, se escogió como punto de partida el hidrógeno del carbono 6a, el cual posee la misma configuración (*R*) en las ocho tetraponerinas naturales. La configuración relativa de este hidrógeno con el nitrógeno más cercano, definió la fusión de este fragmento de quinolicidina como *cis*- o *trans*-, es decir, *c*- o *t*-; la relación entre este nitrógeno y el hidrógeno del carbono aminal, se definió como *cisoide*- o *transoide*-, es decir, *c*- o *t*-; y por último, la fusión del fragmento de indolicidina, es decir, la relación entre el hidrógeno del carbono aminal y el otro nitrógeno, se describió como *cis*- o *trans*-, es decir, *c*- o *t*-. De esta manera, cada isómero configuracional se definió con tres descriptores, como en el ejemplo mostrado, que se refiere al isómero *trans-transoide-cis*, es decir, el isómero *ttc*.



Mediante el uso de los cálculos DFT, se observó que para la tetraponerina **T3**, el isómero configuracional más abundante era el *ttc*-, representando el 65% de la población a 25 ºC y seguido por el isómero *ttt*- con un 34% de la población. El tercer isómero más estable resultó ser el *ctt2*-, representado tan sólo por el 0.47% de la población. Por otro lado, en el caso de la tetraponerina **T4**, el isómero configuracional más abundante con diferencia resultó ser el *ttt*- representando el 95% de la población y seguido por el isómero *ttc*- representando tan solo un 4.5% de la población.

A grandes rasgos, la primera conclusión general que se extrajo a la vista de estos resultados fue que, tanto para **T3** como para **T4**, al menos el 99% de la población estaba representada por los isómeros *ttc*- o *ttt*-. Este hecho implica que en el 99% de la población de cada una de las tetraponerinas, el carbono aminal posee la misma configuración (*S*), con independencia del tipo de fusión en el fragmento

de indolicidina. Conviene destacar que, esta configuración no se observa sólo en las tetraponerinas **T3** y **T4**, sino también en el resto de tetraponerinas naturales.

Por otro lado, dado que los isómeros configuracionales más poblados fueron los mismos en ambas tetraponerinas (*ttc* y *ttt*), y que podrían interconvertirse po inversión del átomo de nitrógeno 4, se realizó un estudio de dicha barrera energética de interconversión para cada una de las tetraponerinas.

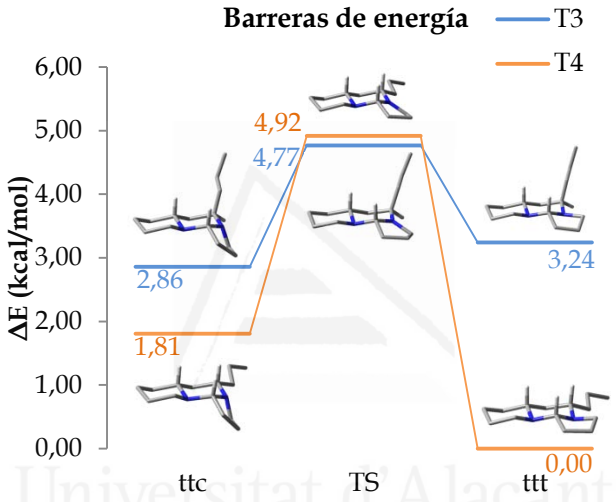
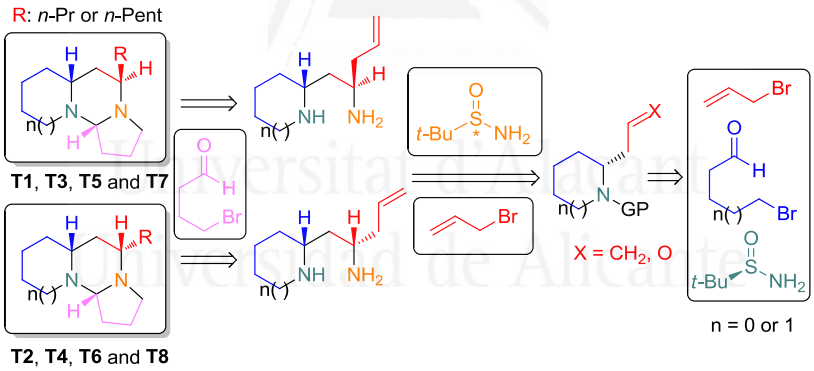


Gráfico 1: En este gráfico se muestran las energías de activación necesarias para la inversión del N_4 para **T3** (ΔE = 1.90 kcal·mol^{-1}) y para **T4** (ΔE = 4.92 kcal·mol^{-1}) al nivel de B3LYP/6-311+G-7(2d,p). En las estructuras calculadas para los estados de transición en ambas tetraponerinas (mostrados en el centro del gráfico) se puede observar la estructura trigonal plana que adquiere el nitrógeno para conseguir la inversión.

Como se muestra en el **Gráfico 1**, la tetraponerina **T4** resultó ser más estable que su homóloga **T3**, concretamente 2.52 kcal·mol^{-1} más estable. Además, en ambos casos la barrera de interconversión calculada entre los dos isómeros resultó ser menor de 5 kcal·mol^{-1} (4.92 kcal·mol^{-1} en el caso de **T4** y 1.90 kcal·mol^{-1} en el caso de **T3**). Esto implica una rápida interconversión entre ambos isómeros conformacionales.

Análisis Retrosintético.

Basándonos en estudios de degradación encontrados en la bibliografía y en los cálculos DFT anteriores, se propuso una ruta sintética en la cual la formación de los anillos B y C (de igual tamaño en todas las tetraponerinas) se llevaría a cabo mediante la doble ciclación intramolecular de 4-bromobutanal sobre las adecuadas diaminas. Sabiendo que todas las tetraponerinas poseen la misma estereoquímica en el centro formado en esta reacción y suponiendo que los alcaloides deben corresponder a los aminales más estables, se dedujo que la estereoquímica de este último centro vendría gobernada por la estabilidad del aminal intermedio y que, por tanto, correspondería a la de las tetraponerinas naturales. Teniendo en cuenta que en estas diaminas los grupos amino se encuentran situados en posiciones contiguas a los dos estereocentros de la molécula, se pensó en el uso iterativo del proceso de aminoalilación desarrollado en nuestro grupo de investigación y utilizado también en el capítulo anterior de esta memoria (**Esquema 5**).



Esquema 5

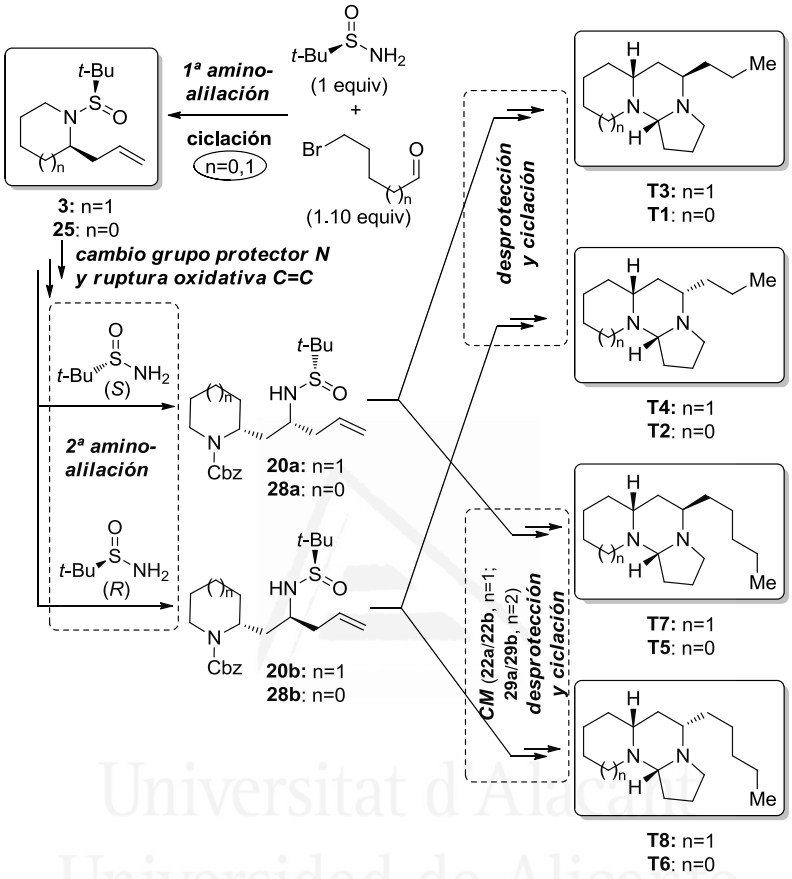
Síntesis de Todas las Tetraponerinas Naturales Conocidas.

Con todo lo anteriormente mencionado, se procedió a la preparación de las tetraponerinas, como muestra el **Esquema 6**, partiendo de 4-bromobutanal o 5-bromobutanal en función del tamaño de anillo A de la tetraponerina en cuestión. La primera aminoalilación se realizó, en los dos casos, usando la (*R*)-*terc*-butilsulfinamida ya que en todas las tetraponerinas este centro posee la misma configuración absoluta. Tras la posterior ciclación, se obtuvo la piperidina **3** o

pirrolidina **25** con buenos rendimientos globales así como diastereoselectividades (76%, 95:5 rd para **25**; y 90%, 94:6 rd para **3**).

Se llevó a cabo el cambio del grupo protector del nitrógeno, por el grupo Cbz y la ruptura oxidativa del doble enlace usando tetraetóxido de osmio catalítico obteniendo los aldehídos **19** o **27**. Tanto para n=0 como para n=1, los rendimientos de ambos pasos fueron superiores al 80%.

La segunda aminoalilación sobre los aldehídos anteriores, se llevó a cabo utilizando uno u otro enantiómero de la *terc*-butilsulfinamida: en la síntesis de las diaminas precursoras de las tetraponerinas impares (**T1**, **T3**, **T5**, **T7**), se escogió en enantiómero (*S*) y, en el caso de las diaminas precursoras de las tetraponerinas pares (**T2**, **T4**, **T6**, **T8**), el (*R*). Para el éxito de la ruta propuesta en la síntesis de la totalidad de las tetraponerinas naturales, era fundamental que, en esta segunda aminoalilación, la estereoquímica del nuevo carbono formado estuviera regida por la estereoquímica de la sulfinamida utilizada, y no del aldehído de partida. En caso contrario, el procedimiento sintético quedaría limitado a la síntesis de sólo cuatro de las tetraponerinas naturales: las pares o las impares. Por ello la obtención de las correspondientes diaminas **20a**, **20b**, **28a** y **28b** con la estereoquímica deseada como productos mayoritarios de la aminoaliación, confirmó que ésta estaba gobernada, como era deseado, por la quiralidad de la sulfinamina. Cabe destacar que para cada pareja de diaminas (**20a**/**20b** y **28a**/**28b**) se encontró un caso en el cual la diastereoselectividad fue claramente peor, pero incluso así, estas diaminas se obtuvieron con buenos rendimientos (69 - 90%) y, además, como únicos diastereoisómeros tras purificación por columna cromatográfica.



Esquema 6

Para la síntesis de las tetraponerinas con grupo propilo en el carbono 5 (**T1** a **T4**), las diaminas sintetizadas fueron directamente sometidas a eliminación del sulfinilo en medio ácido, eliminación del grupo Cbz e hidrogenación del doble enlace bajo atmósfera de H_2 (4 atm) y final ciclación, la cual se realizó en CH_2Cl_2 en presencia de K_2CO_3 en tan solo 4 h a 25 ºC. Es importante resaltar que las cuatro tetraponerinas se obtuvieron con rendimientos moderados pero excelentes diastereoselectividades, observando un sólo diastereoisómero en cromatografía de gases y siendo el espectro de masas de todas ellas igual al descrito en la bibliografía.

En el caso de las tetraponerinas con grupo pentilo en el carbono 5 (**T5** a **T8**), se necesitó un paso previo de alargamiento de la cadena. Para ello se recurrió a la metátesis cruzada (CM) con *cis*-3-hexeno utilizando el catalizador de Grubbs de

segunda generación y en presencia de $Ti(OEt)_4$, obteniendo las correspondientes diaminas **22a**, **22b**, **29a** y **29b** con excelentes rendimientos (78-86%). Siguiendo los mismos pasos descritos para las anteriores diaminas, se obtuvieron finalmente las tetraponerinas de cadena larga, observando de nuevo la presencia de un sólo diastereoisómero mediante cromatografía de gases, al igual que un espectro de masas idéntico al descrito en la bibliografía.

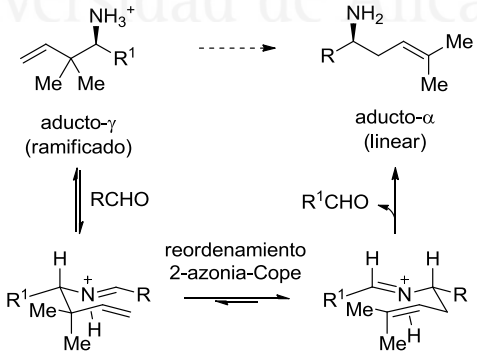
Por tanto, ha quedado demostrado que esta metodología es aplicable a la síntesis de todas las tetraponerinas naturales conocidas. Además, la presencia del grupo alilo en las diaminas sintetizadas podría permitir la obtención de análogos de estas tetraponerinas mediante la reacción de metátesis cruzada con otros alquenos, abriendo la puerta a nuevos derivados que podrían superar las propiedades que poseen los derivados naturales.

Capítulo III:

Un Protocolo General para Acceder a Homoprenilaminas Lineales.

Las α-homoprenilaminas han sido muy utilizadas en ciclaciones 5-*endo*-*trig* para la obtención de pirrolidinas, así como en la síntesis de productos naturales. Su reactividad bajo condiciones catiónicas y radicalarias también ha sido muy estudiada, haciendo de estas aminas unos productos de partida muy interesantes. Sin embargo, hasta la fecha se conocen muy pocos procedimientos que permitan sintetizar homoprenilaminas lineales y aún menos de manera enantioselectiva.

Como ya ha sido descrito en varias ocasiones en la bibliografía, el reordenamiento 2-azonia-Cope permite la aminoalilación estereoselectiva de un aldehído en medio ácido utilizando para ello un donor quiral. Sin embargo, esta metodología no ha sido empleada hasta la fecha para la síntesis de homoprenilaminas lineales. Por ello nos planteamos la posibilidad de usar este reordenamiento partiendo de un donor quiral, el cual sería, en este caso, una homoprenilamina ramificada (**Esquema 7**). En nuestro grupo de investigación ya se ha observado que la adición de bromuro de prenilindio a la imina derivada del 3-fenilpropanal, produce la correspondiente homoalilprenilamina ramificada enantiomérica enriquecida, la cual podría ser el donor quiral que se requiere.



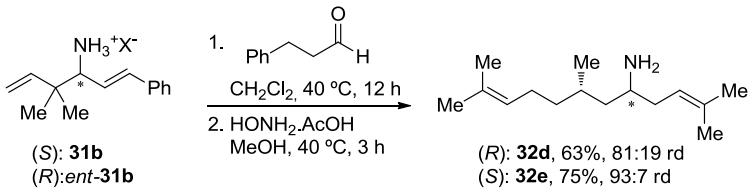
Esquema 7

Síntesis del Donor Quiral y Optimización de las Condiciones de Reacción

Las condiciones de reacción escogidas para llevar a cabo el reordenamiento 2-azonia-Cope fueron muy sencillas, usando CH_2Cl_2 como disolvente, el clorohidrato de la homoprenilamina ramificada y 3-fenilpropanal como aldehído aceptor. Tras probar dos posibles candidatos a donores, el que mejor diastereoselectividad ofreció fue el derivado del cinamaldehído, con el cual se obtuvo la correspondiente homoprenilamina libre en un 65% de rendimiento con una enantioselectividad de 88:12 re. Tras la optimización de condiciones a diferentes temperaturas, diferentes tiempos de reacción y en presencia de cantidades catalíticas de un ácido quiral, las mejores condiciones fueron con CH_2Cl_2 a 40 ºC, obteniendo la misma enantioselectividad mencionada en las anteriores condiciones (88:12 re) pero con un mejor rendimiento (78%).

Alcance y Limitaciones de la Metodología

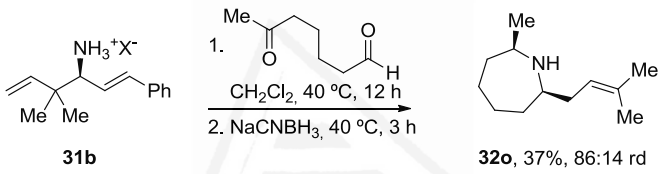
Una variedad de aldehídos fue estudiada bajo estas condiciones de reacción, incluyendo sustratos tanto alifáticos como aromáticos. En el caso de los aldehídos alifáticos, se obtuvieron buenos rendimientos (63 - 78%) y de moderadas a buenas enantioselectividades (81:19 - 93:7 re). Cabe resaltar que cuando se utilizó un aldehído quiral como el (*S*)-citronelal con ambos enantiómeros del donor quiral, los resultados tanto en rendimiento como en diastereoselectividad de las dos homoprenilaminas obtenidas fueron muy diferentes, observándose un efecto cooperativo significativo entre el centro estereogénico del aldehído y el del sulfinilo (**Esquema 8**).



Esquema 8

En el caso de la utilización de aldehídos aromáticos con sustituyentes electrón-atrayentes, los rendimientos obtenidos fueron algo peores (30 - 83%), pero las enantioselectividades fueron mejores (89:11 - 94:6 re). Además se observó que la metodología toleraba la presencia de grupos nitro y halógenos en el esqueleto del aldehído. Por ello se extendió el uso de esta metodología a aldehídos con un grupo éster a 2, 3, o 4 metilenos de distancia. Bajo las condiciones de reacción

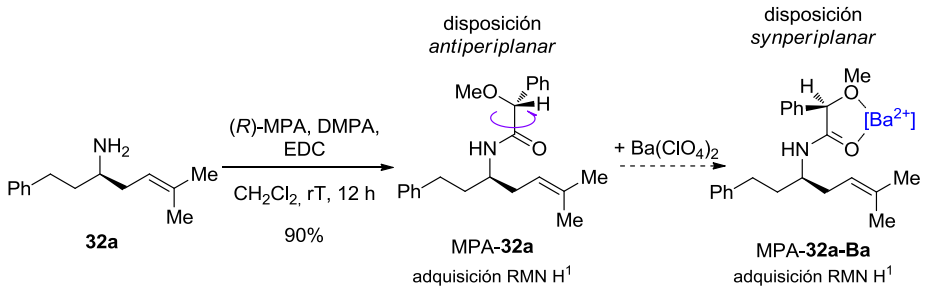
descritas se logró la ciclación *in situ* obteniéndose las correspondientes β- y γ-lactamas. La δ-lactama no se obtuvo directamente, sino que el correspondiente aminoéster abierto, una vez aislado, se trató con MeONa en MeOH consiguiendo, ahora sí, la correspondiente lactama. Sin embargo, un ejemplo más interesante todavía es el de la utilización de un cetoaldehído, concretamente el 6-oxoheptanal. En este caso el reordenamiento sólo se llevó a cabo en el carbonilo del aldehído, produciéndose de nuevo la ciclación *in situ*. Esta ciclación dio lugar al correspondiente iminio cíclico que fue reducido añadiendo $NaCNBH_3$ al mismo matraz de reacción. El correspondiente azepano se obtuvo con moderado rendimiento y enantioselectividad, pero con una muy buena diastereoselectividad, observándose sólo el diastereoisómero *cis* (**Esquema 9**).



Esquema 9

Asignación de la Configuración Absoluta de las Aminas Sintetizadas

Para asignar la configuración absoluta de estas homoprenilaminas se utilizó un método descrito en la bibliografía, que consiste en el análisis del espectro de RMN ^1H del correspondiente derivado de (*R*)-MPA en presencia y en ausencia de Ba^{2+}. Según este modelo, en las aminas derivadas de MPA los confórmeros mayoritarios son aquellos que poseen una disposición *antiperiplanar* entre el grupo metoxi del sustituyente MPA y el átomo de oxígeno que este carbonilo. Sin embargo, la adición de Ba^{2+} ($Ba(ClO_4)_2$) provoca la quelación con estos dos grupos, el metoxi y el oxígeno carbonílico, de manera que se produce una inversión del confórmero mayoritario, siendo en este caso aquel en el que estos dos grupos se encuentran en una disposición *synperiplanar* (**Esquema 10**). Este hecho produce un cambio apreciable en el desplazamiento de las señales de RMN ^1H de aquellos hidrógenos pertenecientes al esqueleto carbonado de la amina de partida, ya que se produce un apantallamiento de los hidrógenos situados espacialmente cerca del grupo fenilo del MPA. En este caso concreto, se sintetizó, entre otros, el derivado de MPA de la amina **32a**, observándose que, tras la adición de la sal de bario, se produjo un apantallamiento de los dos metilos del doble enlace y también del hidrógeno de este doble enlace, pudiéndose deducir la estereoquímica de la amina de forma sencilla.

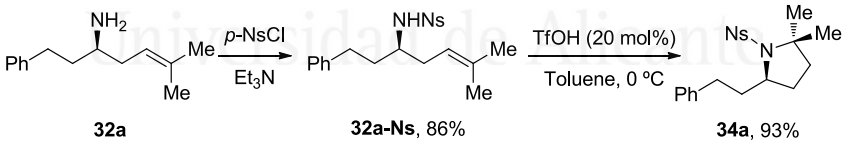


Esquema 10

Por otro lado, la configuración absoluta de las aminas derivadas tanto de aldehídos aromáticos como alifáticos reultó ser la predicha por el modelo de reordenamiento anticipado (**Esquema 7**).

Aplicaciones Sintéticas de Homoprenilaminas Lineales

Se ejemplificó el potencial de estas homoprenilaminas como precursores sintéticos mediante la obtención de la correspondiente pirrolidina 2,2,5-trisustituída a través de una hidroaminación del doble enlace prenílico. Para poder llevar a cabo esta reacción se necesitó proteger las correspondientes aminas libres con *p*-toluensulfonilo, siendo el rendimiento global de protección e hidroaminación muy bueno (80%) (**Esquema 11**).



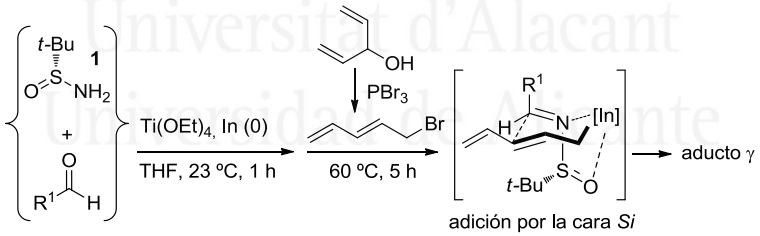
Esquema 11

Capítulo IV:

Aminopentadienilación de Compuestos Carbonílicos.

Los compuestos pentadienil metálicos pueden sufrir reordenamientos metalotrópicos 1,3 o 1,5 y por tanto, en presencia de compuestos electrófilos, podrían dar hasta tres diastereoisómeros diferentes: el aducto α, el aducto γ o el aducto ε. Otros autores han estudiado la adición de pentadienil indio a aldehídos observando la formación del aducto-γ mayoritariamente. Por otro lado, los alcoholes obtenidos, se han utilizado en múltiples aplicaciones, mostrando la versatilidad de estos productos.

Teniendo en cuenta la experiencia de nuestro grupo de investigación en adiciones a *terc*-butilsulfinil iminas, se empleó el protocolo de aminoalilación mediada por indio con bromuro de 2,4-pentadienilo en lugar de con bromuro de alilo (**Esquema 12**). Este bromuro de 2,4-pentadienilo se sintetizó a partir de 1,4-pentadien-3-ol mediante la adición de PBr_3 a una disolución del alcohol en Et_2O seco y a 0 ºC. La conversión de la reacción fue completa y el correspondiente bromuro se obtuvo con un 60% de rendimiento. El crudo se usó directamente en la reacción de aminoalilación.



Esquema 12

Aminopentadienilación de Aldehídos.

Una gran variedad de aldehídos se sometieron a estas condiciones de aminoalilación usando la (*R*)-*terc*-butilsulfinamida. El protocolo se pudo emplear sin modificaciones en la aminoalilación de aldehídos, tanto aromáticos como alifáticos con algunas limitaciones, pero obteniendo siempre el aducto-γ casi exlcusivamente. En el caso de los aldehídos aromáticos, el benzaldehído reultó no ser un buen sustrato, ya que la correspondiente homoalilamina se obtuvo con tan solo un 14% de rendimiento y una diastereoselectividad de 90:10. Sin

embargo, la presencia de un sustituyente electrón-aceptor como es el cloro en las posiciones 3 y 4 del anillo aromático, produjo una mejora notable en el rendimiento del producto (83% y 66% respectivamente). Sólo en el caso del 2-clorobenzaldehído, el considerable impedimento estérico condujo a un bajo rendimiento (21%). Un cambio importante se produjo cuando la reacción se llevó a cabo sobre aldehídos alifáticos monosustituídos o aldehídos α,β-insaturados. Los rendimientos obtenidos en este caso fueron mucho mejores (70 - 90%) así como las diastereoselectividades (97:3 - >98:2 dr). Sin embargo, la presencia de un sustituyente en la posición 2 del aldehído provocó un descenso en el rendimiento. Éste fue el caso del ciclohexilcarbaldehído, un aldehído más voluminoso, donde el rendimiento obtenido fue de un 55%, ya que el crudo de reacción mostró la presencia de una mezcla 74:26 de regioisómeros de γ-adición y α-adición.

Esta reacción de aminopentadienilación se probó también sobre un aldehído quiral, como el (*S*)-citronelal, usando para ello ambos enantiómeros de la *terc*-butilsulfinamida. Tanto en la utilización del enantiómero (*R*) como en la del (*S*) de la *terc*-butilsulfinamida, los rendimientos de los diastereoisómeros obtenidos fueron similares: 84% cuando se usó el enantiómero (*R*) y 86% en el caso del enantiómero (*S*). Además las diastereoselectividades fueron muy buenas en ambos casos (> 97:3 rd), no evidenciándose un efecto cooperativo apreciable entre el aldehído quiral y la *terc*-butilsulfinamida quiral.

La asignación de la configuración absoluta de las nuevas pentadienilaminas sintetizadas se realizó siguiendo la metodología empleada en el capítulo anterior, es decir, obteniendo los correspondientes derivados de (*R*)-MPA y analizándolos por RMN ^{1}H en presencia y en ausencia de Ba^{2+}. La estereoquímica obtenida mediante este experimento concordó con la esperada según el modelo propuesto para la reacción de aminoalilación mediada por indio.

Aminopentadienilación de Cetonas.

En el caso de las cetonas se llevó a cabo una modificación de la metodología, alargando el tiempo de reacción de formación de la correspondiente cetoimina a 8 h y aumentando la temperatura de reacción a 60 ^{o}C. De esta manera, se sometieron varias metil alquil cetonas a estas nuevas condiciones de reacción, y se obtuvieron las correspondientes pentadienilaminas con rendimientos en torno al 65%, y excelente diastereoselectividad (≥ 97:3). Cabe destacar que, pese al impedimento estérico extra que presentan las cetonas en comparación con los

aldehídos, en ninguno de estos casos se observó la formación del aducto α, lo que implica que esta metodología es altamente regioselectiva para estas metil alquil cetonas.

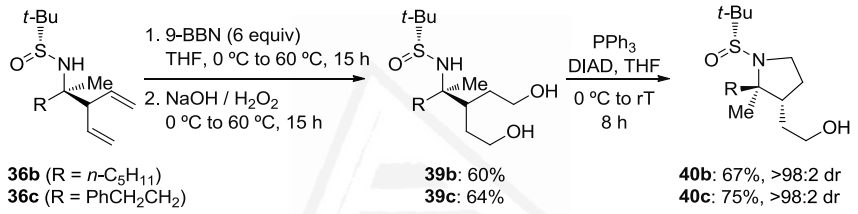
Este procedimento *one-pot* se comparó con el procedimiento por pasos, en el cual se produce el aislamiento y purificación de la correspondiente cetoimina seguida por la adición del reactivo organoíndico. Curiosamente, el rendimiento obtenido en el procedimiento *one-pot* fue bastante superior al obtenido en el procedimiento por pasos (65% *vs* 32%). Este hecho implica que puede que la presencia del $Ti(OEt)_4$ aumente de alguna manera la electrofilia de la imina coordinándose al grupo sulfinilo y al indio, de manera que acelere la adición a la imina. Por otro lado, el Ti(IV) también puede facilitar la isomerización *E*/*Z* de las iminas y con ello la resolución dinámica cinética observada en esta reacción, donde las diastereoselectividades observadas en los productos es superior a las relaciones *E*/*Z* de las iminas obtenidas.

Aplicaciones Sintéticas

La aplicación más inmediata debido a la presencia de los dos dobles enlaces, es la hidrogenación de los mismos para obtener los correspondientes aminoalcanos. Esta aplicación, a pesar de su sencillez, presenta un matiz interesante, ya que la estructura obtenida es difícil de conseguir mediante la adición de reactivos 3-pentanometálicos. Debido a su gran volumen, estos reactivos participarían en reacciones de eliminación, transferencias electrónicas, pero difícilmente de adición a iminas. La doble reducción se llevó a cabo usando PtO_2 como catalizador de la reacción, el cual permitió que la reducción se completara en presencia del sulfinilo (92% de rendimiento aislado). Esta quimioselectividad es relevante porque muchos catalizadores de paladio son envenenados por el grupo sulfinilo.

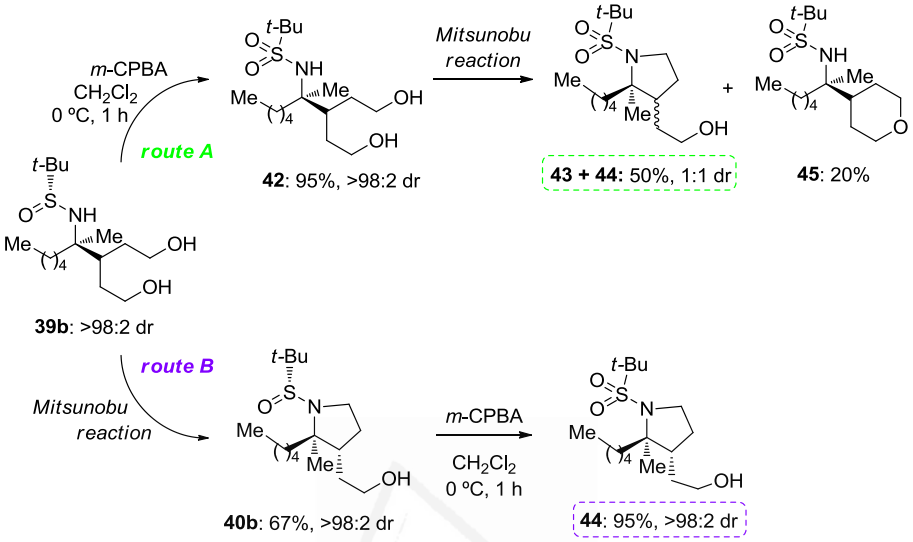
Una aplicación más interesante, es la relacionada con la síntesis de pirrolidinas, ya que éstas se encuentran presentes en muchos productos naturales y sintéticos de actividad biológica reconocida. Para la síntesis de estas pirrolidinas, se intentó, en primer lugar, la monooxidación/hidroboración de uno de los dos dobles enlaces de la molécula de forma selectiva. Para ello se recurrió al 9-BBN, que posee un sustituyente muy voluminoso. Sin embargo, la adición de 1.2 equivalentes provocó la obtención de una mezcla diastereomérica de los correspondientes monoalcoholes, de manera que se intentó la doble hidroboración/oxidación de las pentadientilaminas, añadiendo para ello un

exceso de 9-BBN a la reacción. Los correspondientes dioles se obtuvieron con rendimientos moderados, en torno al 60% pero con una regioselectividad excelente obteniéndose el producto anti-Markonikov en ambos enlaces. Tras ello, como se muestra en el **Esquema 13**, se llevó a cabo la reacción intramolecular de ciclación utilizando para ello las condiciones de reacción de Mitsunobu. Afortunadamente, bajo estas condiciones se obtuvo un sólo diastereoisómero de los dos posibles, con buen rendimiento (~70%). La determinación de la configuración del nuevo estereocentro formado en la ciclación se elucidó inequívocamente observando el resultado de irradiar algunas señales del espectro de RMN ^{1}H del correspondiente derivado benzoilado (nOes)



Esquema 13

Para intentar explicar la alta selectividad en la ciclación, se eliminó la información estereoquímica del grupo sulfinilo mediante la oxidación selectiva del azufre. Esta oxidación se llevó a cabo mediante la utilización del ácido *m*-cloroperbenzóico, en disolución de CH_2Cl_2 en tan sólo 1 hora a 0 ºC. El correspondiente derivado sulfonilo **42** se obtuvo con un excelente rendimiento (95%). La ciclación de este compuesto, condujo a la obtención de las correspondientes sulfonilpirrolidinas **43+44** como mezcla diastereomérica 1:1 según el espectro de RMN ^{1}H, acompañadas del tetrahidropirano **45** que se obtiene como subproducto en la Mitsunobu. Con el fin de asegurar que la mezcla 43+44 eran distereoisómeros, se llevó a cabo la oxidación del grupo sulfinilo de la pirrolidina **40b**, obteniendo de esta manera la pirrolidina **44**. La comparación de los espectros de las sulfonilpirrolidinas obtenidas por ambas rutas confirmó que si se oxidaba el azufre antes de la ciclación, se obtenía una mezcla 1:1 de diastereoisómeros (**Esquema 14**).



Esquema 14

De este experimento, se pudo concluir que la presencia del centro estereogénico del azufre era fundamental en la posterior ciclación para obtener una buena selectividad. Para explicar estos hechos se propuso un posible mecanismo de reacción en el cual uno de los dos grupos hidroxilo del diol formaba un enlace de hidrógeno con el oxígeno del sulfinilo, dejando el otro grupo hidroxilo susceptible de recibir el ataque por parte del nitrógeno. Según esta explicación, el hecho de oxidar el azufre y tener dos oxígenos en lugar de uno, permitiría la formación de este enlace de hidrógeno con ambos hidroxilos, siendo igual de probables la obtención de los dos diastereoisómeros de la pirrolidina.

En definitiva, la síntesis de pirrolidinas enantioméricamente puras conteniendo dos centros estereogénicos consecutivos permitió ilustrar el potencial de las pentadienilaminas preparadas como precursores en la síntesis de compuestos de interés biológico. También ha quedado demostrado que la presencia del grupo sulfinilo enantioméricamente puro juega un papel fundamental en la obtención de estas pirrolidinas como únicos diastereoisómeros.

Conclusiones Generales:

En general, se puede decir que la síntesis de la 2-alilpiperidina de forma tan efectiva ha facilitado la preparación de muchos productos naturales, entre los que se encuentran las tetraponerinas.

Además, el protocolo de aminoalilación *one-pot* ha sido usado en: (a) la síntesis de un donor quiral que ha permitido la obtención de homoprenilaminas lineales con buenas enantioselectividades; (b) la síntesis de homopentadienilaminas quirales, las cuales se ha demostrado que poseen un gran potencial sintético como precursores de pirrolidinas 2,2,3-sustituídas.