UNIVERSITAT ROVIRA I VIRGILI

SYNTHESIS OF SPHINGOID BASES BY TRANSITION METAL-CATALYZED REACTIONS

Josep Llaveria Cros

ISBN:
Dipòsit Legal: T. 1036-2011

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JOSEP LLAVERIA CROS

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DOCTORAL THESIS

Supervised by

Dr. Sergio Castillón Miranda and Dr. M. Isabel Matheu Malpartida

Departament de Química Analítica i Química Orgànica

UNIVERSITAT ROVIRA I VIRGILI

Tarragona, 2011

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Departament de Química Analítica i Química Orgànica
Facultat de Química
c/ Marcel·lí Domingo, s/n
43007, Tarragona

Sergio Castillón Miranda, Catedràtic d'Universitat i M. Isabel Matheu Malpartida, Professora Titular d'Universitat del Departament de Química Analítica i Química Orgànica de la Universitat Rovira i Virgili

FEM CONSTAR que aquest treball titulat "Synthesis of Sphingoid Bases by Transition Metal-Catalyzed Reactions" presentat per Josep Llaveria Cros per a l'obtenció del títol de Doctor, ha estat realitzat sota la nostra supervisió al Departament de Química Analítica i Química Orgànica d'aquesta mateixa universitat i en altres laboratoris universitaris en el marc de col·laboracions científiques, i que compleix els requeriments per poder optar a la Menció Europea.

Tarragona, 24 de Febrer de 2011

Dr. Sergio Castillón Miranda Dra. M. Isabel Matheu Malpartida

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El presente trabajo ha sido desarrollado con una beca para la Formación de Personal Universitario (FPU) financiada por el Ministerio de Ciencia e Innovación. Los siguientes proyectos han financiado el trabajo que se describe en esta tesis:

Síntesis de monómeros, oligómeros, dendrímeros y polímeros derivados de carbohidratos con propiedades antibióticas y antivirales. CTQ2005-03124-BQU

New synthetic methods in carbohydrate chemistry. CTQ2008-01569-BQU

Diseño de Catalizadores para una Química Sostenible: Una Aproximación Integrada (INTECAT). Consolider Ingenio (CSD2006-0003)

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En primer lloc voldria agrair al Professor Sergio Castillón per dirigir aquesta tesi doctoral en el seu grup d'investigació. Gràcies pels consells, perseverança, dedicació i per la formació que m'ha donat. Vull donar les gràcies a la co-directora d'aquesta tesi doctoral, la professora M. Isabel Matheu per la seva ajuda durant aquests anys, especialment en aquest últim tram. Agrair també a la professora Yolanda Díaz pels consells i comentaris.

Quiero agradecer al profesor Pedro J. Pérez y a la profesora M. Mar Díaz-Requejo por darme la oportunidad de trabajar en colaboración con su grupo en la Universidad de Huelva. A todos los compañeros de trabajo de la Universidad de Huelva, especialmente a Álvaro, con el que he trabajado conjuntamente, por todo el apoyo, ayuda y optimismo aportado tanto dentro como fuera del laboratorio.

I want to thank Professor Amir H. Hoveyda at Boston College for giving me the opportunity to work in his lab and get the fascinating *Z*-selective cross-metathesis project. I would also like to thank all the members, specially Mo- and Ru- group for their kindly welcome. Gràcies Rosa per tot el suport donat durant els quatre mesos a Boston.

I want to thank Professor A. Fürstner for giving me the opportunity to work in the Lactimidomycin project at Max-Planck-Institut and I would also like to thank all the members of his group.

Evidentment, no em puc oblidar dels companys de laboratori amb els que he passat tantes i tantes hores, que he compartit tants bons moments i tantes històries que no oblidaré. Gràcies Miguel, Omar i Andrea, que ja marxaveu quan vaig arribar, que tot i compartir poc temps em vau ensenyar les meves primeres nocions de treball. Amb els que he compartit moltes més experiències David, Patri i Antonio, per formar-me, per tenir sempre una resposta i per les converses de química a l'hora que sigui. A l'Isidro, amb qui he compartit aquest quatre anys que segur que no oblidarem mai, per les rialles, per suport i per tots els teus coneixements (el final esta més a prop del que ens pensem, molta força i molta sort en aquest darrer tram). Gràcies als que han estat els meus companys de batalla en els últims anys, a l'Irene, al Javi, la Miriam, la Mariam i a l'Isma, cadascú ha aportat la seva part en el dia a dia, en les converses, els congressos i

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tantes coses més. I als recent vinguts Isa, Emma, Joan i Sebastien, que la sort us acompanyi.

Han estat moltes les anèctodes pasades fora del labo (converses pels pasadissos, esmorzars, dinars, sopars, entre moltíssimes coses més). Per tant, vull agrair als companys de Polímers (Foix, Quique, Camilo, Mariluz, Rodolfo, Cristina, Silvana, Mireia, Asta, ...), als de Química Inorgànica i com no, algun de Química Analítica (Vane, Idoia) són moltes les converses perdudes. Gràcies Vane, no són pocs els moments passats, de dia i de nit, ni els favors ni les vivences per recordar.

Gràcies a la meva família per tot l'esforç en aquest camí, per donar-me un cop de mà sempre que ho he necessitat, per intentar entendre'm en totes les meves decisions.

Tampoc no em puc oblidar dels meus amics i amigues vinyolencs, tot i que no sempre han entès el què ni el perquè del que estava fent. El suport és necessari per tirar endavant. Ferran, són moltes les aventures viscudes, espero que la memòria no ens falli mai. Laia, gràcies per aquest disseny.

Moltes gràcies a tu, Helena per aguantar-me durant tants anys. Per donar-me tot el suport necessari per fer aquesta tesi, per la paciència que has tingut en deixar-me quedar treballant fins tard, per deixar-me anar els cap de setmana al labo, per tota l'ajuda que m'has donat fora del laboratori. Per escoltar-me en els mals moments i intentar fer-me desconnectar quan més ho he necessitat, i tantes i tantes coses més que t'hauria d'agrair i només et puc dir: gràcies per estar sempre al meu costat.

Gràcies a tots.

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Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda. A. H. **Z-Selective Catalytic Olefin Cross-Metathesis for Efficient Synthesis of Biologically Active Natural Products.** *Nature* **2011**, *471*, 461-466.

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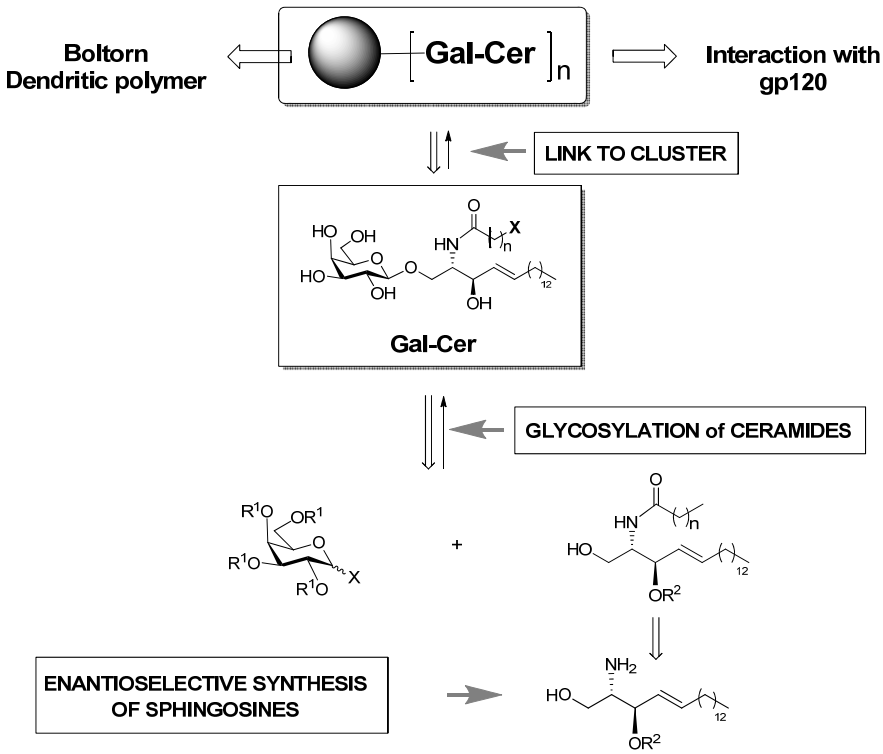
Summary

The objectives of the present work are part of a more general objective that aims to prepare glycoclusters of GalCer for testing the interaction with gp120 of HIV. The entry process of HIV into the T-4 lymphocytes cells is known to be a complex process that involves several steps, that begins with inicial recognition triggered by gp120 and a specific receptor placed in the surface of the cell (CD4). However HIV can infect some cells without this receptor, which indicates the existence of alternative receptors. One of these receptors is galactosylceramide (GalCer). Consequently, GalCer analogues with a strong interaction with gp120 are potential inhibitors of the virus entry, and therefore of infection. We hypothesize in this context, that glycoclusters containing GalCer could inhibit the entry of the virus into de cell.



Scheme I

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To achieve this general objective it is necessary to provide efficient procedures for synthesizing sphingosines for the glycosylation of ceramides, and to select the cluster and the way to anchor GalCer (Scheme I). During the last years we have simultaneously developed all these methodologies. The present work focuses on developing new methods for synthesizing sphingosines and analogues.

Due to the relevant biological role of sphingosines, ceramides and glycosyl ceramides, and the increasing demand of these compounds for biological evaluations, it is necessary to develop new synthetic methods of these compounds. The synthetic procedures using starting materials of the chiral pool, mainly carbohydrates and serine derivatives, are progressively shifted by asymmetric synthesis procedures, and particularly by those based on catalytic processes.

The present work has been oriented to develop new synthetic procedures to obtain sphingoid bases. Two main synthetic procedures have been explored:

a) **An enantioselective synthesis of sphingoid bases** which is based in three main synthetic procedures, i) enantioselective allylic amination of butadiene monoepoxide, ii) stereoselective cross-metathesis, and iii) stereoselective dihydroxylation.

b) **Regio- and stereoselective aziridination of conjugated dienes,** followed by regioselective opening of the resulting vinylaziridine.

Enantioselective Synthesis of Sphingoid Bases

In the enantioselective method, we studied the allylic amination of vinyloxirane (**A**) with different imido nucleophiles by a Dynamic Kinetic Asymmetric Transformation (DYKAT) catalyzed by palladium using (S,S)-DACH Trost ligand to afford 2-(*R*)-N-phtalimido-3-buten-1-ol (**C**) in a 99% yield and 99% e.e (Scheme II).

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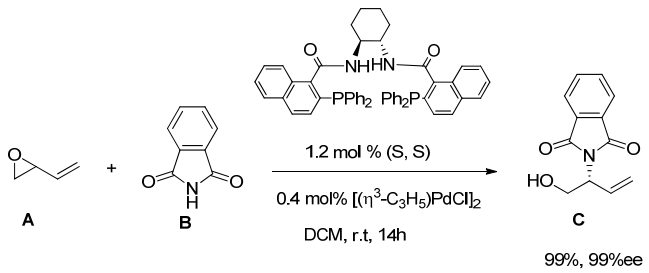
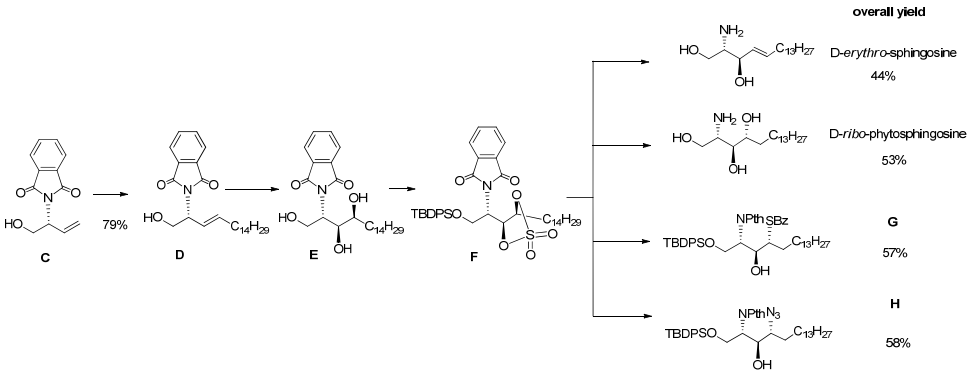


Scheme II

With the aim of synthesizing D-*erythro*-sphingosine and D-*ribo*-phytosphingosine, we studied the cross metathesis of compound **C** with 1-hexadecene using a second generation Grubbs catalyst, obtaining the *E*-alkene (**D**) in excellent yield and stereoselectivity. Then, the dihydroxylation reaction was optimized and it was found that the catalytic system $OsO_4/(DHQ)_2PYR$ provides a full conversion and a high diastereomeric ratio of compound **E**. The key intermediate **E** was transformed in the target compounds D-*erytrho*-sphingosine, D-*ribo*-phytosphingosine, and their 4-mercapto (**G**) and 4-azido (**H**) analogue (Scheme III).



Scheme III

We developed a short and efficient divergent enantioselective catalytic method to synthesize the natural anhydrosphingosine, Jaspine B (Pachastrissamine) and three of its 2-, 3- and 2,3-isomers (**I**, **J** and **K**) from racemic butadiene monoepoxide in 54%, 55%, 36% and 24%, respectively (Scheme IV).

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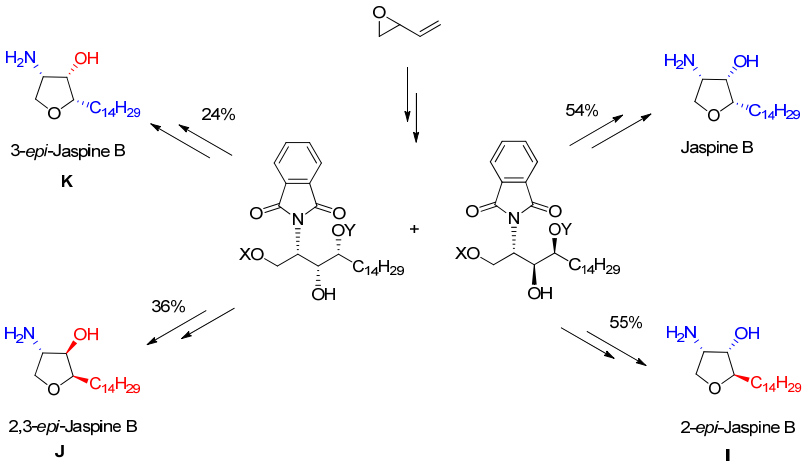
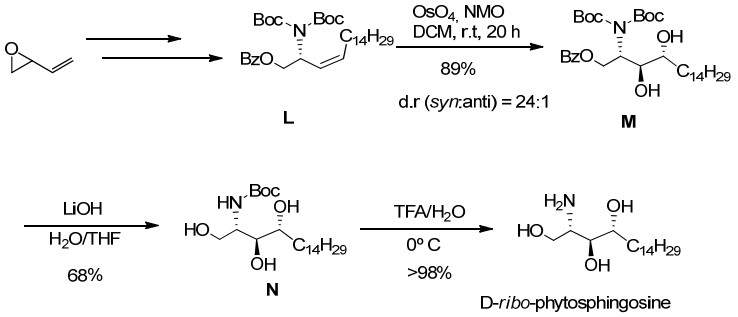


Scheme IV

Synthesis of *Z*-alkenes by Cross-Metathesis

An efficient method for preparing exclusively *Z*-1,2-disubstituted allyl amines using Z-selective cross-metathesis catalyzed by Mo-catalyst is described. Several modifications in the catalyst and the process have been studied, finding that the Mo-adamantyl-tetrahydroaryloxide is the most efficient catalyst for that purpose. The presence of vacuum to remove ethylene is necessary to obtain high conversions.



Scheme V

This methodology is completely new and opens up interesting possibilities in organic synthesis. The methodology was applied to the synthesis

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of D-*ribo*-phytosphingosine affording the shortest enantioselective method described until now with high values of diastereoselectivity in *Z*-cross-metathesis. The obtained product in cross-metathesis **L** showed to be high stereoselective in the dihydroxylation reaction to afford compound **M**.

Aziridination of Dienes

The second method is based in a regio- and stereoselective aziridination of conjugated dienes. An efficient, regioselective and stereospecific method of aziridination of dienols affording vinyl aziridines has been developed. The main characteristics of this method are the following:

i) $[Tp^{*,Br}Ag]$ resulted to be the more active catalyst providing exclusively aziridines *trans* from alkenes *trans*, and aziridines *cis* from alkenes *cis,* which indicates that the reaction is stereospecific

ii) The regioselectivity was driven by the OH group, being mainly the obtained aziridine resulting from aziridination of the double bond close to the OH.

iii) The process is highly regioselective for conjugated dienes and for homoallylic alcohols, but the regioselectivity decreases when the dienes are not conjugated.

iv) catalyst loading as low as 0.5% can be used.

v) stoichiometric mixtures of diene and PhINTS (the nitrene source) were used.

Moreover, vinyl aziridines were regioselectively opened by S_N2 process, by attack at the allylic position. Selective S_N2' processes have been also observed for some nucleophiles such as azide (Scheme VI).

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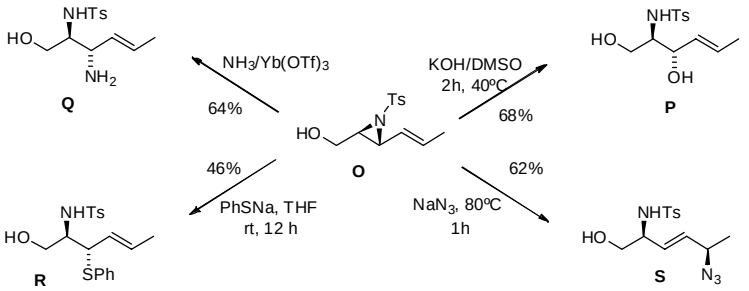
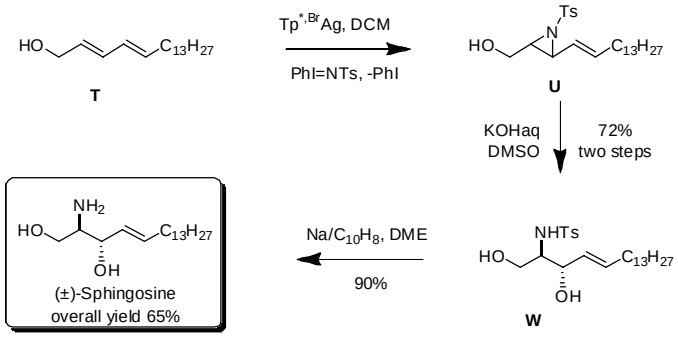


Scheme VI

Driven by our interest in developing new methods for the synthesis of aminoalcohols of biological interest, we applied this methodology to the synthesis of (±)-sphingosine. Diene **T** was employed as starting material for such purpose. Aziridination with PhINTs gave a mixture of aziridines in 86:14 ratio, being the major isomer that resulting from the reaction on double bond vicinal to the OH group. The final reaction mixture of aziridines was treated with KOH to induce ring opening and thus, the formation of the N-protected aminoalcohol **W** that was isolated and characterized. Further treatment of **W** with Na/naphthalene provided the targeted (±)-sphingosine in 65% isolated yield based on the starting diene (Scheme VII).



Scheme VII

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Abbreviations and Acronyms

AQN:	Anthraquinone
BHT:	*tert*-Butyl hydroxytoluene
Boc:	*tert*-Butyl carbamate
Bz:	Benzoyl
c. a.:	Aproximately
CLB:	*p*-chlorobenzoate
CM:	Cross-metathesis
Conv:	Conversion
CSA:	Camphorsulfonic acid
DCM:	Dichloromethane
DEAD:	Diethylazodicarboxylate
DHQ:	Dihydroquinine
DHQD:	Dihydroquinidine
DIBAL:	Diisobutyl aluminum hydride
DIAD:	Diisopropylazodicarboxylate
DIPT:	Diisopropyl tartrate
DMAP:	4-Dimethylaminopyridine
DMF:	Dimethylformamide
DMSO:	Dimethyl sulfoxide
DYKAT:	Dynamic Kinetic Asymmetric Transformation
EWG:	Electron Withdrawing Group
GalCer:	Galactosyl Ceramide
HPLC:	High-pressure liquid chromatography
IBX:	2-Iodobenzoic acid
^{i}Pr:	*iso*-propyl
MEQ:	4-Methyl-2-quinolil
NaHMDS:	Sodium bis(trimethylsilyl)amide
NMO:	*N*-methyl-morpholine-*N*-oxide
NMR:	Nuclear Magnetic Resonance
PHAL:	Phthalazine
PHN:	Phenanthryl ether
Py:	Pyridine
Pyr:	Pyrimidine

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PMB:	*p*-methoxybenzyl
RCAM:	Alkyne ring-closing metathesis
RCM:	Ring-closing metathesis
Red-Al:	Sodium bis(2-methoxyethoxy)aluminium hydride
TBAF:	Tetra-*n*-Butylammonium fluoride
TBDPSCl:	*tert*-Butyldiphenylsilyl chloride
TBHP:	*tert*-butyl hydroperoxide
TBSCl:	tert-butyldimethylsilyl chloride
TEA:	Triethylamine
Temp:	Temperature
Tf_2O:	Trifluoromethanesulfonyl anhdride
THF:	Tetrahydrofurane
TLC:	Thin Layer Crhomatography
TMEDA:	Tetramethylethylenediamine
Ts:	Tosyl
Tp:	Trispyrazolyl ligand
TsOH:	*p*-Toluenesulfonic acid

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El que sabem és una gota d'aigua,
el que ignorem és tot un oceà

Isaac Newton

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Recent Advances in the Synthesis of Sphingoid Bases

CHAPTER 1

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1. Introduction

In the fluid mosaic model of biological membranes, lipids form a homogeneous two-dimensional solvent phase for membrane proteins. Membrane lipids comprise several hundreds of distinct molecules that exist in different physical states controlled by several physicochemical parameters such as the temperature, the presence of cholesterol or the chemical nature of the hydrocarbon chains. Biological membranes are thus better described as a 'mosaic of lipid domains' rather than a homogeneous fluid mosaic. Membrane cholesterol, for instance, is unevenly distributed into cholesterol-rich and cholesterol-poor domains, consistent with the notion that specialized lipid domains with specific biochemical composition and physicochemical properties do exist in membranes.[1]

Among these domains, those containing sphingolipids and cholesterol, referred to as lipid rafts or caveolae (when associated with the integral membrane protein caveolin), have been extensively studied.[2] For cell biologists, lipid rafts are chiefly involved in cellular trafficking and signalling functions.[3] For pathologists, these membrane areas are preferential sites for host–pathogen/toxin interactions[4] and for the generation of pathological/infectious forms of proteins associated with Alzheimer's[5] and prion diseases.[6] As a matter of fact, both the physiological and pathological aspects of lipid raft functions have been the subject of excellent reviews.[7]

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Glycosphingolipids[8] (GSLs) are characteristic membrane components of eukaryotic cells,[9] where they are found in the carbohydrate-rich glycocalix, which consists of glycoproteins and glycosaminoglycans in addition to GSLs.[10] Minor sites of location are the subcellular organelles, where glycosphingolipid metabolism occurs, or the vesicles or other transport structures involved in glycosphingolipid intracellular traffic.

2. Sphingolipid Structure

Each GSL carries a hydrophobic ceramide (Cer) moiety and a hydrophilic extracellular mono or oligosaccharide chain that protrudes from the membrane surface (Figure 1).[11]

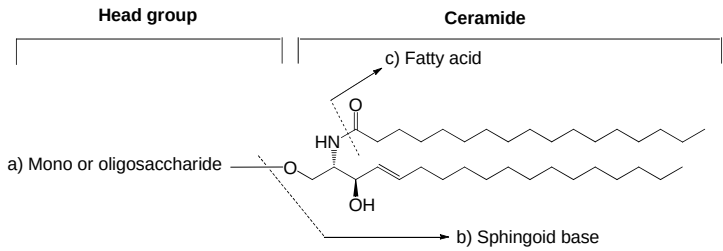

Figure 1. General structure of sphingolipids

The saccharide moiety is represented by a single saccharide unit, as in the case of cerebrosides (β-Galcer **1**) (Figure 2); sulphated mono- or di-saccharides, as in the case of sulphatides (Sulfatide β-Galcer **3**) (Figure 2); and as linear or branched oligosaccharide chains (iGB_3 **2** or GM_3 **4**) (Figure 2). The saccharide units present in glycosphingolipids are glucose, galactose, *N*-acetylglucosamine, *N*-acetylgalactosamine, fucose, sialic acid and glucuronic acid. The mono- or multi-sialosylated glycosphingolipids are named gangliosides that, together with

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sulphatides, constitute the group of acidic glycosphingolipids. The remainder glycosphingolipids are neutral.

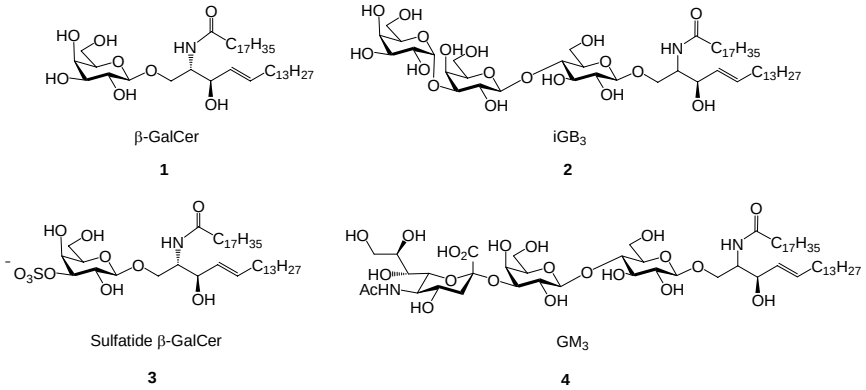

Figure 2. Naturally occurring β-glycosphingolipids

Ceramide (**5**) (Figure 3) is constituted by a long chain amino alcohol (sphingoid base) linked to a fatty acid, most commonly with a long chain of carbons atoms (18-20) that is sometimes hydroxylated. The most frequently occurring long chain sphingoid bases contain a C4-C5 *trans* double bound in the D-*erythro* configuration, and are C_{18} and C_{20} sphingosines (**6**) (Figure 3). Less frequent are dihydrosphingosine (**7**) (Figure 3), which lacks the double bond, and phytosphingosine (**8**) (Figure 3), which carries a hydroxyl group on C4.

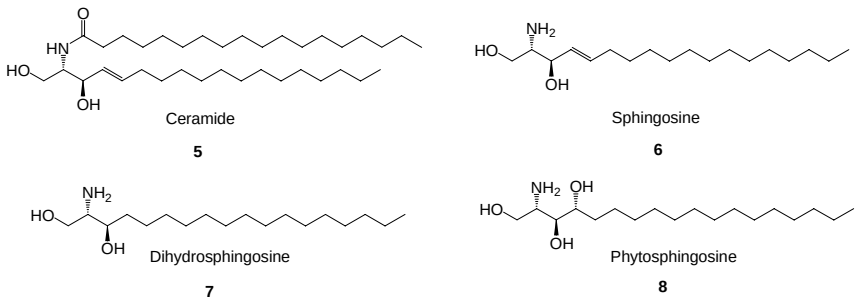

Figure 3. Naturally occurring sphingolipids

3. Biological importance

Sphingolipids, named by Johann Ludwig Wilhelm Thudichum in 1884 after the Greek mythological character, the Sphinx, "in commemoration of the

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many enigmas which it has presented to the inquirer",[12] have emerged over the last several decades as a family of key signalling molecules.[13] Sphingolipids are structurally diverse constituents of membranes in mammals, plants, fungi, yeast and in some prokaryotic organisms and viruses.[14] These compounds, such as **5-8** (Figure 3),[15] together with glycerophospholipids and cholesterol are building blocks[16] that play essential roles as structural cell membrane components[17] and participate in higher order physiological processes including inflammation,[18] vasculogenesis,[19] proliferation, differentiation, immune response, cell recognition, apoptosis, adhesion and signal transduction.[20]

In this context, GSLs and related compounds have mainly been investigated in reference to storage diseases, which are a group of genetic diseases. However, recent studies implicate GSL involvement in many of the most common human diseases, and thus this field of research has been addressed as a strategy for preventing different diseases: viral infections (HIV),[21] microbial

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infections,[22] cancer, [23] diabetes,[24] Parkinson's,[25] Alzheimer's,[26] and many others.[27]

Enhanced levels of ceramides after treatment of mammalian cells with stress response inducers (cytokines, environmental stress, such as UV radiation or high temperatures) and chemotherapeutic agents, among others, have suggested the pivotal role of ceramides as a key sphingolipid in stress responses,[28] senescence,[29] cell cycle arrest[30] and apoptosis.[31] Apoptosis, a form of programmed cell death, is possibly the most studied process concerning sphingolipid functions, since many tumors show reduced levels of ceramides and exogenously added short chain ceramides can mimic apoptotic responses. These Cer-activated responses are mediated by specific interaction of sphingolipids with intracellular effectors, including phosphatases, proteases and kinases,[32] leading to the activation of a series of downstream targets.[33]

Since the isolation of a group of marine galactosyl ceramides in the 1990s from *Agelas mauritianus*,[34] and subsequent synthesis of analogues,[35] this family

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of glycosphingolipids has been a subject of great interest because of the potent antitumor activity found *in vivo* at the organism level. Phytosphingosine is the principal sphingoide base of these compounds, as illustrated by KRN7000 (**9**) and related compounds like Agelasphin-9b (**10**) (Figure 4). From a structural point of view, galactosylceramides contain α-glycosidic bonds, whereas in general glycoshingolipids found in higher organisms only have β-glycosidic linkages. At the molecular level, glycolipid **10** has been shown to act as a connecting ligand presented by the CD1d molecule of antigen-presenting cells to the murine Vα14 receptor and the human Vα24 receptor of natural killer T (NKT) cells. Upon recognition of the galactosyl ceramide in the context of CD1d, the NKT cell then is stimulated to produce interferon-γ (IFN-γ), interleukin-4 (IL-4), and interleukin-2 (IL-2).[36] Other exploration of the biological effects of KRN7000 has unveiled its remarkable activity against a group of diseases, such as cancer,[37] malaria,[38] juvenile diabetes,[39] hepatitis B,[40] and autoimmune encephalomyelitis.[41]

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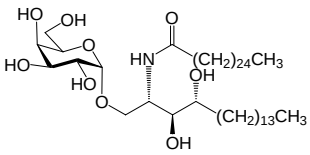

α-GalCer or KRN7000

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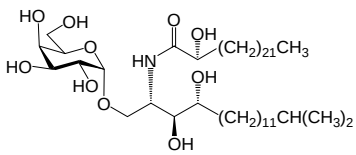

Agelasphin-9b

10

Figure 4. α-Glycosphingolipids

4. Biochemical synthesis

In the cell, the formation of ceramide is catalyzed by membrane-bound enzymes on the cytosolic leaflet of the endoplasmic reticulum (ER).[42] Serine palmitoyltransferase catalyse the condensation of the amino acid L-serine (**11**) and two molecules of the palmitoyl-coenzyme A (**12**) to produce 3-ketodihydrosphingosine (**13**). N-acyl-sphinganine **14** was obtained in two steps by a reduction of compound **13** to afford sphinganine (**7**), followed by acylation catalyzed by sphinganine-N-acyltransferase (Scheme 1). Sphingosine **6** is obtained by hydrolysis catalyzed by a ceramidase from compound **5**. The key step that differs from both the fungal and mammalian biosynthetic pathways[43] is the hydroxylation of dihydrosphingosine **7** and dihydroceramide **14** to give phytosphingosine **8** and ceramide **15**, respectively, which takes place in fungi. At the membranes of the Golgi apparatus, hydrophilic head groups are attached to ceramide leading to sphingomyelin, galactosylceramide, glucosylceramide, and higher glycosphingolipids, which are synthesized by the stepwise addition of monosaccharides to glucosylceramide.

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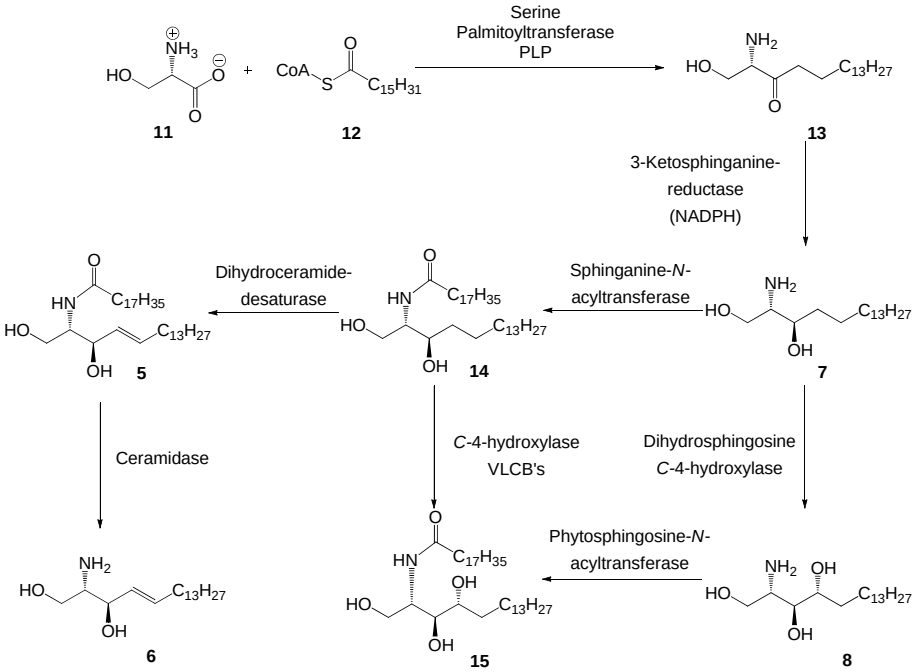

Scheme 1. Biosynthetic pathways of sphingolipids

5. Chemical synthesis

Due the relevant biological role of sphingosines, ceramides and glycosyl ceramides, and the increasing demand of these compounds for biological evaluations, developing new methods targeting sphingosine,[44] phytosphingosine[45] and derivatives[46] have attracted the interest of researchers. Recently, a revision of new methods of synthesis of these compounds has been reported by our group.[47] The synthetic procedures using products of the chiral pool, mainly carbohydrates and serine derivatives, are progressively shifted by asymmetric synthesis procedures, and particularly to those based on catalytic processes. In this section, only the more recent enantioselective syntheses will be presented in detail.

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Concerning procedures based on chiral pool, L-Serine (**11**) and particularly their commercially available derivative the Garner's aldehyde (**16**), occupy a central position because the hydroxyl-amino function with the appropriate configuration makes this compound especially suitable for synthesizing sphingoide bases (Scheme 2). In this context, highly efficient and versatile methods for synthesizing sphingosine (**6**)[48] and phytosphingosine (**8**)[49] and their diastereoisomers have been described.[50]

D-glyceraldehyde (**16**) correlates with the Garner's aldehyde (**17**), but secondary hydroxyl must be replaced by an amino function, usually azide, with inversion of configuration. In both cases the aldehyde can undergo a reaction with an alkynyllithium to afford after reduction of the triple bond sphingosine (**6**).[51] An olefination of glyceradehyde (**16**) achieved compound **18**, which after dihydroxylation creates the functionalities of phytosphingosine (**8**)[52] (Scheme 2). Concerning sugars, the requirements for synthesizing sphingosine and phytosphingosine are a bit different, although in every case the general strategy is

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based on the introduction of the amino function by inversion of configuration at C-5 of the sugar. Only one example correlates the amino group of glucosamine (**20**) with the amino group of sphingosine (**6**), but then the carbonyl group (C1) of the sugar must be converted into the hydroxymethyl (C1) of the sphingosines, and the configuration of 3-OH must be inverted.[53] For the synthesis of sphingosine (**6**) and phytosphingosine (**8**), D-galactose (**22**),[54] D-xylose (**23**),[55] D-glucose (**24**),[56] D-lyxose (**21**)[57] and 2-desoxycarbohydrates[58] were used as starting materials. D-Galactose (**22**) also occupies a central position among sugars because the matching of all the stereocenters (Scheme 2). Moreover the protecting group chemistry facilitates the manipulation for introduction of the amino group. D-lyxose (**21**) fulfils similar requirements, although their lower availability has shifted the protagonist role to D-Galactose (**22**). An interesting observation is that the removal of the hydroxymethyl group in D-mannose (**19**) affords a substitution pattern similar to D-lyxose (**21**).

D-tartaric acid (**25**) has also been used as a chiral starting material in the synthesis of D-*erythro*-sphingosine (**6**)[59] and phytosphingosine (**8**) by inversion of the configuration of the hydroxyl group in position 2.[60] Mannitol (**26**) was used in

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55 For the synthesis of sphingosine see: a) Compostella, F.; Franchini, L.; De Libero, G.; Palmisano, G.; Ronchetti, F.; Panza, L. *Tetrahedron* **2002**, *58*, 8703-8708. b) Kumar, P.; Schmidt, R. R. *Synthesis* **1998**, 33-35. For the synthesis of phytosphingosine see: c) Lin, C.-C.; Fan, G.-T.; Fang, J.-M.; *Tetrahedron Lett*. **2003**, *44*, 5281-5283.

56 Chaudhari, V. D.; Kumar, K. S. A.; Dhavale, D. *Org. Lett.* **2005**, *7*, 5805-5807.

71 a) Chang, C.-W.; Chen, Y.-N.; Adak, A. K.; Lin, K.-H.; Tzou, D.-L. M.; Lin, C.-C. *Tetrahedron* **2007**, *63*, 4310-4318. b) Chiu, H.-Y.; Tzou, D.-L. M. *J. Org. Chem*. **2003**, *68*, 5788-5791. c) Veerapen, N.; Reddington, F.; Salio, M.; Cerundolo, V.; Besra, G. S. *Bioorg. Med. Chem.* **2011**, *19*, 221-228.

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59 a) Lu, X.; Bittamn, R. *Tetrahedron Lett*. **2005**, *46*, 1873-1875. b) Lu, X.; Arthur, G.; Bittman, R. *Org. Lett.* **2005**, *7*, 1645-1648.

60 a) Liu, W.; Szewczyk, J. M.; Waykole, L.; Repiê, O.; Blacklock, T. *Tetrahedron Lett.* **2002**, *43*, 1373-1375. b) He, L.; Wanunu, M.; Byun, H.-S.; Bittman, R. *J. Org. Chem.***1999**, *64*, 6049-6055. c) Mathieu-Pelta, I.; Evans, S. A., Jr. *J. Org. Chem.* **1992**, *57*, 3409-3413. d) Rai, A. N.; Basu, A. *Org. Lett*. **2004**, *6*, 2861-2863.

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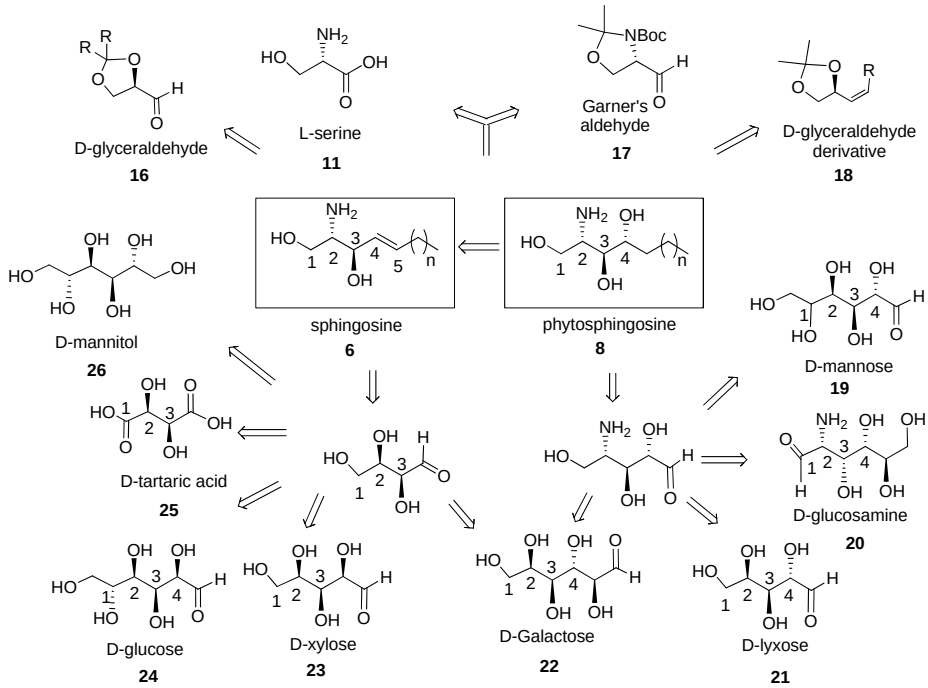
the synthesis of sphingosine[61] and phytosphingosine.[62] The synthesis of D-*erythro*-sphingosine (**6**) and also phytosphingosine stereoisomers[64a,63] were also achieved from commercially available D-*ribo*-phytospingosine (**8**).[64]



Scheme 2. Described synthesis of D-*erythro*-sphingosine (**6**) and D-*ribo*-phytosphingosine (**8**) from the chiral pool

The stereochemistry auxiliary-controlled stoichometric asymmetric synthesis began in the second half of 1970s. This methodology has been also used in the synthesis of sphingosine. For instance, zirconium-BINOL alkoxide was

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61 Parameswar, A. R.; Hawkins, J. A.; Mydock, L. K.; Sands, M. S.; Demchenko, A. V. *Eur. J. Org. Chem.* **2010**, 3269-3274.

62 Pandey, G.; Tiwari, D. K. *Tetrahedron Lett.* **2009**, *50*, 3296-3298.

63 a) Kim, S.; Lee, N.; Lee, S.; Lee, T.; Lee, Y. M. *J. Org.Chem*. **2008**, *73*, 1379-1385. b) Lee, Y. M.; Baek, D. J.; Lee, S.; Kim, D.; Kim, S. *J. Org. Chem.* **2011**, *76*, 408-416.

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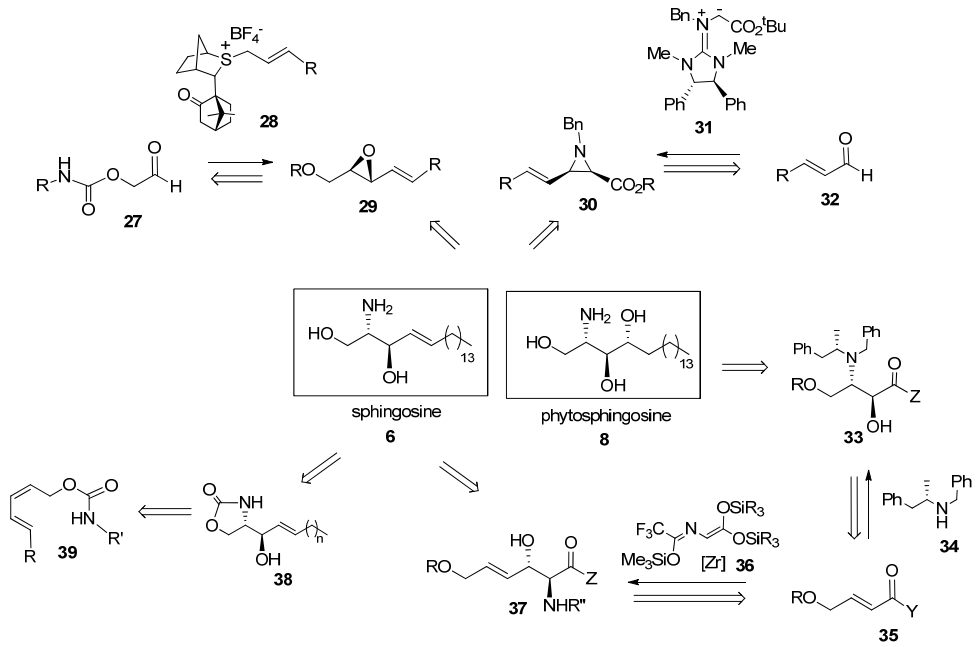
used in the asymmetric aldol reaction[65] (Scheme 3) between compound **35** and **36** to afford compound **37** as an intermediate in the synthesis of sphingosine.



Scheme 3. Synthesis of D-*erythro*-sphingosine and D-*ribo*-phytosphingosine using chiral auxiliaries

Diastereoselective synthesis based on the tandem conjugate addition of a chiral lithium amine **34** to a tri-*iso*-propylsilyloxy-α,β-unsaturated ester **35** followed by enolate oxidation to obtain compound **33** has been described.[66] The addition of chiral ylides such as guanidinium **31**[67] or sulfur **28**[68] to the corresponding aldehydes **34** and **35**, was also applied to the synthesis of the vinyl-aziridine **32** or epoxide **27**, respectively, as a key intermediate for the synthesis of

65 Kobayashi, J.; Nakamura, M.; Mori, Y.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc*. **2004**, *126*, 9192-9193.

66 Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem*. **2008**, *6*, 1655-1664.

67 Disadee, W.; Ishikawa, T. *J. Org. Chem.* **2005**, *70*, 9399-9406.

68 Morales-Serna, J. A.; Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Biomol. Chem.* **2008**, *6*, 4502-4504.

the natural D-*erythro*-sphingosine (**6**). The last procedure was developed in our laboratory.

In addition, stereoselective nucleophilic addition of enolates to chiral nitrones, as Mannich-type reaction, has been applied in the enantiodivergent synthesis of L- and D-*erythro*-sphingosine.[69] The diastereoselective synthesis of racemic D/L-*erythro*-sphingosine[70] was achieved in our group by employing tethered aminohydroxylation (TA) of compound **39** to introduce the 2-amino and 3-hydroxy functions with the required stereochemistry in compound **38**.[71]

6. Enantioselective catalytic procedures

Progressively, a shift of procedures using products of chiral pool to asymmetric synthesis sequences, and particularly to those based on catalytic reactions it is appreciated. In a related trend, it is also observed an increasing use of cross-metathesis reaction for building up the double bond of sphingosines. In the case of phytosphingosine, the 3,4-diol moiety is mainly constructed by dihydroxylation reaction. The use of the asymmetric dihydroxylation allows obtaining selectively different configurations independently of the configuration of 2-amino group. However, in order to obtain the correct configuration of the diol moiety the double bond must be *Z*, and for this purpose the Wittig type reactions was the procedure of choice. Alternatively, alkynes were precursors of *E* or *Z* configurations.

6.1. Synthesis of sphingosine

D-*erythro*-sphingosine **6** was enantioselectively synthesized[72] by a tin(II)-catalyzed asymmetric aldol reaction (Scheme 4). Thus, when trimethylsilylpropynal **40** was reacted with silylenol ether **41** in the presence of 20% tin(II) triflate and chiral diamine **42**, compound **43** was obtained in high diastereo- and enantioselectivity (*syn*/*anti*=97/3, 91% ee for *syn*). The phenyl

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69 Merino, P.; Jimenez, P.; Tejero, T. *J. Org. Chem.* **2006**, *71*, 4685−4688.
70 Morales-Serna, J. A.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Synthesis* **2009**, 710-712.
71 Donohoe, T. J.; Johnson, P. D.; Pye, R. J. *Org. Biomol. Chem.* **2003**, *1*, 2025-2028.
72 Kobayashi, S.; Furuta, T. *Tetrahedron* **1998**, *54*, 10275-10294.

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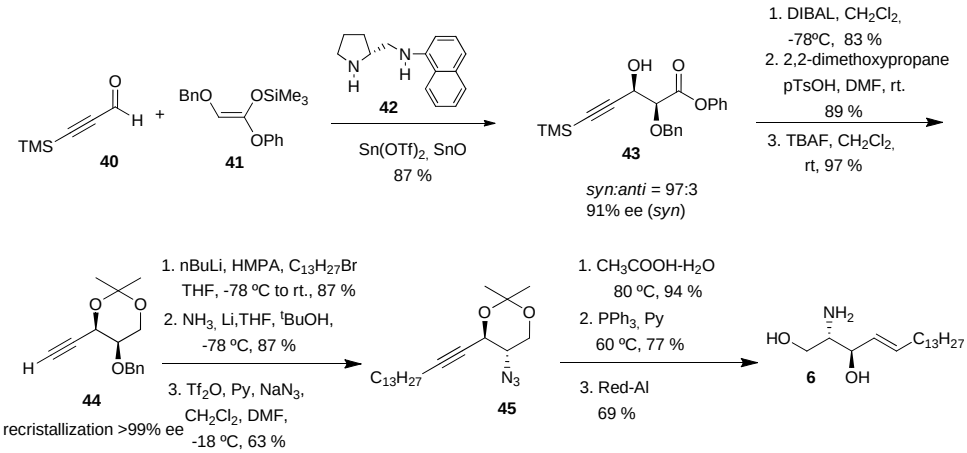
ester **43** was then reduced with DIBAL to the corresponding diol, which was protected as its acetonide. Finally, desilylation with tetrabutylammonium fluoride gave the desired intermediate **44**. The lipidic chain was introduced by alkylation of the acetylene-lithium derivative. Installation of the amino functionality at position 2 was carried out by removal of the benzyl group under Birch conditions, triflation of the resulting alcohol and reaction with NaN_3 to give **45** through an S_N2 process. The synthesis of sphingosine **6** was completed by deprotection of the acetonide, reduction of the azide under Staundinger conditions and acetylene *trans* reduction with Red-Al (Scheme 4).



Scheme 4. Synthesis of D-*erythro*-sphingosine (**6**) by a tin(II)-catalyzed asymmetric aldol reaction

Sharpless asymmetric dihydroxylation was also used as the key step in the synthesis of D-*erythro*-sphingosine **6** (Scheme 5).[73] The synthesis is very short and efficient, and starts by formylation of lithium 1-pentadecyne **46** with 1-formylpiperidine to give the hexadec-1-ynal, which was reacted with diisopropyl(ethoxycarbonylmethyl)phosphonate to give unsaturated ester **47** by a Horner-Wadsworth-Emmons reaction. Next, asymmetric dihydroxylation of enyne ester **47** with AD-mix-β provided diol **48** in high yield and 98% ee. Reaction of **48** with thiophosgene quantitatively afforded the corresponding cyclic thionocarbonate, which was subject to a ring-opening reaction with NaN_3. The

[73] He, L.; Byun, H.S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7627-7633.

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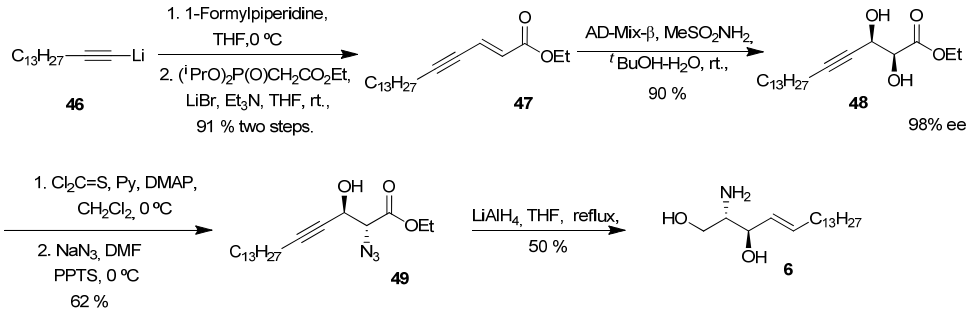
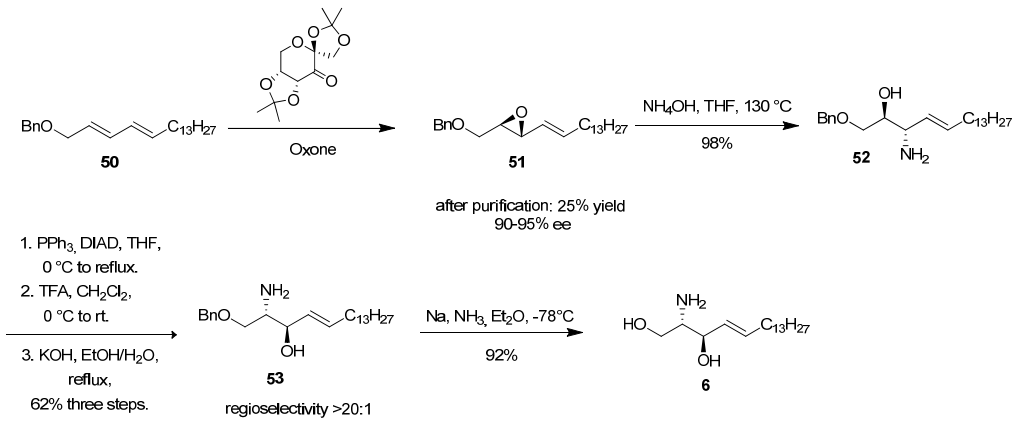
reaction proceeded with exclusive attack of the azido group at the α position to yield compound **49**. In the last stage of the synthesis, the triple bond, the azide and ester functional groups in **49** were reduced simultaneously by $LiAlH_4$ in THF to furnish D-*erythro*-sphingosine **6**.



Scheme 5. Synthesis of D-*erythro*-sphingosine (**6**) by Sharpless asymmetric dihydroxylation

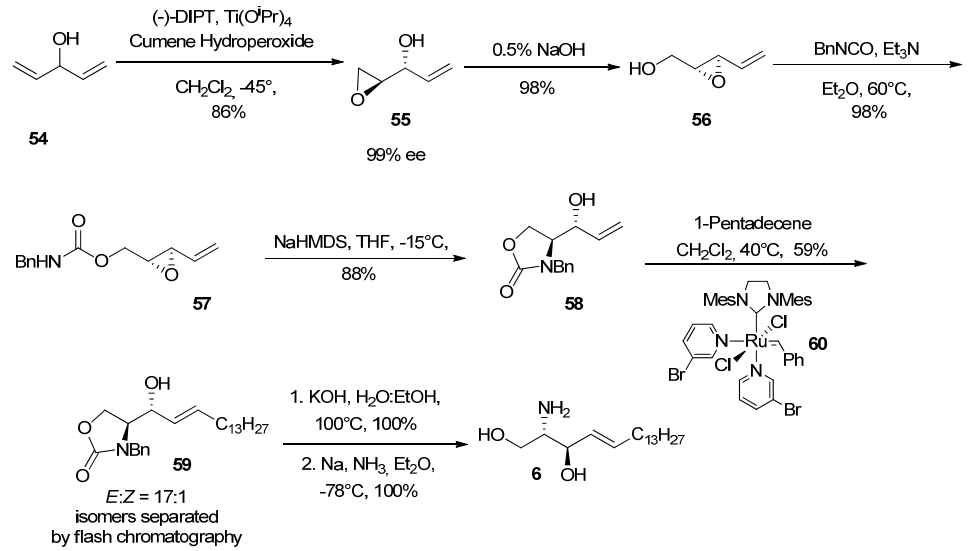
A divergent synthesis[74] of D-*erythro*-sphingosine (**6**) focused on the enantioselective epoxidation of diene **50** (Scheme 6). Thus, benzylated diene **50** was reacted under Shi's asymmetric epoxidation conditions to afford a 1:1 mixture of vinylepoxides in a 90% of conversion. Flash chromatography rendered **51** in a 25% yield and high optical purity (90-95% ee, HPLC). Diastereospecific and regioselective opening at the allylic position of vinyl epoxide **51** was carried out with ammonium hydroxide,[75] furnishing *anti*-amino alcohol **52**. In order to install the amino and the hydroxyl functionalities in the correct positions, compound **52** was reacted under Mitsunobu conditions[76] to give the vinylaziridine, which was opened in the presence of trifluoroacetic acid to generate the *anti*-amino alcohol **53**. Finally, the synthesis was completed by removal of the benzyl group under Birch conditions (Scheme 6).

74 Olofson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514−2517.
75 Olofson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574−8583.
76 Olofson, B.; Wijtmans, R.; Somfai, P. *Tetrahedron* **2002**, *58*, 5979−5982.



Scheme 6. Synthesis of D-*erythro*-sphingosine (**6**) by Shi epoxidation

Asymmetric Sharpless epoxidation was also used as the key step in the synthesis of sphingosine (**6**) (Scheme 7).[77] The synthesis starts with Sharpless epoxidation of **54** to give the alcohol **55**,[78] followed by base-induced Payne rearrangement to furnish the corresponding epoxide **56**, which was treated with benzyl isocyanate and Et_3N to provide benzyl carbamate **57**.



Scheme 7. Synthesis of D-*erythro*-sphingosine (**6**) by Sharpless epoxidation

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77 Torsell, S.; Somfai, P. *Org. Biomol. Chem.* **2004**, *2*, 1643-1646.

78 Romero, A.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 8264-8268.

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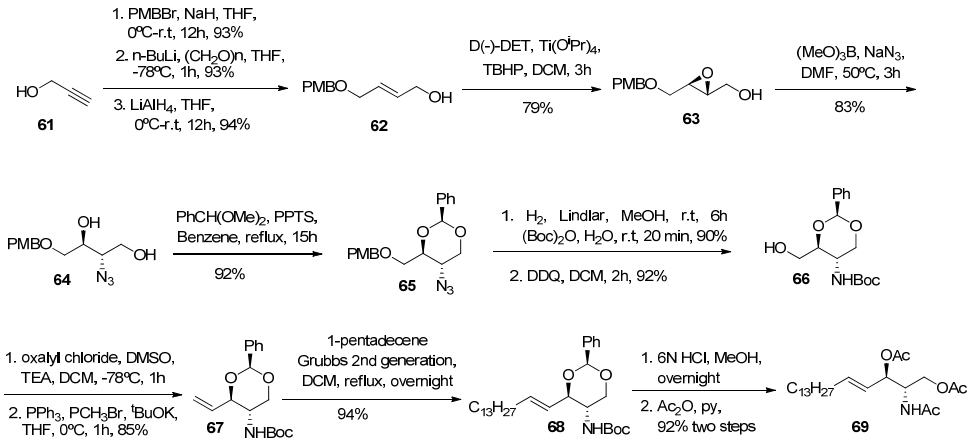
Subsequent intramolecular ring-opening using NaHMDS afforded oxazolidinone **58**. The use of Grubbs catalyst **60** in the *E*-selective cross-metathesis provided intermediate **59**, and hydrolysis with KOH and removal of the benzyl group with sodium in liquid ammonia generated **6** in a quantitative yield (Scheme 7).

In a different approach, propargylalcohol **61** was protected as its PMB ether, further treatment with n-BuLi and formaldehyde, followed by stereoselective reduction of triple bond gave the desired *trans*-allylic alcohol **62** in 94% yield (Scheme 8). This alcohol was subjected to Sharpless asymmetric epoxidation by using D-(−)-diethyl tartrate, $Ti(^{i}PrO)_4$ and TBHP to afford epoxyalcohol **63** in 79% yield. The efficient C2 selective azide substitution of **63** was accomplished by using NaN_3-$(CH_3O)_3B$ system developed by Miyashita.[79] This reaction proceeds via an intramolecular boron chelate through a novel endo-mode epoxide opening with extremely high C2 selectivity. Under these conditions, the desired azido diol **64** was produced in good yield and high diastereoselectivty (C2/C3 opening 1:4).



Scheme 8. Synthesis of protected D-*erythro*-sphingosine (**69**) by Sharpless epoxidation

The resulting 1,3-diol **64** was protected as benzylidene dimethyl acetal in good yield (92%). Reduction of the azide with Lindlar catalyst, protection $(Boc)_2O$ and deprotection of PMB group gave the alcohol **66**. The alcohol was

79 Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* **2003**, *5*, 1789-1791.

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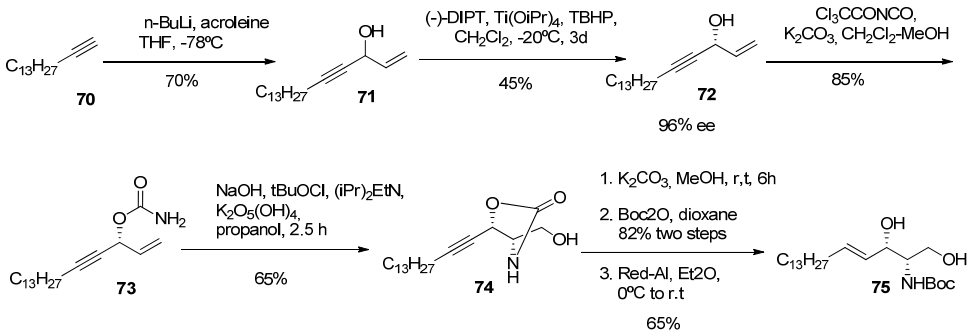
oxidized to aldehyde and then a Wittig methylation produced the desired olefin **67** in 85% yield. Olefin cross-metathesis with 1-pentadecene in the presence of Grubbs II generation catalyst provided product **68** with complete *E*-stereoselectivity in a 94% yield. Finally deprotection of **68** with 6N HCl in MeOH, followed by reaction of Ac_2O gave the protected sphingosine **69** (Scheme 7).[80]

One of the most recently synthesis started from commercially available pentadec-1-yne (**70**) to obtain protected L-*threo*-sphingosine (**75**).[81] Treatment of **70** with n-BuLi followed by addition of acroleine furnished the allylic alcohol **71** in 70% yield. The treatment of **71** with titanium tetraisopropoxide and *tert*-buthylhydroperoxide in the presence of (-)-DIPT under Sharpless asymmetric kinetic resolution conditions provide the chiral allylic alcohol **72** in a 45% yield and 96% ee (determined from the ^1H NMR of the corresponding Mosher's ester) together with the epoxy alcohol. Alcohol **72** was then reacted with trichloroacetylisocianate in CH_2Cl_2 to give the corresponding isocyanate, which on treatment with K_2CO_3 and methanol furnished the carbamate **73** in an 85% yield.



Scheme 9. Synthesis of L-*threo*-sphingosine **(75**) by aminohydroxylation

The obtained carbamate was converted into the oxazolidinone derivative **74** by a tethered aminohydroxylation protocol[82] in 65% yield with complete regio- and good stereoselectivty (*syn:anti* 13:1). Subsequent protection using Boc_2O

[80] Sridhar, R.; Srinivas, B.; Rao, K. R. *Tetrahedron* **2009**, *65*, 10701-10708.
[81] Kumar, P.; Dubey, A.; Puranik, V. *Org. Biomol. Chem.* **2010**, *8*, 5074-5086.
[82] Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354-362.

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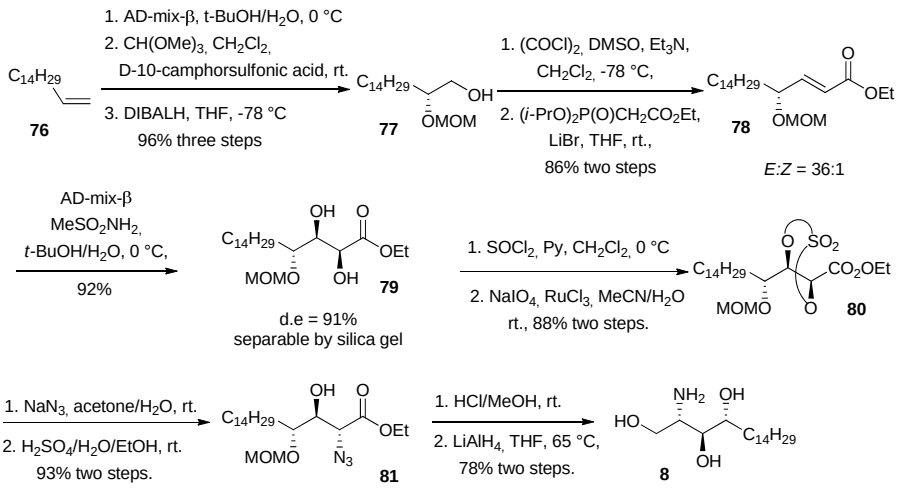
gave the product in 82% yield, which was finally converted to the crystalline enantiomerically pure *N*-Boc-L-*threo*-sphingosine **75** in 65% yield (Scheme 9).

6.2. Synthesis of phytosphingosine

The efficient enantioselective methods for the synthesis of sphingosine were also expanded to the synthesis of phytosphingosine since its biological importance. An efficient and highly enantioselective method has been described for the preparation of both D-*ribo* and L-*lyxo*-phytosphingosine via asymmetric dihydroxylation and formation of the cyclic sulfate intermediate. Asymmetric dihydroxylation of 1-hexadecene (**76**) with AD-mix-β provided a diol, which was converted to the 2-*O*-methoxymethyl derivative **77** in one pot via an isolated *ortho* ester intermediate.[83] Oxidation of alcohol **77** to the corresponding aldehyde followed by Horner-Wadsworth-Emmons olefination provided unsaturated ester **78**. Subsequent asymmetric dihydroxylation with AD-mix-β furnished **79** from which formation of cyclic sulphate **80**, and subsequent selective opening by reaction with sodium azide yielded **81**. Removal of the protecting groups and reduction of the azido and ester functions furnished D-*ribo*-phytosphingosine **8** (Scheme 10).



Scheme 10. Synthesis of D-*ribo*-phytosphingosine (**8**) by a Sharpless dihydroxylation

[83] He, L.; Byun, H. S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7618-7626.

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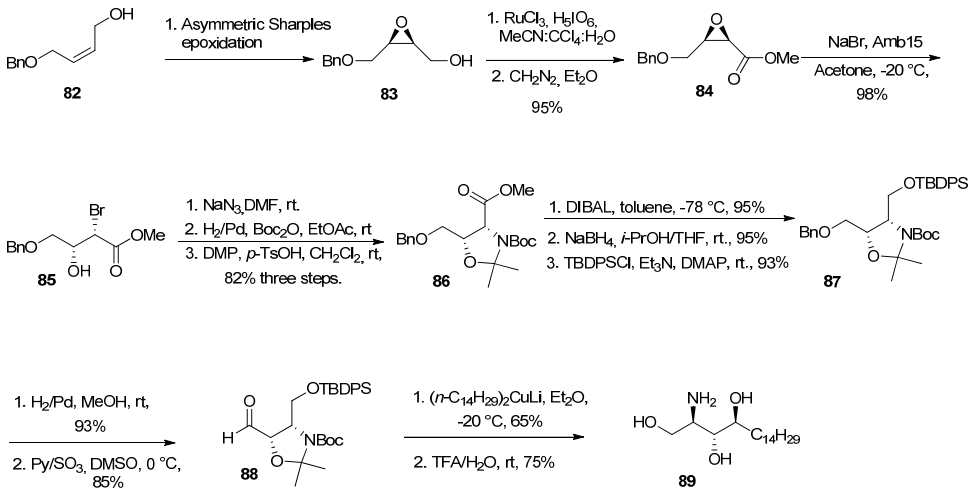
Asymmetric Sharpless epoxidation was also used in the synthesis of L-*lyxo*-phytosphingosine **89**. Thus, chiral epoxide **83** was prepared from allylic alcohol **82** by asymmetric epoxidation, subsequent oxidation and methylation afforded compound **84** (Scheme 11).[84] Treatment of **84** with the NaBr/Amberlyst 15 system, already utilized for the regioselective opening of differentially substituted α,β-epoxy esters,[85] furnished bromohydrin **85** with excellent stereoselectivity and chemical yield. Stereoselective azide nucleophilic substitution, followed by hydrogenation and subsequent protection of the amino alcohol furnished compound **86**. Subsequently, **86** was converted into **87**, first by reducing the ester to the aldehyde with DIBAL, a second reduction with $NaBH_4$ to give the alcohol and finally protection of the hydroxyl function as silyl ether. Compound **87** was debenzylated and the free alcohol was oxidized to the aldehyde with Py/SO_3 to give **88**. L-*lyxo*-phytosphingosine (**89**) was finally prepared through the stereoselective addition of the required lithium cuprate, obtained from tetradecyl bromide, and subsequent deprotection of the amino alcohol (Scheme 11).

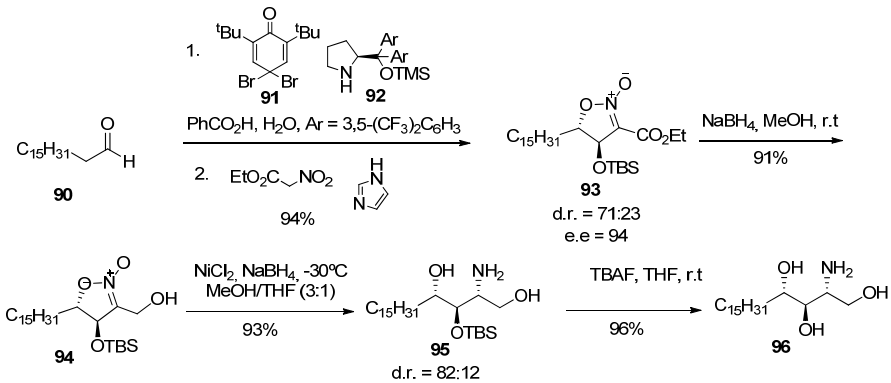


Scheme 11. Synthesis of D-*lyxo*-phytosphingosine (**89**) by a Sharpless epoxidation

[84] Righi, G.; Ciambrone, S.; D'Achille, C.; Leonelli, A.; Bonini, C. *Tetrahedron* **2006**, *62*, 11821-11826.

[85] Righi, G.; D' Achile, C.; Pescatore, G.; Bonini, C. *Tetrahedron Lett.* **2003**, *44*, 6999-7002.

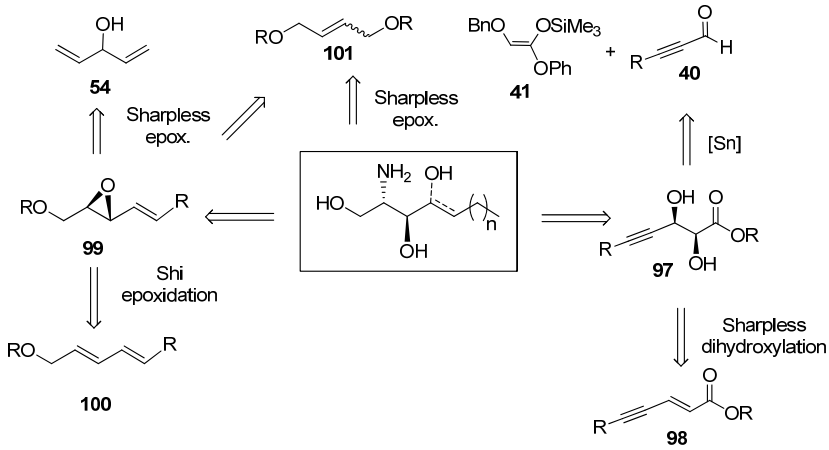
Jorgensen and co-workers developed an one-pot procedure for the formation of optically 4,5-disubstituted-isoxazoline-N-oxides.[86] The direct α-bromination of aldehyde **90** by the electrophilic bromination reagent **91** catalyzed by TMS-protected diaryl-prolinol **92**, furnishes the enantio- and diastereoselective synthesis of 4,5-disubstituted isoxazoline-N-oxide **93** in one pot. Ethyl ester **93** was successfully reduced, to provide the isoxazoline **94** (Scheme 12). Treatment of **94** with nickel borohydride afforded **95** in 93% (82:12 d.r) and then removal of the silyl protecting group furnished L-*ribo*-phytosphingosine (**96**) in 96% yield.



Scheme 12. Synthesis of L-*ribo*-phytosphingosine (**96**) *via* isoxazoline-N-oxide

Nowadays, the use of the enantioselective procedures in the synthesis of sphingoid bases is increasing. Epoxide or 1,2-diols have been the most used intermediates in the synthesis of sphingoid bases (Scheme 13). Diol **97**, which can be obtained by Sharpless dihydroxylation from **98** or by a tin-catalyzed aldol reaction from **41**, was transformed in a sphingosine precursor by a SN_2 diplacement of 3-OH by azide. On the other hand, epoxide **99** was obtained by a regio- and enantioselective Shi epoxidation from the diene **100** or from allylic alcohol **54** by a Sharpless epoxidation. The ring opening by an unmasquerede amino group is necessary to invert the configuration at C-2. Also, other allylic alcohols such as **101** have been studied as a intermediate compounds to obtain phytosphingosine by a sequence based on asymmetric Sharpless epoxidation.

[86] Jiang, H.; Elsner, P.; Jensen, K. L.; Falcicchio, A.; Marcos, V.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 6844-6848.



Scheme 13. Summary of enantioselective synthesis of D-*erythro*-sphingosine (**6**) or D-*ribo*-phytosphingosine (**8**)

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Objectives

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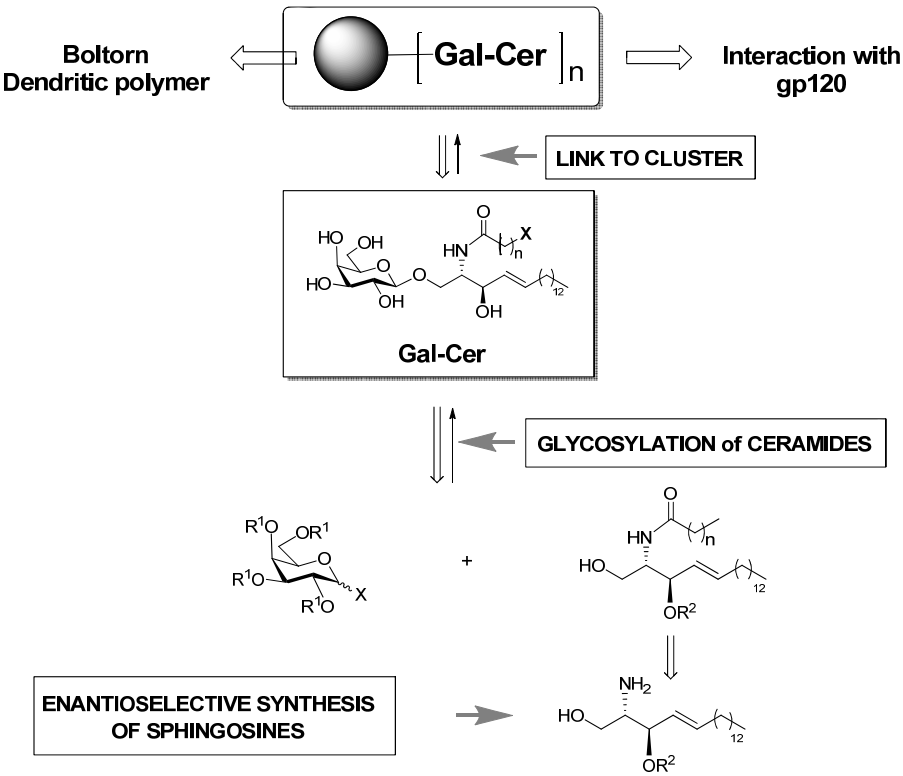
The objectives of the present work are part of a more general objective that aims to prepare glycoclusters of GalCer for testing the interaction with gp120 of HIV. The entry process of HIV into the T-4 lymphocytes cell is known to be a complex process that involves several steps, that begins with initial recognition triggered by gp120 and a specific receptor placed in the surface of the cell (CD4). However HIV can infect some cells without this receptor, which indicates that the existence of alternative receptors. One of these receptors is galactosylceramide (GalCer). Consequently, GalCer analogues with a strong interaction with gp120 are potential inhibitors of the virus entry, and hopefully of infection.



Scheme 14. General objective

We hypothesize, in this context, that glycoclusters containing GalCer could inhibit the entry of the virus into de cell. To achieve this general objective it was necessary to provide efficient procedures for synthesizing sphingosines for the glycosylation of ceramides, and to select the cluster and the way to anchor GalCer. During the last years we have simoultaneously developped all these

methodologies. The present work focuses in developping new methods for synthesizing sphingosines and analogues, which is the first target of the overall objective.

The research described in this thesis aims to investigate new methods for the stereoselective synthesis of sphingoid bases such as sphingosine, phytoshingosine and related compunds based on new enantio-, stereo- and diastereoselective methods catalyzed by transition metal complexes. In this context, the concrete objectives of the present work are the following:

1. Enantioselective synthesis of sphingosine and phytosphingosine based on the following key reactions.

- Enantioselective synthesis of the key synthon 2-*N*-protected-3-buten-1-ol by allylic amination of vinyloxirane with different imido nucleophiles catalyzed by palladium (Dynamic Kinetic Asymmetric Transformation (DYKAT)).

- Study of the ruthenium-catalyzed cross-metathesis reaction of the allyl amines prepared previously with alkenes, in order to obtain different precursors of natural products.

- Optimize the dihydroxylation reaction as one of the key steps in the proposed synthesis.

- Complete effectively the enantioselective synthesis of D-*erythro*-sphingosine and D-*ribo*-phystosphingosine.

2. To apply the before mentioned synthetic methodology to the synthesis of related natural products such as Jaspine B and its isomers.

3. To explore alternatives to develop new procedures for obtaining alkenes of configuration *Z* by molybdenum-catalyzed cross-metathesis.

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4. To study the aziridination reaction of allylic dienols in terms of regio and stereoselectivity, aiming to develop a new method of synthesis of vinyl aziridines.

5. To study the regioselective opening of vinylaziridines

6. To apply the developed methodology to the synthesis of D-*erythro*-sphingosine.

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Enantioselective Synthesis of Sphingoid Bases

CHAPTER 3

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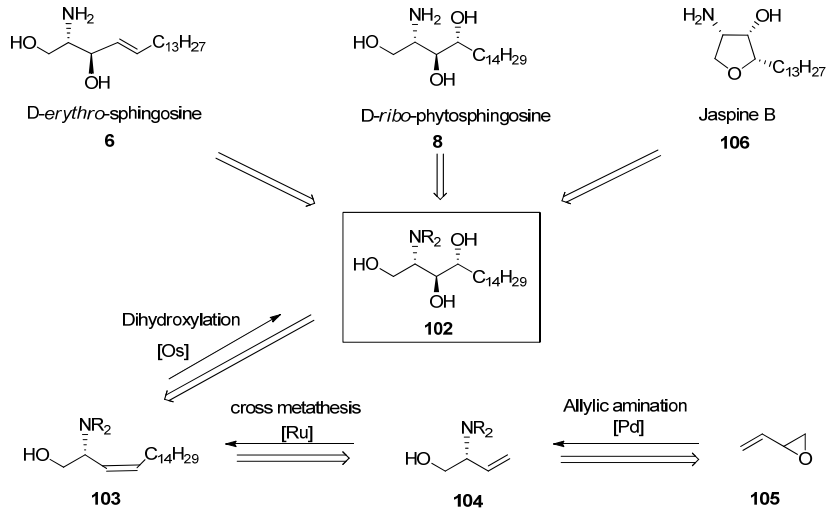
1. Retrosynthetic Scheme

Our aim at the beginning of this work was to explore a new enantioselective method to obtain the sphingoid bases sphingosine, phytosphingosine, and additionally the structurally related Jaspine in an efficient way. Our retrosynthetic proposal is shown in Scheme 15. (*2S*,*3R*,*4R*)-phytosphingosine (**8**) could be obtained by diastereoselective dihydroxylation reaction of *Z*-alkene derivative **103** using osmium reagents followed by deprotection of compound **102**. Compound **103** in turn, can be synthesized from compound **104** via chain elongation mediated by cross-metathesis reaction. Lastly, chiral synthon **104** could be obtained by a palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) from the racemic butadiene monoepoxide (**105**).



Scheme 15 . Retrosynthetic approach for the synthesis of sphingoid bases **6**, **8** and **106**

In the retrosynthesis proposed, the common intermediate **102** could be selectively activated at position C-4 to allow, via elimination reaction, *D-erythro*-sphingosine (**6**). On the other hand, a selective activation of hydroxyl in positions 1 or 4 and subsequent cyclization reaction could afford Jaspine B (**106**) and its C-2-stereoisomer.

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The key step of this sequence will be the asymmetric transformation of racemic butadiene monoepoxide (**105**) into enantiopure allylic amine 104 by means of allylic amination.[87] Moreover, cross-metathesis reaction must enable the introduction of different substituents in the long hydrophobic chain, although obtaining the required *Z* alkene by this procedure is a challenge. Finally, the diastereoselectivity of the dihydroxylation reaction will be controlled by the chiral centre present in the molecule at position C-2 and/or by using chiral ligands in the reaction. In this section, a short background of each different metal-catalyzed reaction will be presented in order to provide a context for them. Thus, the proposed approach relies on three metal-catalyzed reactions: i) palladium-catalyzed Dynamic Kinetic Asymmetric Transformation, ii) ruthenium-catalyzed cross-metathesis and iii) osmium-catalyzed dihydroxylation. They could provide to our methodology the versatility needed to obtain sphingoide bases with a large variety of modifications in order to study their biological effects in the future.

2. Background

2.1. Synthesis of Allyl Amines by a Dynamic Kinetic Asymmetric Transformation

Transition metal-catalyzed Asymmetric Allylic Alkylation (AAA) reactions have proven to be extremely useful and versatile synthetic transformations. Transition metals such as iron, cobalt, nickel, molybdenum, ruthenium, rhodium, tungsten and platinum have been used for this purpose.[88] However, iridium,[89] palladium[90] and copper[91] have been more extensively used.

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87 a) Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stiles, D. T. *Angew. Chem. Int. Ed.* **2007**, *46*, 6123-6125. b) Trost, B. M.; Bunt, R.C.; Lemoine, R.C.; Calkins, T.L. *J. Am. Chem. Soc.* **2000**, *122*, 5968-5976. b) Trost, B. M.; Calkins, T. L.; Oertelt, C.; Zambrano, J. *Tetrahedron Lett.* **1998**, *39*, 1713-1716.

88 For selected publications see a) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813-5837. b) Mori, M. *Chem. Pharm. Bull.* **2005**, *53*, 457-470. c) Trost, B. M.; Crawley. *Chem. Rev.* **2003**, *103*, 2921-2943. d) Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159-167. e) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857-871. f) Trost, B. M. *Pure. Appl. Chem.* **1996**, *68*, 779-784.

89 For selected publications see: a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164-15165. b) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525-9534. c) Kiener, C. A.; Shu, C. T.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272-14273. d) Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*,

Between them, palladium has so far proven to be the most versatile metal catalyst for these transformations because its easy manipulation, high catalytic activity and high enantioselectivity.

In this context, the ability to transform a racemic compound into a single enantiomer is a process that has emerged from transition metal-catalyzed asymmetric allylic alkylation and is infrequently or not often observed in other types of asymmetric transformations. This desracemization constitutes a Dynamic Kinetic Asymmetric Transformation (DYKAT). DYKAT reactions differ from traditional kinetic asymmetric reactions because both enantiomers of the racemic starting material are converted into a single chiral product. This transformation allows full conversion into a particular enantiomer as opposed to only 50% for a traditional kinetic resolution process.[92]

The generally accepted mechanism for palladium-catalyzed allylic substitution is shown in Scheme 16. The cycle involves the initial coordination of palladium (0) to the alkene (Scheme 16, Step 1, complexation) to , followed by an oxidative addition process to afford an intermediate η^3-allyl complex (Scheme 16, Step 2, ionization of the leaving group). Nucleophilic addition (Scheme 16, Step 4, nucleophilic addition) to the cationic complex is favoured and occurs at one of the allylic termini to afford the product coordinated to palladium (0) complex. Dissociation of the palladium (0) liberated the product (Scheme 16, Step 5, decomplexation), regenerates the active palladium catalyst. The ability to utilize each of the first four steps as an enantiodiscriminating event is a key feature of

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8025-8026. e) Garcia-Yebra, C.; Janssen, J. P.; Rominger, F.; Helmchen, G. *Organometallics* **2004**, *23*, 5459-5470. f) Lipowsky, G.; Miller, N.; Helmchen, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4595-4597.

90 For selected publications see: a) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747-760. b) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1-14. c) You, S.-L.; Dai, L.-X. *Angew. Chem. Int. Ed.* **2006**, *45*, 5246-5248. d) Hirakawa, T.; Ikeda, K.; Ogasa, H.; Kawatsura, M.; Itoh, T. *Synlett* **2010**, *19*, 2887-2890. e) Shi, C.; Chein, C.-W.; Ojima, I. *Chem. Asian J.* **2011**, *6*, 674-680.

91 For selected publications see: a) Falciola, C. A.; Alxakis, A. *Eur. J. Org. Chem.* **2008**, 3765-3780. b) Geurts, K.; Fletcher, S. P.; Van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Pure Appl. Chem.* 2008, *80*, 1025-1037.

92 Trost, B. M.; Horne, D. B., Woltering, M. J. *Chem. Eur. J.* **2006**, *12*, 6607-6620.

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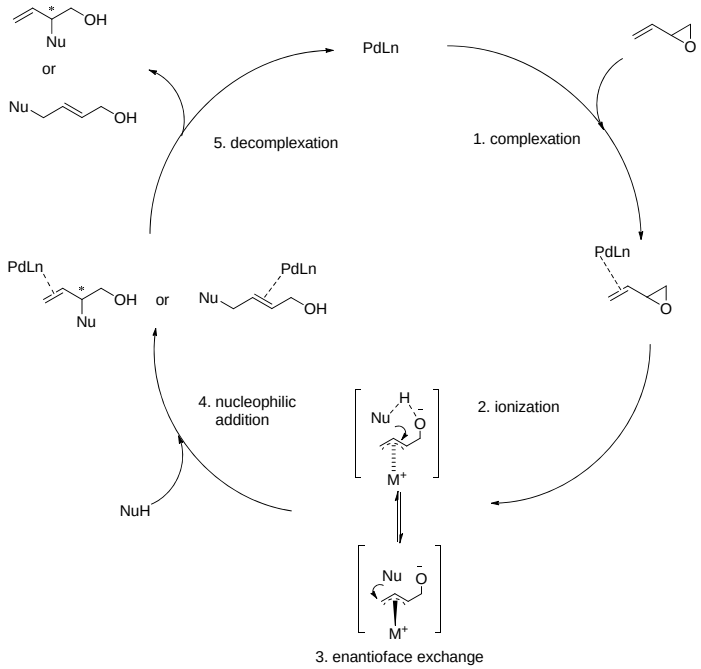
this process and allows facile preparation of enantiopure compounds from racemic starting materials.



Scheme 16. Catalytic cycle proposed by Trost for Pd-catalyzed asymmetric allylic substitutions starting from vinyl epoxide

The enantiodiscrimination arises from the different rate between the reaction of the two diastereomeric complexes **109** and **111** and the nucleophile to give either the enantiomeric product **112** or *ent*-**113**. A quick equilibration between the two complexes takes place, whereby one of the enantiomers of the racemate is selectively consumed while *in situ* concurrent racemisation, via σ-complex, of the other enantiomer occurs at a faster rate (Scheme 17).[93]

[93] Eliel, E. L.; Wilen, S. H. Stereochemistry of organic compounds. Wiley Interscience. **1992**.

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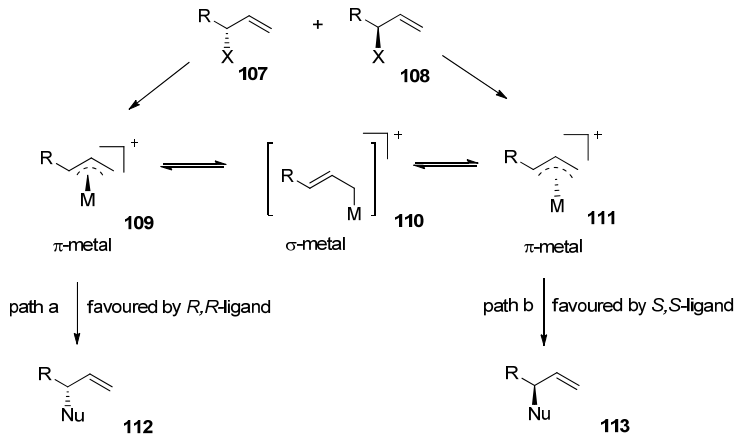

Scheme 17. Asymmetric induction with monosubstituted allyl systems

With regard to the substrate, vinyl epoxides have shown a broad utility in DYKATs because these compounds are excellent electrophiles for Pd-catalyzed DYKAT with oxygen,[94] carbon[95] and some nitrogen[87] nucleophiles. Concerning the reactant, nitrogen nucleophiles have generally presented challenges in several aspects. First, double alkylation frequently occurs with primary amines since the product, a secondary amine, is more nucleophilic than the starting material, leading to mixtures of products. Second, regioselectivity of the substitution with unsymmetrical allyl systems can be a significant problem and frequently mixtures of products are obtained. Moreover, palladium-catalyzed allylic alkylations normally favours nucleophile addition to the less substituted allyl terminus with unsymmetrically substituted allylic substrates obtaining the undesired regioisomer. Ir-catalyzed allylic amination with linear allylic allylic derivatives have been reported to take place at the most substituted allylic terminus to give secondary allylic amines. This method has been applied to the synthesis of allylic amine intermediate **121** and involves the use of the protected form of achiral hydroxycrotonyl carbonate.[96]

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94 Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702-12703.

95 Trost, B. M.; Jiang, C. *J. Am. Chem. Soc.* **2001**, *123*, 12907-12908.

96 Gnamm, C.; Franck, G.; Miller, N.; Stork, T.; Brçdner, K.; Helmchen, G. *Synthesis* **2008**, 3331-3350.

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In the palladium-catalyzed process, Trost and co-workers studied different nucleophiles that could coordinate to the leaving group in order to improve the regioselectivity. In this sense, sulfonamide and imide[87] nucleophiles have been effectively employed, in particular, phthalimide, an excellent primary amine surrogate, has shown to provide more enantioselection than other imido nucleophiles.

The last issue to consider in allylic substitutions is the chiral ligand used; the regioselectivity presumably does not stem only from the coordination effect, but the chiral ligands also help to control the regioselectivity to direct nucleophiles to the more hindered position.[97] Thus, the types of ligands studied by Trost and col. (Figure 5) in order to effect this transformation have followed three general concepts in design: i) creating chiral space with an array of groups whose conformational bias originates from primary stereogenic centers; ii) electronic desymmetrization on the donor atoms of the ligand where different bond lengths on each side of the chiral space promote different reactivity at each terminus; and iii) attaching a tether to coordinate the incoming nucleophile.

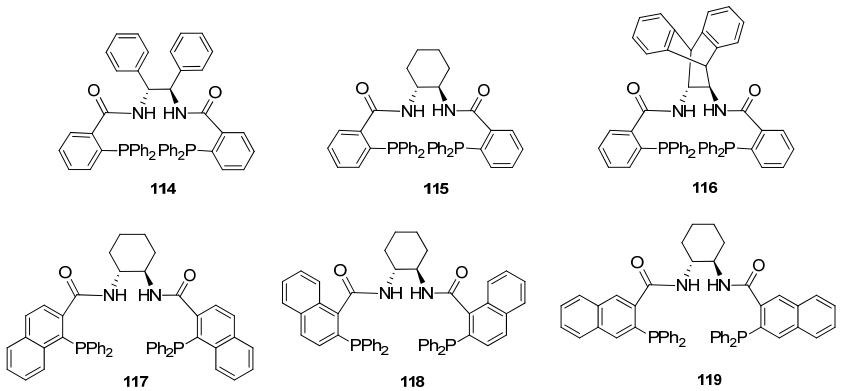

Figure 5. Chiral ligands developed by Trost for asymmetric allylic transformations

The cartoon model (Scheme 18) derives from the ground state structure of the ligand-palladium-π-allyl complex based on molecular modelling structures. Thus, the model nicely rationalizes both the regio- and enantioselectivity. The

[97] a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545-4554. b) Hayashi, T.; Kawatsumura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681-1687.

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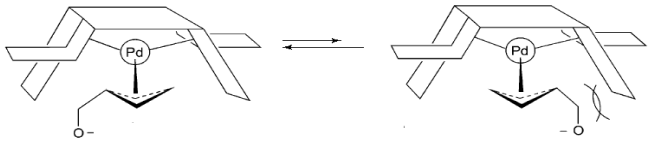
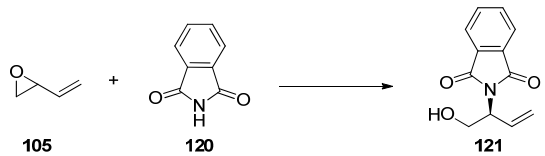
model depicts the more reactive and probably the more stable π-allylpalladium complex. In this model, the walls represent the chiral space created by the propeller-like array of the phenyl rings; the raised flaps represent the phenyls which lie in a plane approximately parallel to the allyl, while the lowered flaps represent phenyls which are somewhat perpendicular to the allyl. Minimizing any steric interactions between the approaching nucleophile and the chiral ligand also directs it to approach from the front left quadrant. On the other hand, the ligand must afford a chiral environement in which one of the diastereomeric π-allyl complex is favoured, being both diastereomeric species equilibrated faster than nucleophilic attack to achieve a dynamic kinetic asymmetric transformation.



Scheme 18. Model of chiral pocket afforded by the chiral ligand in DYKAT

The reaction of butadiene monoepoxide (**105**) with phtalimide (**120**) to obtain 2-(*S*)-*N*-phtalimido-3-buten-1-ol (**121**) (Scheme 19) has been optimized in order to obtain the desired product with high enantioselectivity (>98%) and yield (99%).[98] On the other hand, the obtained intermediate **121** is a useful starting material in the synthesis of different natural products.[92,98]



Scheme 19. Synthesis of 2-(*S*)-*N*-phtalimido-3-buten-1-ol (**121**)

[98] a) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem. Int, Ed.* **2003**, *42*, 5987-5990. b) Harris, M. C. J.; Jackson, M.; Lennon, I. C.; Ramsden, J. A.; Samuel, H. *Tetrahedron Lett.* **2000**, *41*, 3187-3191. c) Trost, B. M.; O'Boyle, B. M. *Org. Lett.* **2008**, *10*, 1369-1372. d) Trost, B. M.; Lemoine, R. C. *Tertrahedron* **1996**, *37*, 9161-9164.

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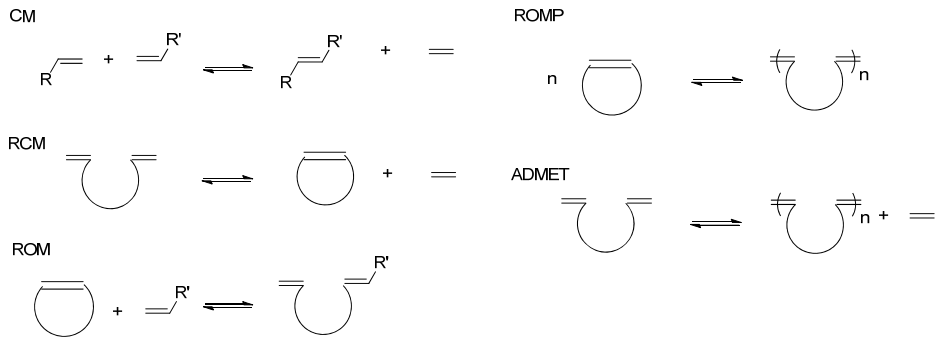
2.2. Cross metathesis

Olefin metathesis transformation entails a redistribution of alkylidene fragments by the scission of carbon-carbon double bonds in two olefin moieties. It can be used in five closely related types of reactions: cross metathesis (CM), ring-opening metathesis polymeration (ROMP), ring-closing metathesis (RCM), acyclic diene metathesis polymerization (ADMET) and ring-opening metathesis (ROM) (Scheme 20).



Scheme 20. Types of olefin metathesis

In the last years, olefin cross metathesis (CM) has emerged as a powerful method for the formation of carbon-carbon double bonds[99] while reducing formation of undesired self metathesis product. In comparison with the classical olefination Wittig reaction, cross metathesis reaction is an economical atom reaction since ethylene is the secondary product. Moreover, contrary to other cross-coupling processes, such as Stille or the Miyaura-Suzuki reactions, in cross-metathesis no sophisticated coupling partners need to be prepared.[100]

The first metallic systems used in metathesis reactions consisted on transition metals salts combined with main group alkylating agents or deposited on solid supports. The classic combinations include WCl_6/Bu_4Sn, $WOCl_4/EtAlCl_2$, MoO_3/SiO_2 and Re_2O_7/Al_2O_3, among many others. The utility of these catalysts were limited by the harsh conditions and the strong Lewis acids

[99] Cossy, J.; Arseniyadis, S.; Meyer, C. *Metathesis in Natural Product Synthesis*, **2010**, Willey-VCH, Weinheim.

[100] Grubbs, R. H. *Handbook of Metathesis 2*, **2009,** Willey-VCH, Weinheim.

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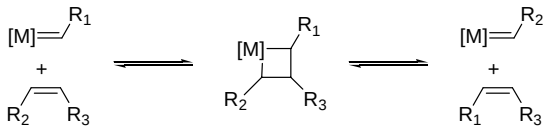
required. Many mechanistic proposals have been suggested for this reaction over the years, but the one proposed by Chauvin was found to be the most consistent with the experimental evidences and it remains the generally accepted mechanism. Chauvin proposed that olefin metathesis involves the interconversion of an olefin and a metal alkylidene. This process is believed to occur via a metallacyclobutane intermediate by alternating [2+2] cycloadditions and cycloreversions (Scheme 21).[101]



Scheme 21. Mechanism of olefin metathesis proposed by Chauvin

The first single-component homogeneous catalyst for olefin metathesis was developed during the late 1970s and early 1980s and involved alkoxide-alkylidene tungsten complexes. These new catalysts included $[(CO)_5W{=}CPh_2]$,[102] bis(cyclopentadienyl)titanocyclobutanes[103] and various dihalo-alkoxide-alkylidene complexes of tungsten.[104,105] As well-defined complexes, these catalysts exhibited better initiation times and higher activity under milder conditions than ever before. The molybdenum and tungsten alkylidenes with the general formula $(NAr)(OR')_2M{=}CHR$ were the first of these catalysts to become widely used, in particular the molybdenum complex **122** or the more active **123** (Figure 6) developed by Schrock and co-workers.[106,107] These catalysts and others

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101 Hérrison, J. L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161.

102 a) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737-738. b) Katz, T. J.; Lee, S. J.; Acton, N. *Tetrahedron Lett.* **1976**, *47*, 4247-4250.

103 Grubbs, R. H.; Tumas, W. *Science* **1989**, *243*, 907-915

104 Wallace, K. C.; Liu, A. H.; Dewan, J. C.; Schrock, R. R. *J. Am. Chem. Soc.* **1988**, *110*, 4964-4977.

105 a) Kress, J.; Osborn, J. A.; Greene, R. M. E.; Ivin, K. J.; Rooney, J. J. *J.Am. Chem. Soc*. **1987**, *109*, 899-901. b) Kress, J.; Aguero, A.; Osborn, J. A. *J. Mol. Catal.* **1986**, *36*, 1-12. c) Quignard, F.; Leconte, M.; Basset, J.-M. *J. Chem. Soc., Chem. Commun.* **1985**, 1816-1817.

106 a) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R.R. *J. Am. Chem. Soc*. **1991**, *113*, 6899-6907. b) Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378-8387. c) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am.*

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based on the early transition metals are highly active, long-lived catalyst systems and do not require Lewis acidic co-catalyst or promoters. However, they show moderate to poor functional group tolerance, high sensibility to air and moisture or even to trace impurities present in solvents, thermal instability on storage and they suffer from expensive preparation.

The ruthenium vinylidene complex $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (**124**) (Figure 6) has been used extensively in organic chemistry due to its high reactivity with olefinic substrates in the presence of most common functional groups.[108]

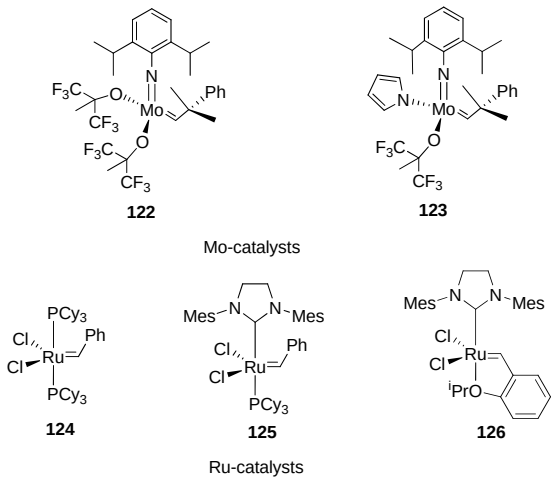


Figure 6. Schrock, Grubbs and Hoveyda-Grubbs catalysts

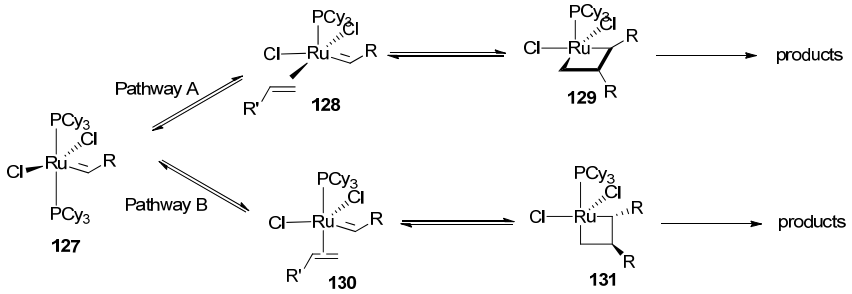
The mechanism of olefin metathesis reactions catalyzed by ruthenium vinylidine complex **127** and its analogues has been the subject of an intense experimental and theoretical investigation, with the ultimate goal of facilitating the rational design of new catalysts displaying higher activity, stability and selectivity.

Chem. Soc. **1990**, *112*, 3875-3886. d) Schrock, R. R.; Feldman, J.; Cannizzo, L. F.; Grubbs, R. H. *Macromolecules* **1987**, *20*, 1169-1172.

107 For reviews of this area, see: (a) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141-8153. (b) Schrock, R. R. *Acc. Chem. Res.* **1990**, *23*, 158-165.

108 Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18-29.

As illustrated in Scheme 22, the first step involves olefin coordination to the metal center, presumably *cis* to the alkylidene and concominant phosphine dissociation. In one possible pathway (Scheme 22, A), alkylidene rotation occurs in order to generate the intermediate, in which the olefin remains *cis* to the alkylidene. This intermediate then undergoes metallocyclobutane formation *cis* to the bound phosphine, followed by cleavage to release the metathesis products. An alternative pathway (Scheme 22, B) involves phosphine dissociation and rearrangement of the olefin *trans* to the remaining phosphine. Then, this intermediate (**130**) undergoes metallacyclobutane formation *trans* to the phosphine (**131**).



Scheme 22. Proposed mechanism of olefin metathesis for $(PCy_3)_2Cl_2Ru{=}CHR$

Early mechanistic studies of the catalyst established that phosphine dissociation is a critical step along the olefin metathesis reaction. It is demonstrated that catalysts containing sterically bulky and electron-donating phosphine ligands display the highest catalytic activity. This trend was explained on the basis of the increased *trans*-effect of larger and more basic/donating phosphines. One of the contributions of the phosphine ligands is σ-donation to the metal center, which promotes the formation of the mono-(phosphine) olefin complex by facilitating phosphine dissociation and stabilizing the vacant *trans* site. Even more importantly, σ -donation helps stabilize the 14-electron metallacyclobutane intermediate. The steric bulk of the ligands may also contribute to phosphine dissociation by destabilizing the crowded bis(phosphine) olefin complex.

On the basis of these important studies, a new class of ruthenium alkylidenes containing N-heterocyclic carbenes ligands (NHC) (**125-126**) has

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been developed (Figure 6), which are significantly larger and more electron donating than trialkylphosphines. This second generation of ruthenium olefin metathesis catalysts exhibit dramatically increased reactivity with olefin substrates. The high activity of the N-heterocyclic carbene has previously been attributed to its ability to promote phosphine dissociation.[109]

Olefin metathesis has become a standard synthetic method because of the wide variety of applications. The activity and functional group tolerance of ruthenium catalyst is now sufficiently high for olefin metathesis to compete with more traditional carbon-carbon bond-forming methods. Unfortunately, ruthenium catalysts are limited by incompatibility with basic functional groups, notably nitriles and amines.

The attractive features of cross metathesis olefination are: i) high *E*/*Z*-selectivity with good yield in the product, ii) functional group tolerance, iii) high activity providing high yields under mild conditions and iv) reasonable ability in the presence of amino functionality.[110] Minimization of unproductive alkenes from self-metathesis and consequently maximization of productive cross metathesis is a crucial issue to be optimized.

This reaction has recently attracted widespread attention as a versatile and powerful tool for the construction of complex biologically active natural products.[111] In this context, *E*-selective cross-metathesis olefination has been used to synthesize D-*erythro*-sphingosine, which has an *E* double bond in its skeleton (Scheme 23). Thus D-tartaric acid **25**, L-serine **11** or bis-allylic alcohol **54** afforded the key intermediate **132**, which was reacted under cross-metathesis using Ru-catalyst follow by deprotection steps to obtain the protected sphingosine.

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109 Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749-750.
110 Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450.
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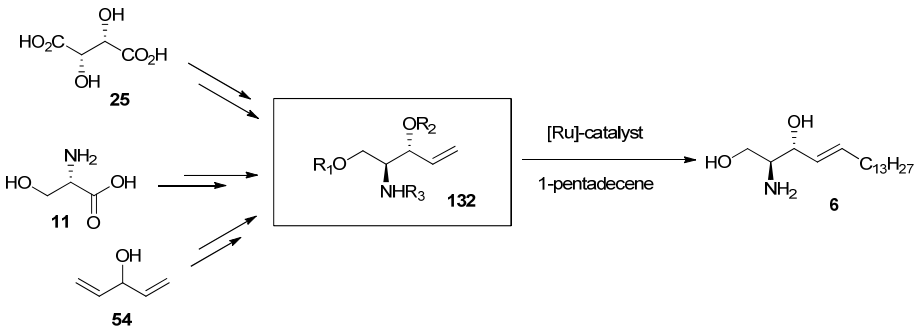

Scheme 23. Synthesis of D-*erythro*-sphingosine (**6**) by a cross-metathesis reaction as a key step

2.3. Dihydroxylation reaction

Osmium-mediated dihydroxylation reaction is a widely used method in the organic synthesis for the transformation of alkenes to 1,2-diols.[112] This reaction has gained popularity since it is a catalytic procedure which avoids the stoichiometric use of the highly toxic, volatile, and expensive osmium tetraoxide.

The asymmetric version expands this powerful reaction to the synthesis of chiral 1,2-diols.[113] A number of features have turned the osmium-catalyzed asymmetric dihydroxylation process into a powerful method for the asymmetric synthesis: i) the reaction is stereospecific leading to 1,2-*cis*-addition of two OH groups to the olefin, ii) it proceeds with high chemoselectivity, iii) the facial selectivity is readily predicted using a simple mnemonic device and exceptions are very rare, iv) it tolerates the presence of most organic functional groups, v) the diols are always derived from *cis*-addition and, side products, such as epoxides or *trans*-diols are never observed, and vi) it usually exhibits a high catalytic turnover, allowing low catalyst loading and good yields.[114]

---

[112] a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547. b) Français, A.; Bedel, O.; Haudrechy, A. *Tetrahedron* **2008**, *64*, 2495-2524.

[113] Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263-4265.

[114] Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*, 2004, Wiley-CVH, 2, Weinheim.Kolb, H. C.; Sharpless, K. B.

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Chiral alkaloid derivatives coordinate to osmium tetraoxide through the nitrogen moiety providing a reaction acceleration and asymmetric induction.[115] In addition, the efficiency of the usually employed stoichiometric reoxidant such as N-methyl-morpholine-N-oxide (NMO),[116] potassium ferricyanide (K_3FeCN_6),[117] or *tert*-butyl hydroperoxide (^tBuOOH)[118] favours the metal regeneration. The use of water as a solvent is necessary to facilitate the cleavage of the intermediate osmate esters **135**, which is the determining step of the reaction and also $CH_3SO_2NH_2$ leads to shorter reaction times.[119]

Much effort has been made to envision the mechanistic features of this reaction[120] and two distinct reaction pathways have been proposed to account for the formation of osmium glycolate **135**:[121] i) a concerted reaction mechanism involving a pericyclic [3+2] transition state **133** (Scheme 24, A)[122] and, ii) a stepwise route involving formation of an osmaoxetane **134** from formal [2+2] addition of the alkene to OsO_4 followed by expansion of the metallacycle (Scheme 24, pathway B).[123] Both mechanisms are currently under consideration,[124] although recently studies based in computational studies support the metallaoxetane mechanism because of the minimum energy in that intermediate. [125]

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121 a) Ojima, I. Catalytic Asymmetric Synthesis, **2000**, 402-406. Willey-VCH, 2nd edition, Canada.

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123 Norrby, P.-O.; Becker, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1996**, *118*, 35-42.

124 a) Göbel, T.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1993**, *32*, 1329-1331. b) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278-1291.

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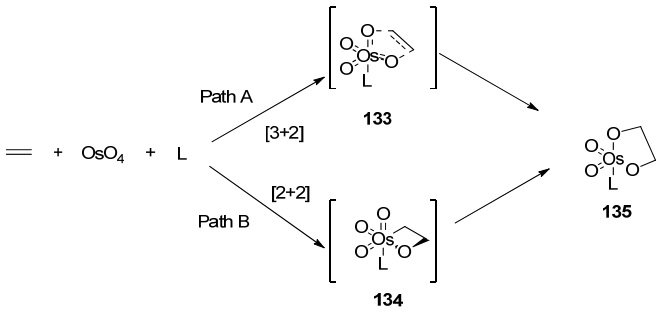

Scheme 24. Schematic representation of the concerted [3+2] mechanism (Path A) and the stepwise osmaoxetane mechanism (Path B)

3. Results and discussion

3.1. Synthesis of allyl amines by DYKAT

Initially we tackled the synthesis of compound **139** from butadiene monoepoxide **105** by enantioselective allylic amination. Diphosphites, and particularly diphosphites bearing a sugar backbone have shown to induce high enantioselectivity in different catalytic processes[126] and particularly in palladium catalyzed allylic amination.[127]

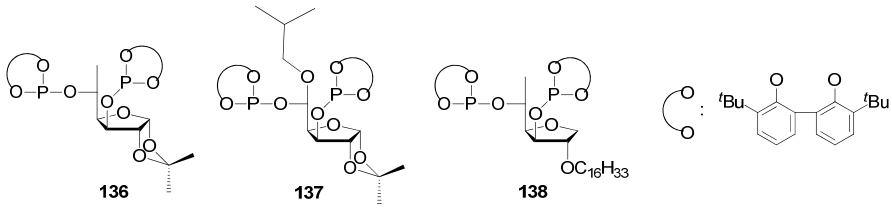

Figure 7. Structure of glucofuranose-derived 1,3-diphosphite ligands tested in the DYKAT reaction

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126 a) Castillón, S.; Claver, C.; Díaz. Y. *Chem. Soc. Rev.* **2005**, *34*, 702-713. b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castillón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165-2192. c) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189-3215. d) Diéguez, M.; Claver, C.; Pàmies, O. *Eur. J. Org. Chem.* **2007**, 4621-4634. e) Woodward, S.; Diéguez, M.; Pàmies, O. *Coord. Chem. Rev.* **2010**, *254*, 2007. f) Diéguez, M.; Pàmies, O. *Acc. Che. Res* **2010**, *43*, 312.

127 a) Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1257-1266. b) Pàmies, O.; Van Strijdonck, G. P. F.; Diéguez, M.; Deerenber, S.; Net, G.; Ruiz, A.; Claver, C.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M. *J. Org. Chem.* **2001**, *66*, 8867-8871.

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Thus, in the framework of collaboration with the Organometallics and Homogenoeus Catalysis group of our University, palladium-catalyzed asymmetric allylic alkylation of vinyloxirane (**105**) using phthalimide (**120**) was studied with ligands **136-138**. The desired branched isomer (**139**) was obtained with quantitative conversion after 1h at room temperature showing the high activity of the 1,3-diphosphite-palladium catalysts **136-138** (Table 1, Entries 1-3).

Ligand **136**, derived from 6-deoxy-1,2-isopropylidene glucose produced the allylic amination, as commented above, with complete conversion, being the regioselectivity, branched:linear products ratio 8:1 (Table 1, Entry 1); although the enantiomeric excess of the branched product was very low (8%). The other C_1-diphosphite ligands **137** and **138** gave moderate regioselectivites (>5:1) (Table 1, Entries 2 and 3). However, despite of the high activity showed by these three ligands and the moderate to good regioselectivity obtained, the enantioselection achieved in that process was extremely poor (<8% e.e.).

In order to improve the enantioselection of the branched product in that process, observing the high activity of these ligands, the reaction was performed at -78ºC (Table 1, Entries 4-12). The conversion was quantitative in all cases after 1 h. The highest regioselectivity (12:1) was obtained using ligand **136** in dichloromethane. Under these conditions, 21% ee was achieved (Table 1, Entry 4). The regioselectivity was good in all cases, which probably indicates the coordination between the imido nucleophile and the alkoxide in agreement with previously studied by Trost.

On the other hand, when tetrahydrofuran was used as a solvent the enantioselectivity decreased (Table 1, Entries 6, 9 and 12) probably due to the fact that nucleophilic attack in that solvent was faster than in dichloromethane. When toluene was used as a solvent a high conversion was obtained, but the regio- and enantioselectivity did not improve (Table 1, Entries 5, 8 and 11).

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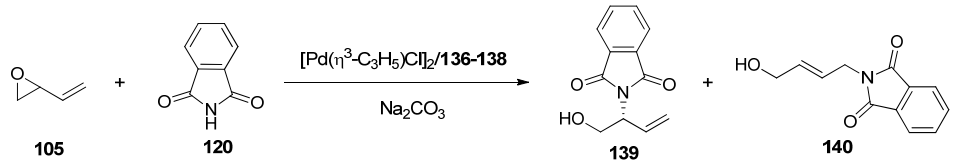
Table 1. Study of allylic amination using diphosphite ligands[a]



Entry	Ligand	Temp.	Solvent	Conversion (%)[b]	Ratio 139/140[c]	ee (%)[d]
1	**136**	r.t.	DCM	>99	89:11	8
2	**137**	r.t.	DCM	>99	83:17	1
3	**138**	r.t.	DCM	>99	82:18	2
4	**136**	-78ºC	DCM	>99	92:8	21
5	**136**	-78ºC	Toluene	>99	89:11	12
6	**136**	-78ºC	THF	>99	91:9	8
7	**137**	-78ºC	DCM	>99	89:11	5
8	**137**	-78ºC	Toluene	>99	82:18	2
9	**137**	-78ºC	THF	>99	89:11	2
10	**138**	-78ºC	DCM	>99	89:11	14
11	**138**	-78ºC	Toluene	>99	88:12	9
12	**138**	-78ºC	THF	>99	89:11	4

[a] [Pd]:[ligand]:[Phthalamide]:[**105**]:[Na_2CO_3] = 1:3:250:250:1, referred to a 0.1 mmol of **105**, 0.4% catalyst loading. [b] Determined by ^{1}H NMR. Phthalimide was accounted. [c] Determined by ^{1}H NMR as branched:linear ratio. [e] Determined by HPLC (90:10 hexanes:^{i}PrOH, 1 mL/min, Column OD-H).

Thus, palladium/diphosphite systems studied were highly active catalysts obtaining quantitative conversions in all tested solvents after 1h at room temperature and also at low temperatures (-78ºC). The regioselectivity was good in all cases with the branched product as a major product. Dichloromethane resulted to be the best solvent although the enantioselectivity was always very low. The possible explanations could justify the obtained results could be that the

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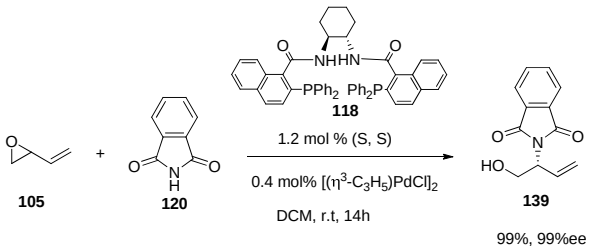
equilibrium between the two diastereoisomeric complexes **109** and **111** (Scheme 17) is not fast enough compared to the rate to the nucleophile attack.

Taking into account the modest results obtained using Pd/**136-138** we performed the synthesis of compound 2-(*R*)-*N*-phtalimido-3-buten-1-ol (**139**) under the conditions optimized by Trost. Thus, using 0.4% of $[(\eta^{3}\text{-}C_3H_5)PdCl]_2$, 1.2% of (*S*,*S*)-DACH-Naphtyl (**118**), and Na_2CO_3 in dichloromethane for 14h, allylic amine **139** was obtained in an excellent yield (99%) and 99% e.e. after recristallization (Scheme 25).[128]



Scheme 25. Synthesis of compound **139**

Compund **141** was obtained directly via palladium-catalyzed allylic substitution from butadiene monoepoxide (**105**) using 2% of $[(\eta^{3}\text{-}C_3H_5)PdCl]_2$, 2% of (*S*,*S*)-DACH-Naphtyl (**118**) using the corresponding imide to afford the desired compound in an 75% yield and 90% e.e.[129] (Scheme 26). Deprotection of benzoyl group in **141** using LiOH in THF affords the desired compound **142** in a quantitative yield.

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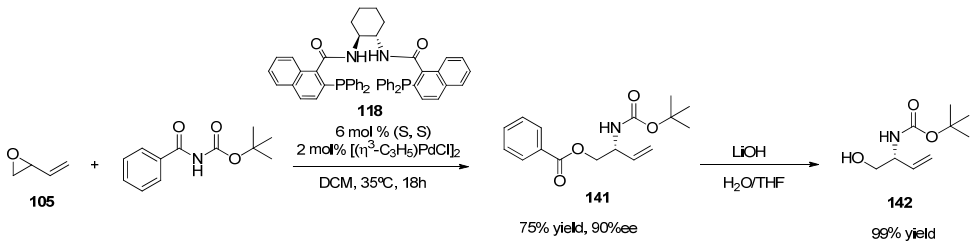
128 Trost, B. M.; Bunt, R. R.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc*. **2000**, *122*, 5968-5976.

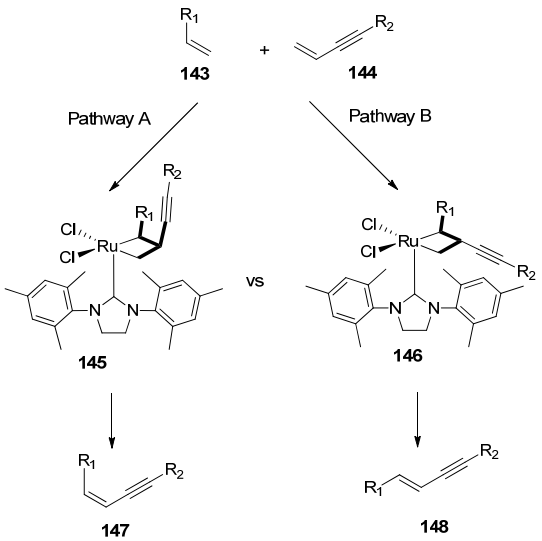
129 Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stilles, D. T. *Angew. Chem. Int. Ed.* **2007**, *46*, 6123-6125.



Scheme 26. Synthesis of compound **142**

3.2. Synthesis of 1,2-disubstituted allyl amines by Ru-catalyzed cross-metathesis

As mentioned before, Ru-catalyzed cross-metathesis usually affords the *E* alkene with high selectivity. However, cross-metathesis with enynes has been observed to afford high selectivity towards the isomer *Z*.[130] This selectivity was associated to steric hindrance present in the metalocycle intermediate (**145** vs **146**) between the alkyne group and the substitutents in the NHC mesityl moiety (Scheme 27).

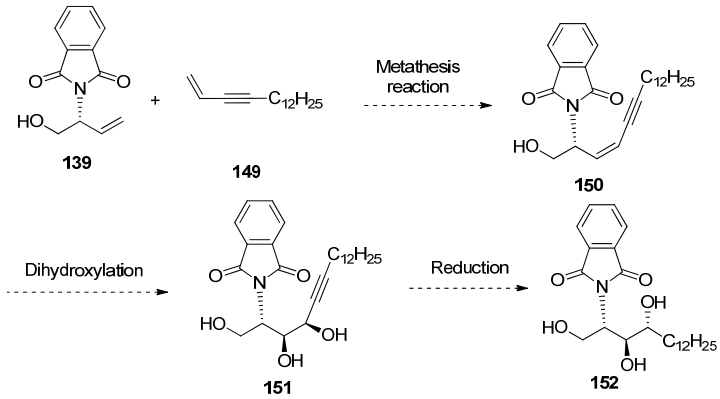


Scheme 27. Intermediates proposed of the formation of *Z*- and *E*-enynes

[130] Kang, B.; Kim, D-H.; Do, Y.; Chang, S. *Org. Lett.* **2003**, *5*, 3041-3043.

The lack of flexibility of the triple bond disfavours the formation of *trans* alkene **148** (Scheme 27, pathway B) over the *cis* product **147** (Scheme 27, pathway A)[131] for steric interactions between the metallacyclobutane and NHC ligands.

We decided to study the cross-metathesis reaction with allyl amine **139** and enyne **149** because of our interest in synthesizing the *Z* isomer (Scheme 28). Thus, the *Z* cross-metathesis product, enyne **150**, could be dihydroxylated to afford compound **151**, which, after reduction, could give the protected D-*ribo*-phytosphingosine **152** with the configuration of the natural product.



Scheme 28. Plausible synthetic route to obtain protected D-*ribo*-phytosphingosine **152**

Thus, 1-hexadecen-3-yne **149** was synthesized (Scheme 29) starting with the protection of alcohol **153** with 3,4-dihydro-(2*H*)-pyrane in presence of a catalytic amount of CSA in dichloromethane for 10h at room temperature, affording compound **154** in an 80% yield.

[131] Kang, B.; Lee. J. M.; Kwak, J. Lee, Y. S. Chang, S. *J. Org. Chem.* **2004,** *69*, 7661.

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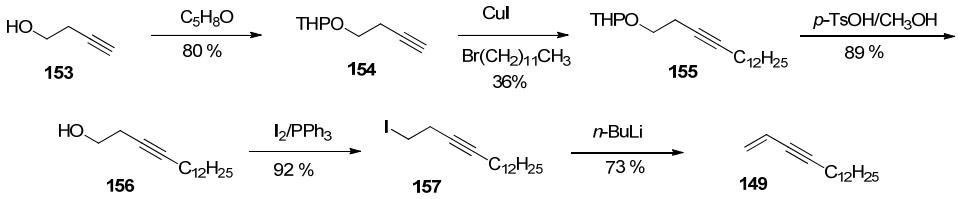
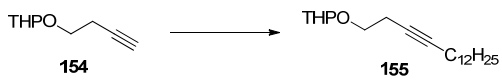


Scheme 29. Synthesis of enyne **149**

Different bases were used to afford the acetylide derivative necessary to carry out the chain elongation by reaction with 1-bromododecane. Unfortunately, the major product of the reaction was 1-dodecene whereas only low yields of the desired product **155** were obtained with the different bases. When $NaNH_2$ was used in THF/DMSO only 18% yield was obtained (Table 2, Entry 1), and the use of different bases like *n*-BuLi or LDA was even less efficient (Table 2, Entries 2 and 3). In view of these results, we decided to perform the reaction with the corresponding alkyne cuprate with the aim of softening the nucleophile and diminish the formation of the elimination product. The yield was slightly improved to 36% (Table 2, Entry 4).

Table 2. Use of different bases of the synthesis of compound **155**[a]



Entry	Base (eq)	Yield (%)[b]
1	$NaNH_2$	18
2	n-BuLi	13
3	LDA	<2[c]
4	CuI	36

[a] 1.2 equivalents of 1-bromodecane. [b] Isolated yield. [c] The product was not observed by TLC or ^{1}H NMR.

In spite of the fact that the yield obtained was very low, we decided to go on with the synthesis. Next step was the deprotection of the tetrahydropyranyl group using *p*-TsOH in methanol affording compound **156** in an 89% yield. The treatment of alcohol **156** with I_2 and PPh_3 afforded iodoalkyne **157** in a 92% yield.

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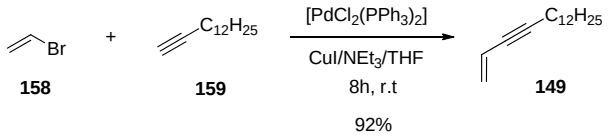
Finally, the deshidrohalogenation with *n*-BuLi afforded the desired product **149** in 73% yield. Thus, enyne **149** was obtained in a 17% overall yield due to the limitations of the acetylide alkylation detailed before.

At the same time, the desired compound **149** was also prepared by coupling of the corresponding alkyne and alkene by a Sonogashira reaction.[132] Vinyl bromide (**158**) and 1-tetradecyne (**159**) were stirred in presence of $[PdCl_2(PPh_3)_2]$ (2%), CuI (4%) and freshly distilled triethylamine in THF for 8 h to afford enyne **149** in a 92% yield (Scheme 30).



158 **159** **149**

Scheme 30. Synthesis of compound **149** by Sonogashira coupling

With enyne **149** in hand, the metathesis reaction was performed by reaction with compound **139** in presence of the second generation Grubbs catalyst (**126**) in dichloromethane at reflux, but no product was observed by TLC and ^{1}H NMR after 12h of reaction (Table 3, Entry 1). The temperature of the reaction was increased to 80ºC using toluene and then, at 110 ºC, but again no new product was observed in the reaction crude (Table 3, Entries 2 and 3). Catalyst **160** has been also described in the metathesis reaction using enynes as substrates.[131] However, in our case, the cross-metathesis between compound **139** and enyne **149** in presence of catalyst **160** in toluene did afford no product (Table 3, Entry 4).

[132] a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653,* 46-49. b) Hansen, E. C.; Lee, D. *Org. Lett.* **2004**, *6*, 2035-2038.

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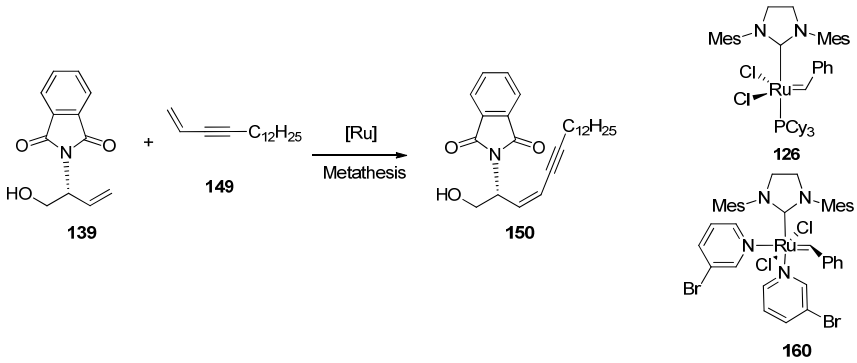
Table 3. Study of cross-metathesis reaction between alkene **139** and enyne **149**[a]



Entry	Catalyst	Solvent	Temperature (ºC)	Conversion (%)[b]
1	**126**	CH_2Cl_2	50	<2
2	**126**	Toluene	80	<2
3	**126**	Toluene	110	<2
4	**160**	Toluene	80	<2

[a] 4 equivalents of enyne **149**, 5 mol % catalyst loading, 0.1 M in dichloromethane.
[b] Determined by ^{1}H NMR spectroscopy.

Thus, no successful result was obtained in the *cross*-metathesis reaction to afford the desired *Z*-product using ruthenium catalysts. However, taking into account that Ru-catalysts favour the formation of the *E* isomer, we decided to modify the synthetic scheme towards the obtention of the *E*-cross-metathesis product. The new proposed retrosynthesis involves the synthesis of the *E* alkene, and dihydroxylation to give the compound with opposite configuration at C-4 to that of the natural phytosphingosine. That will require to invert the configuration of this position in the intermediate **162** with a (2*S*,3*R*,4*S*) configuration. Product **162** in turn, could be obtained by a dihydroxylation catalyzed by osmium of the *E*-alkene **161** (Scheme 31).

This modification, however, should not affect the synthesis of *D-erythro*-sphingosine (**6**), since 4-OH can be selectively activated to allow the elimination

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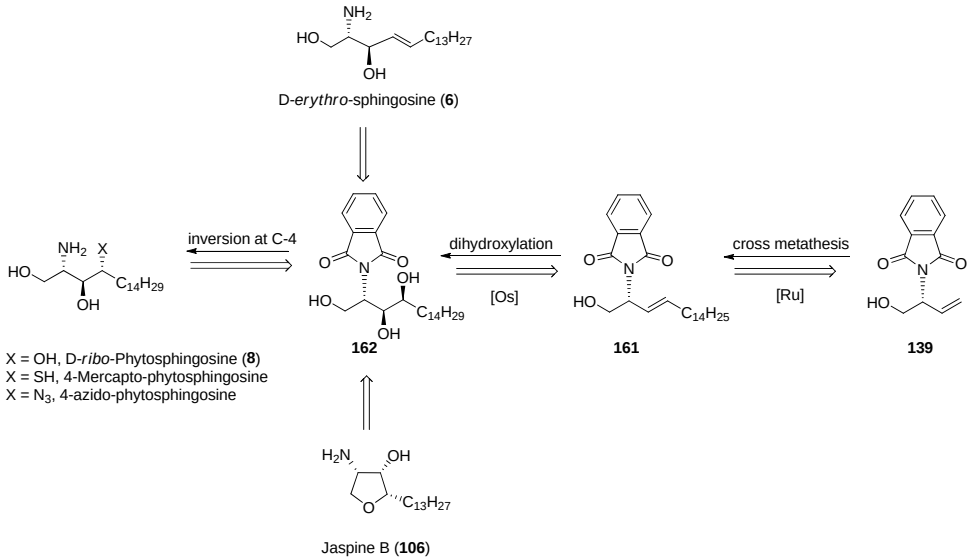
reaction. Moreover, this strategy should advantageously allow the synthesis of a range of C-4 structural analogues of phytosphingosine from a common precursor.



Scheme 31. Proposed synthesis of sphingoid bases by an Os-catalyzed dihydroxylation of *E*-alkene **161**

With the aim of synthesizing D-*erythro*-sphingosine **6** and D-*ribo*-phytosphingosine (**8**), we studied the cross metathesis of compound **139** with 1-hexadecene (**163**). Assuming that the second generation Grubbs catalyst is compatible with a wide range of functionalities,[133] in a preliminary set of experiments, compound **139** was reacted with two equivalents of 1-hexadecene (**163**) in refluxing dichloromethane to afford after 6 h product **161** with a 85% conversion and 82% yield as a mixture *E*/*Z* in a ratio of 94:6 (Table 4, Entry 1). When four equivalents of 1-hexadecene were used, the conversion was improved to 99%; however the diastereoselectivity did not improve in 7h (Table 4, entry 2). For this reason, we decided to run the reaction at reflux for 12h using four equivalents to produce quantitative conversions to exclusively the *E*-isomer, as shown by ^{1}H NMR (Table 4, Entry 3). Compound **141** and **142** were reacted with

133 a) Yamamoto, T.; Hasegawa, H.; Hakogi, T.; Katsumura, S. *Org. Lett.* **2006**, *8*, 5569-5572. b) Chaudhari, V. D.; Kumar, K. S. A.; Dhavale, D. D. *Org. Lett.* **2005**, *7*, 5805-5807. c) Morales-Serna, J. A.; Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Biomol. Chem.* **2008**, *6*, 4502-4504. d) Torsell, S.; Somfai, P. *Org. Biomol. Chem.* **2004**, *2*, 1643-1646.

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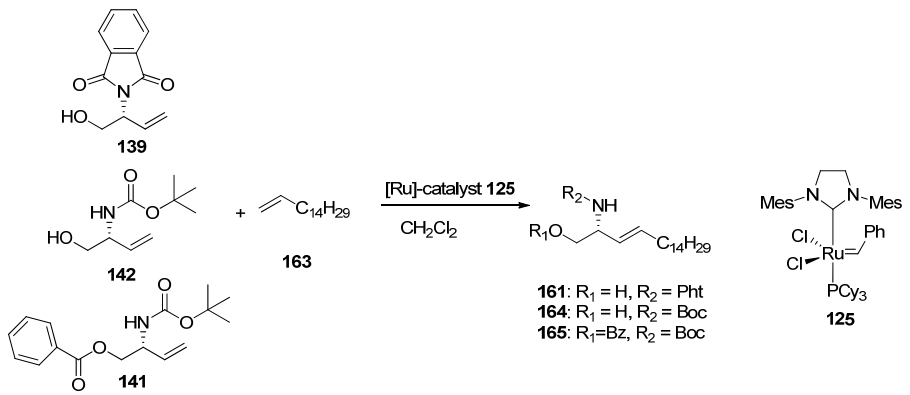
1-hexadecene for 12h at reflux obtaining the desired compound **164-165** in high stereoselectivities and a 40% and 33% yield, respectively (Table 4, Entries 4 and 5).

Table 4. Cross-metathesis results using allyl amines (**139**, **141** and **142**) and hexadecene[a]



Entry	alkene (equiv.)	Allyl amine	Time (h)	Product	Conv.[b] (%)	Yield (%)	Stereoselectivity (*E*/*Z*)[b]
1	2	**139**	6	**161**	85	82	94:6
2	4	**139**	7	**161**	>99	93	95:5
3	4	**139**	12	**161**	>99	99	>98:<2[c]
4	4	**142**	12	**164**	44	40	93:7
5	4	**141**	12	**165**	33	29	92:8

[a] 5 mol % catalyst **125**, 0.4 M in DCM referred to allyl amine. [b] Determined by ^{1}H NMR spectroscopy. [c] *cis* isomer was not detected by ^{1}H NMR spectroscopy.

Taking into account the reversibility of this system, it would afford the more stable *E*-alkene **169**. Moreover, the energy of the *trans*-metallacyclobutane intermediate **168** (Scheme 32) is probably lower than the more sterically hindered *cis*-metallacyclobutane **166**.

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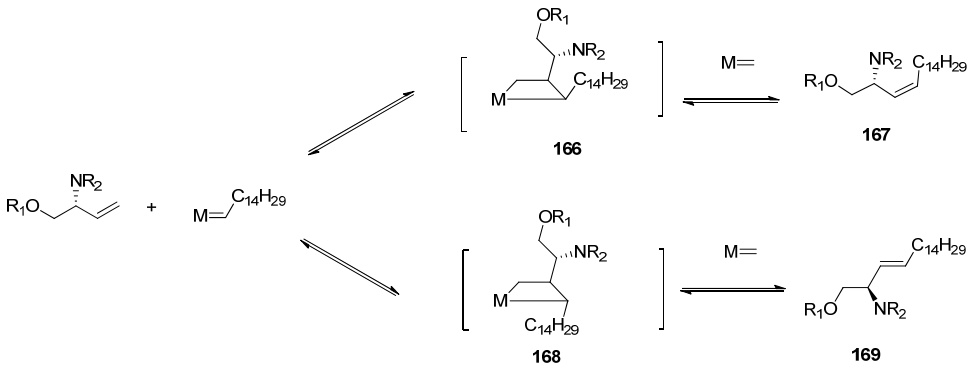

Scheme 32. Cyclic intermediates proposed to the production of *E* an *Z* products by CM

From this study, it can be concluded than compound **139** with phthalimide as a protecting amine group and the free hydroxyl group shows to be the most appropriate substrate in cross metathesis using II generation of Grubbs catalyst, to obtain product **161** with high yield and *E*-diastereoselectivity.

With this good result in terms of yield and stereoslectivity, we decided to study the scope of the cross-metathesis reaction between allyl amine **139** and other cross-partners since the resulting compounds could be of interest in the synthesis of biologically active compounds, such as azasugars, which are currently under study in our group.

The generation of olefins with electron-withdrawing functional groups, such as α,β-unsaturated aldehydes, ketones and esters, remains a difficult task in organic synthesis. Other π-conjugated functional groups compatible with alkylidene Schrock catalyst failed to react with first generation of Grubbs catalyst. However, second generation of ruthenium catalyst and, Hoveyda-Grubbs catalyst were found to be very efficient in the reaction with α,β-unsaturated carbonyl compounds.[134]

Other cross-partners such as ethyl acrylate (**170**), acrolein (**171**) or 2-vinyldioxolane (**172**) and β,γ-unsaturated carbonylic products such as 3-butenoic

[134] Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783-3784.

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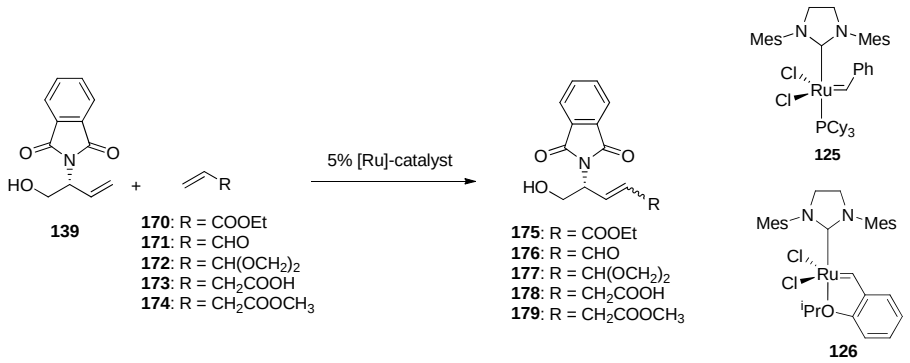
acid (**173**) or methyl 3-butenoate (**174**) were tested in cross-metathesis with allyl amine **139**.

Table 5. Results in the optimization of cross-metathesis reaction between allyl amine **139** and alkenes **170**-**174**[a]



Entry	Subtrate	R	Catalyst	Solvent	Product	Yield (%)[c]	Selectivity (E:Z)[d]
1	**170**	COOEt	**125**	CH_2Cl_2	**175**	71	>98:<2
2	**171**	CHO	**125**	CH_2Cl_2	**176**	<2	-
3	**171**	CHO	**125**	Toluene	**176**	<2	-
4	**171**	CHO	**126**	CH_2Cl_2	**176**	78	96:4
5	**172**	$CH(OCH_2)_2$	**125**	CH_2Cl_2	**177**	<2	-
6	**172**	$CH(OCH_2)_2$	**125**	Toluene	**177**	<2	-
7[b]	**172**	$CH(OCH_2)_2$	**125**	CH_2Cl_2	**177**	52	95:5
8	**173**	CH_2COOH	**125**	CH_2Cl_2	**178**	<2	-
9	**174**	CH_2COOCH_3	**125**	CH_2Cl_2	**179**	65	>98:<2

[a] 4 equivalents of alkene, 5 mol % catalyst loading, 0.5M in solvent, 12h. [b] The substrate was added over 8h by syringe. [c] Isolated yield. [d] Determined by ^{1}H NMR.

The reaction of ethyl acrylate (**170**) in presence of second generation of Grubbs catalyst at reflux of dichloromethane afforded the product **175** in a 71% yield with an excellent *E*-selectivity (Table 5, Entry 1). However, acrolein (**171**)

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in presence of the same catalyst did not give the cross-product (Table 5, Entry 2). Instead, the homocross-metathesis of allyl amine **139** was observed with a 48% yield. Using toluene as a solvent, the cross-product **176** was not either observed (Table 5, Entry 3). However, conversion was increased to 78% with a good selectivity using 5% mol of catalyst **126** (Hoveyda-Grubbs) (Table 5, Entry 4).

When vinyldioxolane (**172**) was reacted with **139** in the presence of catalyst **125** in dichloromethane at reflux the cross-product was not observed (Table 5, Entry 5), neither when the reaction was carried out at higher temperatures in refluxing toluene (Table 5, Entry 6). Slow addition of substrate **172** via syringe over 8h afforded the desired product **177** in a 52% yield with a good *E*-selectivity (Table 5, Entry 7). The reaction from **173** did not afford the desired product (Table 5, Entry 8), probably because of the acidity of the substrate. For this reason the corresponding ester was used as reagent affording alkene **179** in a moderate yield (65%) and excellent diastereoselectivity (>98:<2) (Table 5, Entry 9).

In conclusion, cross metathesis reaction allowed synthesizing allylic amines of *E*-configuration with excellent stereoselectivity affording the desired product in moderate to high yields.

3.3. Dihydroxylation of allyl amines

Bearing in mind the retrosynthetic scheme for the synthesis of phytosphingosine, dihydroxylation reaction was subsequently explored. Two possible ways of diastereoselection control could be possible in the dihydroxylation of enantiopure *E*-allylic amines. The presence of a chiral centre in the substrate can control the diastereoselectivity, normally allowing the dihydroxylation *anti* (**162**) to the amine group. Moreover, the use of chiral ligands can allow a double stereodifferentiation stimulated by the substrate and the catalyst control.

Compound **161**, which was obtained with the best yield and stereoselectivity, was initially reacted at room temperature with 5 mol % of OsO_4 and stoichometric amounts of oxidant NMO and in the presence of

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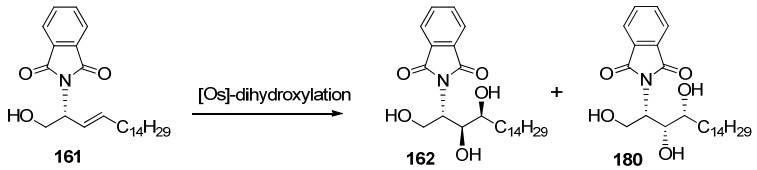
methanosulfonamide ($CH_3SO_2NH_2$). Dihydroxylation products were obtained as a mixture of compounds **162** and **180** in almost quantitative yield in a ratio of 3.3:1 (Table 6, Entry 1). Compound **162** and **180** were carefully separated obtaining a 76% and 23% yield, respectively. In order to improve the diastereoselectivity, the temperature was decreased at 0ºC, this modification had a negative effect on the yield (57%) after 24h and no effect on the stereoselectivity (Table 6, Entry 2). Low catalyst loading (2.5 mol %) was not successful and additional 2.5 mol % more catalyst loading was needed to complete conssumption of the starting material.

Table 6. Dihydroxylation of alkene **161** to afford diols **162** and **180**



161 **162** **180**

Entry	Reagent	Temp. (ºC)	Conversion (%)[a]	Ratio 162:180[a]	Yield of 162 (%)[b]
1	OsO_4/NMO	r.t.	>98	3.3:1	76[e]
2	OsO_4/NMO	0	57	3.4:1	nd
3[c]	OsO_4/TMEDA	-78	>98	3.4:1	95[f]
4[d]	OsO_4/TMEN	-78	>98	3.8:1	93[f]

[a] Determined by ^{1}H NMR. [b] Isolated yield of major disastereoisomer. [c] OsO_4 (1 equiv) and TMDA (1.1 eq) were used. [d] OsO_4 (1 equiv) and TMEN (1.1 eq) were used. [e] Compound **162** was isolated. [f] Mixture of both diastereoisomers were isolated.

Kishi conducted a comprenhensive investigation on acyclic stereocontrol in OsO_4-catalyzed dihydroxylation of allylic alcohols and ethers.[135] The observed stereoselectivity trends in dihydroxylations of allylic substrates led to propose an empirical model for predicting the diastereoselectivity. However, osmylation of allylic amines has been less studied and mechanistic studies are complicated by

[135] Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943-3946.

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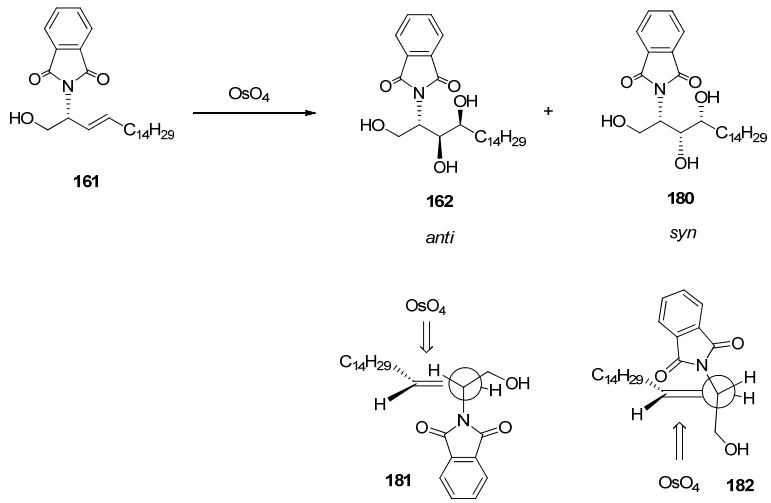
the known complexation of amines with osmium tetroxide.[136] In our case, no complexation with the phthalimide group is expected, and therefore we propose the Kishi model to explain the observed diastereofacial discrimination.

In this model, minimization of both the $A^{1,3}$ strain and electrostatic repulsions between Os=O and the C-heteroatom bond are believed to lead to predominant formation of the 1,2-*anti* product.[137] The smallest group at the stereogenic centre is aligned parallel to the double bond and the osmium attacks on the opposite site from the charged nitrogen of the allylic center. However, the formation of *syn* product **180** could be favoured if intermediate **182** minimizes the steric interactions due to $A^{1,2}$ strain (Scheme 33).



Scheme 33. Proposed model for the attack of osmium teroxide on chiral allylic amine **161**

An attempt was made to increase the stereoselectivity by carrying out the reaction at -78ºC and by using stoichiometric amounts of OsO_4 in the presence of different diamine ligands. When tretramethylethylenediamine (TMEDA) was used as a diamine ligand, the stereoselectivity was similar to the previous results reported in Entry 1 (Table 6, Entry 3). The use of tetraethylethylenediamine (TMEN) slightly increased the **162/180** ratio to 3.8:1, with a 93 % yield (Table 6, Entry 4). Running the reaction at low temperature did not improve significantly

136 Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761-1795.
137 Haller, J.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 8031-8034.

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the diastereoselectivity, although stoichiometric amounts of nitrogen ligand increased the electronic density in the metal centre. No evidence of coordination by a hydrogen bond between the hydroxyl group and oxo-osmium catalyst has been observed.

Trying to improve the diastereoselectivity we attempted the asymmetric dihydroxylation. Dihydroquinine and dihydroquinidine, two pseudoenantiomeric alkaloids from cinchona, in combination with different spacers are the ligands of choice for this process.[138] The enantioselectivity is mainly influenced by the nature of the C9 substituent. Initially, CLB (**185**) (*p*-chlorobenzoate), MEQ (4-methyl-2-quinolil) (**186**) and PHN (phenanthryl ether) (**187**) were used as spacers (first generation), however, second generation spacers which are bonded to two chiral ligands such as PHAL (**188**) (phthalazine), Pyr (pyrimidine) (**189**) and AQN (anthraquinone) (**190**) are preferently used (Figure 8).

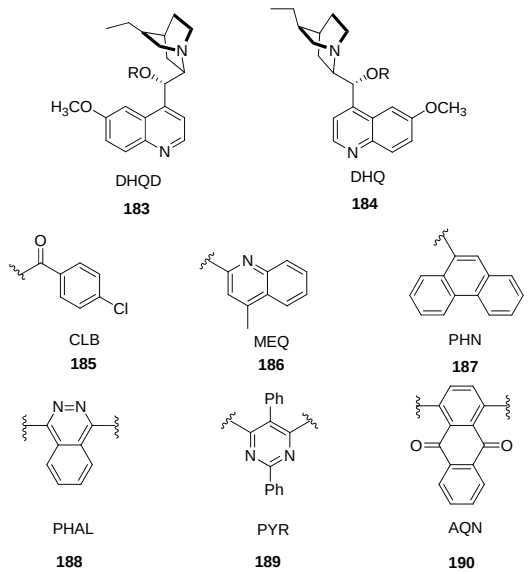

Figure 8. Cinchone ligands

[138] a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H. L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768-2771. b) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585-4588. c) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785-3786.

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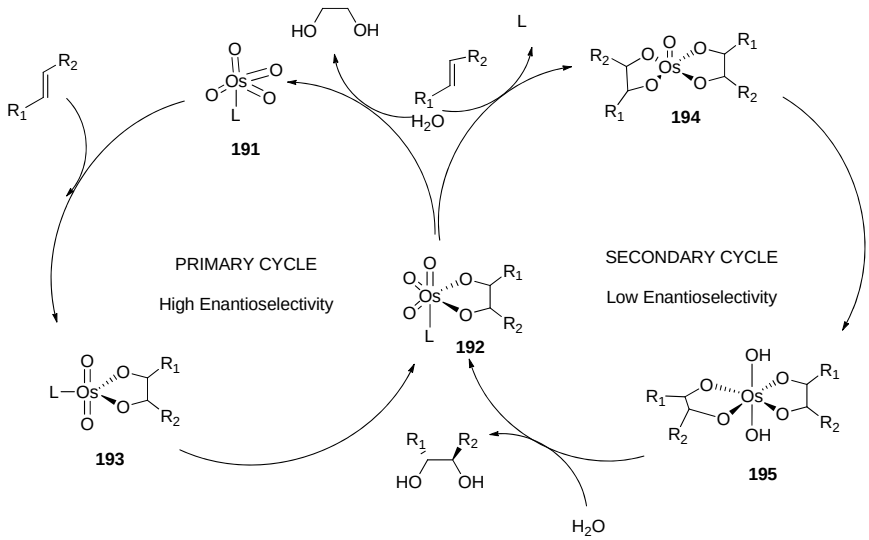
Mechanistic studies revealed the presence of a secondary catalytic system as the culprit of the low enantioselectivities found in osmium-catalyzed dihydroxylation. This secondary cycle proceeds with poor-to-no face selectivity, since it does not involve the chiral ligand (Scheme 34). The desired path involves the hydrolysis of **192** to OsO_4 and the optically active 1,2-diol, whereas the undesired cycle is entered when **192** reacts instead with a second molecule of olefin, yielding the osmium (VI) bisglycolate **195** and thence 1,2-diol of low enantiopurity.[139] The use of $K_3Fe(CN)_6$ in combination with heterogeneous solvent systems, typically *tert*-butanol/water, allows an olefin osmylation and osmium re-oxidation steps uncoupled, since they occur in different phases. The osmylation takes place in the organic layer, giving rise to the osmim(VI) glycolate **192**. This osmium(VI) complex cannot be oxidated to an osmium(VIII) glycolate, because of the absence of the inorganic stoichiometric oxidant $K_3Fe(CN)_6$ in the organic layer. Consequently, the second catalytic cycle cannot occur. This reaction requires hydrolysis of the osmium (VI) glycolate **193** to the 1,2-diol and a water soluble inorganic osmium(VI) species, which enters to the basic aqueous layer ready to be oxidized by $K_3Fe(CN)_6$ to OsO_4.



Scheme 34. Proposed catalytic cycle in osmium-catalyzed dihydroxylation

[139] Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123-1125.

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Asymmetric dihydroxylation reaction of related substrates heve been reported to afford excellent yields and stereoselectivities of phytosphingosines, using commercially avaliable AD-MIX α and β.[140] We tested the asymmetric dihydroxylation in order to obtain higher diastereoselectivities by a double stereodifferentiation. However, when compound **161** was treated with commercial AD-MIX mixtures, no reaction was observed (Table 7, Entries 1 and 2) although both mixtures were employed. The reaction was attempted using a freshly prepared mixture of $[K_2OsO_2(OH)_4]$ and $[K_3Fe(CN)_6]$ in the presence of ligands $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL, in $^tBuOH/H_2O$ (1:1), but unfortunately, the starting material was again exclusively recovered. Finally, other spacers were used in combination with of $[K_2OsO_2(OH)_4]$, $[K_3Fe(CN)_6]$, K_2CO_3 and $NaHCO_3$. When $(DHQ)_2PYR$ was used, the conversion was quantitative and the ratio of the products increased considerably to 5.1:1 which allowed the isolation of major compound **162** in a 86% yield (Table 7, Entry 3). To promote the formation of compound **180**, the *pseudo*enantiomeric ligand $(DHQD)_2PYR$ was tested in the osmium-catalyzed dihydroxylation reaction affording a mixture of the products **162** and **180** with excellent conversion (>98%), and a **162:180** ratio of 1:1.3 allowing to recover compound **180** in a 47% yield. The use of $(DHQD)_2AQN$ did not improve the diastereoselectivity of the reaction, obtaining the products in a 1:1.1 ratio (Table 7, Entry 4).

With these results in hand, we concluded that the presence the stereogenic center at C2 controls moderately the diastereoselectivity of the osmylation which is the result of an *anti* attack to the bulky phthalimido group at C2. The use of commercially or freshly prepared AD-mixture did not afford the dihydroxylation. However, other spacers such as PYR or AQN promoted the dihydroxylation efficiently in terms of conversion. On the other hand, dihydroquinine ligand $(DHQ)_2PYR$ afforded an increment of the diastereoselectivity, while a *mis*-matched process was observed when dihydroquinidine (DHQD) ligand was used.

---

[140] a) Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657–10670. b) Mormeneo, D.; Casas, J.; Llebaria, A.; Delgado, A. *Org. Biomol. Chem.* **2007**, *5*, 3769–3777.

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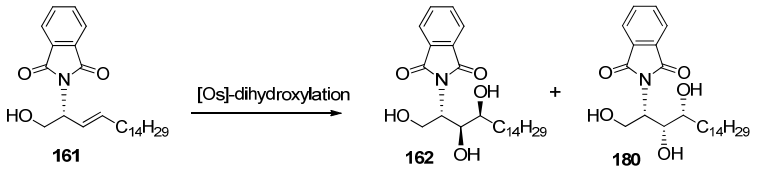
Table 7. Dihydroxylation of alkene **161** using chiral ligands



Entry	chiral ligand	Temp. (ºC)	Conversion (%)[a]	Ratio 162:180[a]	Yield (%)[b]
1	AD-MIX α	r.t.	-	-	
2	AD-MIX β	r.t.	-	-	
3	$(DHQ)_2PYR$[h]	r.t.	>98	5.1:1	86[e]
4	$(DHQD)_2PYR$[g]	r.t.	>98	1:1.3	47[f]
5	$(DHQ)D_2AQN$[g]	r.t.	>98	1:1.1	-

[a] Determined by ^1H NMR. [b] Isolated yield. [c] OsO_4 (1 eq) and TMDA (1.1 eq) were used. [d] OsO_4 (1 eq) and TMEN (1.1 eq) were used. [e] Compound **162** was isolated. [f] Compound **180** was isolated. [g] Ligand (0.03 eq), $CH_3SO_2NH_2$ (1.1 eq), K_2CO_3 (0.3 eq), $NaHCO_3$ (0.3 eq), $K_3Fe(CN)_6$ (3eq), $K_2OsO_2(OH)_4$ (0.02 eq).

Three mnemonic devices in achiral olefins have been stated to help to determine the favorite product configuration depending on the double bond stereochemistry and the nature of the catalyst.[120,138a,141] The plane of olefin is divided into four quadrants and the substituents are placed into these quadrants according to a simple rule. The SE quadrant is sterically inaccessible; no substituent other than hydrogen can be placed here. The NW quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. The SW quadrant is preferenced for the largest groups. The mnemonic rules suggest the use of DHQ ligands provided the dihydroxylation in an *anti* position to the phthalimido group at C-2 as a matched effect with the substrate-control (Scheme 35).

141 Fristrup, P.; Tanner, D,; Norrby, P. O. *Chirality* **2003**, *15*, 360-368.

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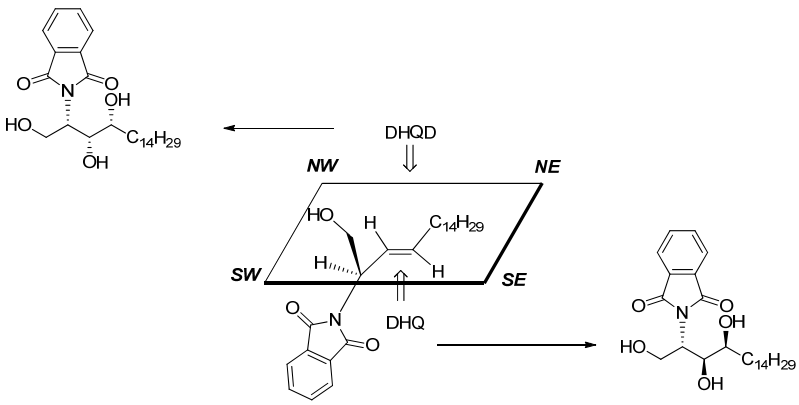

Scheme 35. Dihydroxylation products based on mnemonic rules

3.4. Synthesis of D-*erythro*-sphingosine, D-*ribo*-phytosphingosine and 4-substituted derivatives

As explained in this section, our aim is to propose a new enantioselective method to obtain sphingoid bases in an efficient way. In this sense, intermediate **162** was obtained in high yield (80%) via an asymmetric allylic amination, followed by cross-metathesis and dihydroxylation.

Compound **162** could give access to natural phytosphingosine **8** and different derivatives by nucleophilic substitution at position 4. This approach can open the way to the synthesis of several analogues modified at the ceramide chain, with the hope of developing novel lead compounds with better response. In this sense, although modifications in the carbohydrate moiety[142] and the glycosidic linkage[143] of glycolipids have been extensively studied, few efforts have been concentrated at the ceramide moiety.[144]

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Studies related to CD1d-lipid-antigen recognition by the natural killer T-cell receptor have revealed, among others, the existence of H-bonds between the 3' hydroxyl group of the sphingosine chain in α-GalCer and Arg95 of the CDRα-loop.[145,146] Recently, Van Calenbergh and col. have described the synthesis of analogues of KRN7000 modified at position 3 or 4 of phytosphingosine chain. The biological evaluation of one of these analogues, the 4-deoxy-4,4-difluoro-KRN7000, confirmed that 4-OH is not required for activity since the replacement by a gem-difluoro group at that position does not suppose any decrease in the activity. On the other hand, 3-aminoderivative showed a very small cytokine response, while the opposite trend was observed for the related 4-amino derivative.[147]

Taking into account these precedents, we considered that it would be interesting the preparation of analogues with different H-bond properties at position 4 like a 4-mercapto derivative, which permits and H-bond, or a 4-azide analogue which devoids of a hydrogen bonding. On the other hand, these groups can also modify the hydrogen bond capacity of the crucial 3-OH group.

Herein, we propose to study the mentioned synthetic sequence in order to obtain the target compounds. From the common presented intermediate a procedure based on the activation of the hydroxyl at position C-4 to allow elimination or inversion of the configuration will be studied (Scheme 36). Interesting modifications in the structure of phytosphingosine **8** have attracted attention because some of its analogues introduce morphological changes in neuronal cells and behave as enzyme inhibitors.

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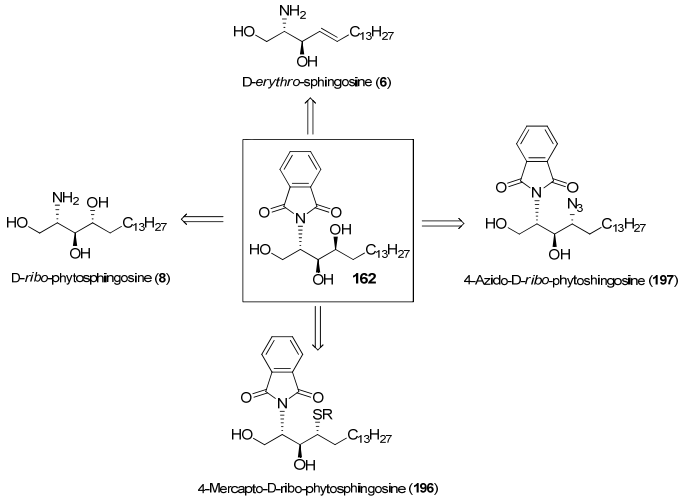

Scheme 36. Synthesis of D-*erythro*-sphingosine, D-*ribo*-phytosphingosine and 4-substituted derivatives

With this idea in mind, the next step involved the selective protection of the hydroxyl groups at positions 1 and 3 and the activation of the 4-OH as a leaving group. We initially explored the simultaneous protection of 1- and 3-OH, which was carried out by reaction of **162** with anisaldehyde dimethyl acetal (**198**) to afford compound **199** in an 87% yield (Scheme 37). The hydroxyl group at position C4 was selectively activated with triflic anhydride to afford compound **200**. Then, the reaction crude was treated with $NaNO_2$ in DMF to afford the desired compound **201** in a modest 27% yield. Besides, when triflate **200** was treated with different bases such as pyridine, triethylamine or DBU, a complex mixture was obtained, from which it was not possible to isolate the desired elimination product **202** (Scheme 37).

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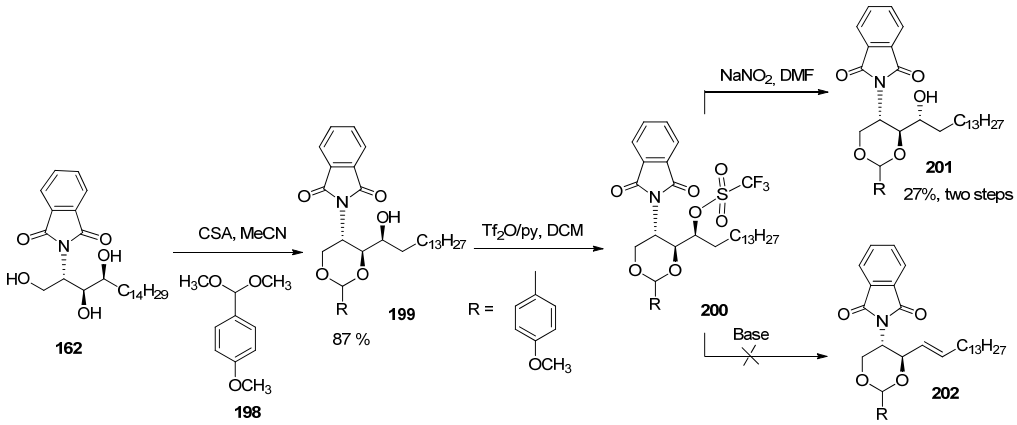
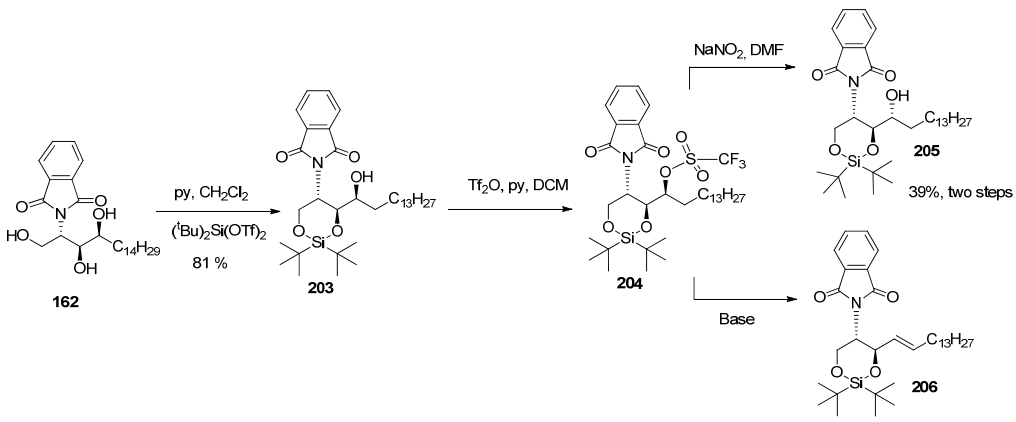


Scheme 37. Synthesis for D-*erythro*-sphingosine and D-*ribo*-phytosphingosine from **162**

As no successful result was obtained, the protection of hydroxyl groups at position 1 and 3 was performed with tBu$_2$Si(OTf)$_2$ and pyridine in acetonitrile to afford compound **203** in a 81% yield. Subsequent activation with Tf_2O rendered triflate **204** (Scheme 38). Treatment with $NaNO_2$ in DMF afforded the desired compound **205** in an 39% yield. However, attempts to invert the configuration at C-4 by a Mitsunobu reaction using *p*-nitrobenzoic or benzoic acid, PPh_3 and DIAD or DEAD did not give the expected product and the starting material was exclusively recovered. As far compound **200**, treatment of compound **204** with different bases provided a very complex mixture.



Scheme 38. Synthesis of protected-D-*erythro*-sphingosine and D-*ribo*-phytosphingosine

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Alternatively, we directed our strategy towards the use of a cyclic sulphate as a key intermediate, for the regio- and stereoselective transformation of the C-4 hydroxyl group of the compound **162**. One of the advantages of cyclic sulphates is that obviated sequential protection-activation processes as both hydroxyl groups react to give a cyclic sulphate, which subsequently selectively opened under SN_2 conditions.[148] In this sense, the base-mediated direct transformation of cyclic sulphate into an allylic alcohol of *E* configuration by regioselective abstraction of a β-hydrogen has been studied, and a limited number of applications of this transformation have been made to install a *cis* double bond in a carbocyclic ring system.[149]

Thus, compound **162** was reacted with TBDPSCl and triethyl amine, DMAP in DCM/DMF (Scheme 39) to protect selectively the primary hydroxyl group, affording compound **207** in an 89% yield. Silyl ether **207** was then treated with thionyl chloride and triethylamine in dichloromethane and after with $RuO_4/NaIO_4$ in a mixture of solvents (CCl_4, CH_3CN and H_2O), to afford sulphate **208** in a quantitative yield (Scheme 39).

Kim and co-workers have demonstrated that nucleophilic substitution of cyclic sulphates by a iodide and subsequent dehydrohalogenation in *one pot* with DBU provided the allylic alcohol in higher yield than performing the direct elimination of the cyclic sulphate with DBU.[150] For this reason, compound **208** was reacted with DBU in the presence of tetrabutylammonium iodide to obtain the desired allylic alcohol **209** in an 82% yield. Further deprotection of compound **209** by reaction with TBAF in THF at room temperature and subsequent

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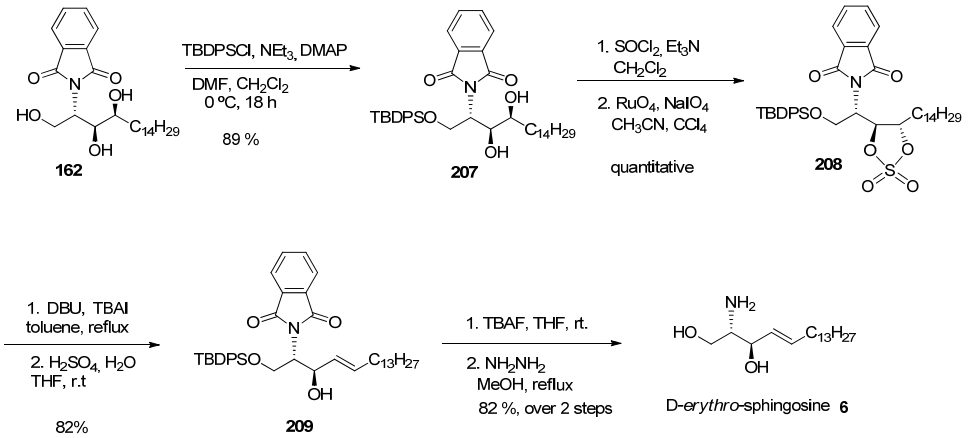
treatment with hydrazine for removing the phthalimido group afforded D-*erythro*-sphingosine **(6**) in an 82% yield.



Scheme 39. Synthesis of D-*erythro*-sphingosine (**6**)

Inversion of configuration at C-4 was also achieved by treating compound **208** with benzoic acid and Cs_2CO_3 in DMF, to produce compound **210**. The acidic hydrolysis of the intermediate *O*-sulphate provided the 4-*O*-benzoate derivative in a 91% yield (Scheme 40). The reaction took place exclusively at C-4, and this excellent regioselectivity was also observed for other nucleophiles. This fact was attributed to steric and electronic interactions between neighbouring sustituents and the incoming nucleophile that precludes the attack at C-3. Compound **210** was also deprotected by reacting it with TBAF and hydrazine to furnish phytosphingosine (**8**) in an 89% yield. NMR spectra and optical rotation of compounds **6**[151] and **8**[152] match the reported values for the natural products.

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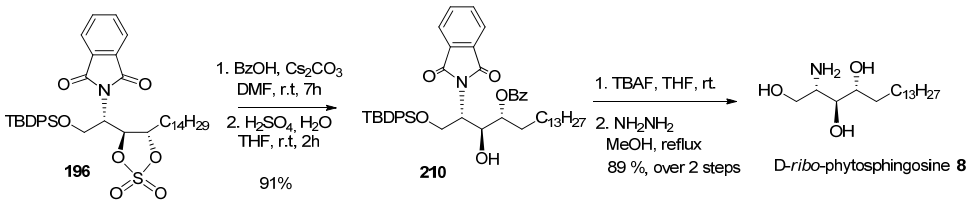
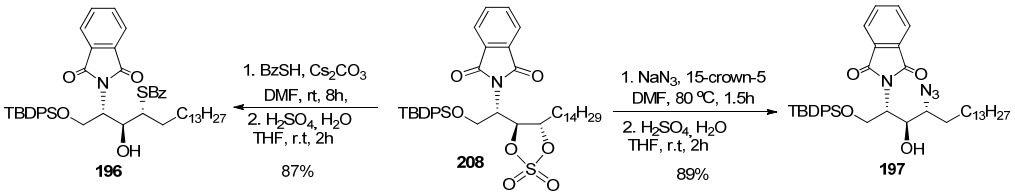


Scheme 40. Synthesis of D-*ribo*-phytosphingosine (**8**)

The possibility to obtain analogues of phytosphingosine modified at position 4 was illustrated by synthesizing new 4-mercapto and 4-azido derivatives (Scheme 41). Thus, compound **208** was reacted with BzSH and Cs_2CO_3 to render compound **196** in an 87% yield. In a parallel experiment, compound **208** was reacted with sodium azide in the presence of 15-crown-5 to afford compound **197** in a 89% yield.



Scheme 41. Synthesis of analogues D-*ribo*-phytosphingosine

In conclusion, D-*erythro*-sphingosine (**6**), *N*-phtalimido-D-*lyxo*- (**162**), D-*ribo*-phytosphingosine (**8**), and 4-mercapto (**196**) and 4-azido (**197**) analogs were prepared by a highly efficient and enantioselective procedure (Scheme 42).

This procedure starts from butadiene monoepoxide and uses a Pd-catalyzed DYKAT process, a cross-metathesis using second generation Grubbs catalysis and a dihydroxylation reaction to produce the key intermediate **162**. From this intermediate **162**, the target compounds were obtained by protection, substitution, or elimination of 4-OH and deprotection. This procedure is the most efficient for preparing **6** and **8** using asymmetric synthesis procedures and opens the way for preparing a large variety of 4-phytosphingosine derivatives.

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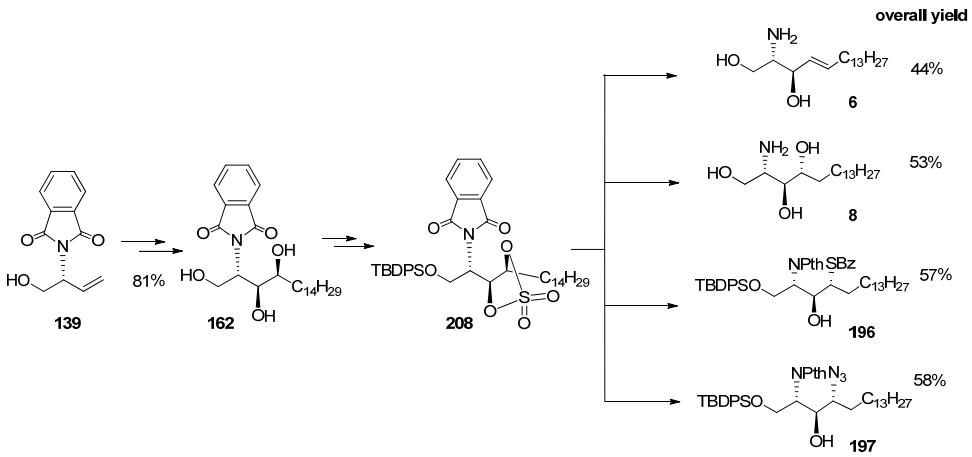

Scheme 42. Synthesis of D-*erythro*-sphingosine (**6**), D-*ribo*-phytosphingosine (**8**) and analogues (**196** and **197**)

3.5. Synthesis of Jaspine B (Pachastrissamine) and its stereoisomers

Jaspine B, also known as Pachastrissamine (**106**) (Figure 9), is a cyclic anhydrosphingosine isolated by Higa and coworkers in 2002 from the marine sponge, *Pachastrissa sp.* (family *Calthropellidae*), which is found in the Okinawan islands.[153] Simultaneously, Debitus and co-workers[154] reported the isolation of Jaspine B from the marine sponge, *Jaspis sp*, which is a main source of many cytotoxic compounds such as jaspamides,[155] jaspisamides,[156] isomalabaricane,[157] toyocamycin and 5-methoxy cabonyltubercidine.[158]

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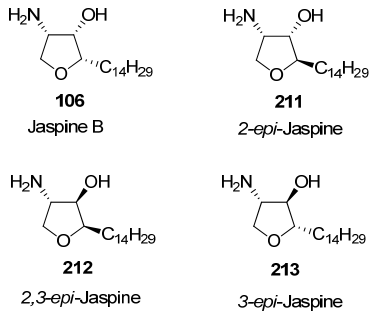

Figure 9. Jaspine B (**106)** and its isomers **211-213**

The all-*syn* trisubstituted tetrahyrofuran structural framework and the (*2S,3S,4S*) absolute configuration of pachastrissamine was assigned on the basis of high-resolution NMR, mass spectral analysis, and chemical derivatization studies. This compound, the most potent compound yet isolated from *jaspis* genus on this cell line, has shown submicromolar cytotoxic activity against P388, HT29, MEL28, A549, B16, HT29 HeLa and CNE tumoral cell lines, indicating potential usage in various cancer treatments.[159,160] This biological activity could act in synergy with classical antitumor molecules, as has been shown for phytosphingosine.[161]

Since its isolation in 2002, and in view of its interesting biological activity, different synthetic methods have been reported for the total synthesis of Jaspine B (**106**),[162] its isomers **211-213** (Scheme 43). Thus, Jaspine B and its derivatives have been prepared using starting materials from the chiral pool, such as L-serine,[163] D-xylose,[159,164,165] D-glucose,[165,166] tri-*O*-benzyl-D-galactal,[167] D-

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ribo-phytosphingosine,[160,168] *R*-glycidol,[169] L-tartaric acid[170] and D-mannitol[171] (Scheme 43).

A few enantioselective catalytic procedures have been reported that are based on: i) Sharpless asymmetric epoxidation of 4-benzyloxy-2*E*-butene-1-ol (Scheme 43 a),[172] ii) Sharpless asymmetric dihydroxylation of ethyl (*E*)-2-heptadecenoate (Scheme 43 b),[173] and iii) methyl (*E*)-5-*p*-methoxybenzyloxy-2-pentenoate (Scheme 43 c).[174] Recently, an asymmetric organocatalytic method that uses aldol[175] or oxidation[176] reaction as a key step, and a diastereoselective synthesis based on the tandem conjugate addition of a chiral lithium amide to a tri-*iso*-propylsilyloxy-α,β-unsaturated methyl ester followed by enolate oxidation, have also been described (Scheme 43 d).[177] The fact that the functionalization of

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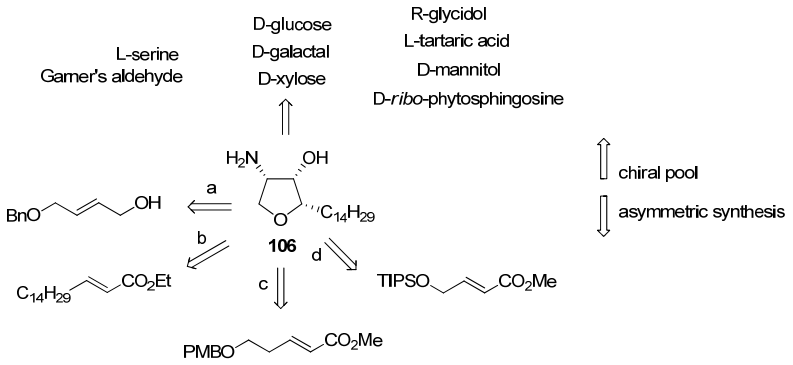
Jaspines is similar to phytosphingosine, including the size of the alkylic chain, has attracted the interest of researchers developing synthetic methods for synthesising jaspine. We thought that our procedure of synthesis of phytosphingosine was particularly suitable for the synthesis of Jaspines.



Scheme 43. Reported approaches to Jaspine B

Herein we report a catalytic enantioselective route to the synthesis of Jaspine B (**106**) and its isomers **211-213** (Scheme 44), starting from racemic butadiene monoepoxide (**105**). In the proposed retrosynthesis, compounds **106** and **211-213** can be obtained from a common intermediate **214** (Scheme 44) previously synthesized. It was key intermediate in the synthesis of phytosphingosine, and was obtained from butadiene monoepoxide (**105**) by an enantioselective palladium-catalyzed allylic amination, followed by a cross metathesis reaction with a ruthenium catalyst (see section 3.2).

I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665-1673.

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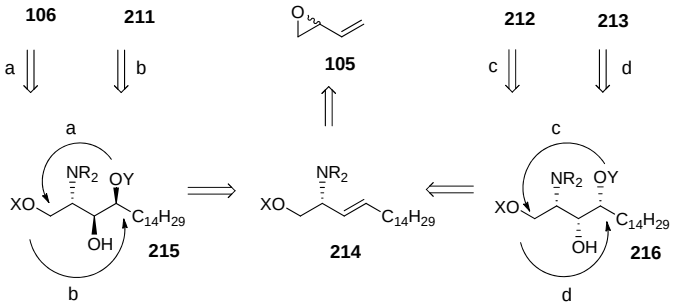
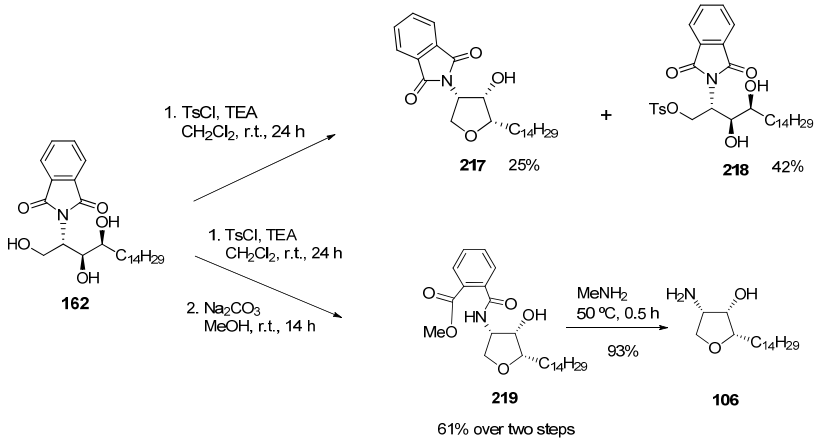


Scheme 44. Retrosynthetic route to Jaspine B (**106**) and its isomers **211-213**

The strategy to synthesize **106** and **211-213** consists on performing the diastereoselective dihydroxylation of **214** to afford intermediates **215** and **216**, from which the target compounds can be obtained by cyclization involving routes a-d.

With **162** in hand, two strategies were studied to obtain Jaspine B and its C-2 epimer (*epi*-Jaspine). One pathway was based on a cyclization involving a leaving group at the primary hydroxyl group (OX, Scheme 44 a). Thus, when compound **162** was treated with TsCl in TEA/DMAP, the isolated tosyl derivative **218** was obtained in a 42% yield, together with the cyclization product **217** in 25% yield (Scheme 45).



Scheme 45. Synthesis of Jaspine B **106** from triol **162**

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However, when the reaction crude was treated with Na_2CO_3 in methanol, the tetrahydrofuran derivative **219** was obtained in a 61% yield over two steps as a consequence of intramolecular tosylate displacement[160,168a,169a] and partial methanolysis of the phthalimido group (Scheme 45). ^{1}H NMR in aromatic zone of product **219** shows that the four aromatic protons are differents. Besides, the methoxy group shows a characteristic displacement (3.8 ppm) as a singlet and also the NH as a doublet signal at 6.2 ppm demonstrated the partial methanolysis of the phthalimido group. The phthalimido group was then fully removed by treatment with $MeNH_2$ to afford Jaspine B (**106**)[160,169a,175] in a 93% yield.

The second strategy involved a reverse cyclization reaction, where the leaving group is now present at the C-4 position (OY, Scheme 44 b) and the 1-OH is the nucleophile (X = H, Scheme 44 b). Given the previous successful application, the 3,4-cyclic sulfate was selected as the leaving group, and taking into account that this group behaves as an epoxide, being however more reactive.[178] The ring opening of cyclic sulphate **208** may occur in either a 4-*exo*-*tet* or 5-*endo*-*tet* fashion as shown in Scheme 46. The 5-*endo* cyclization would result in the formation of the desired 2,3,4-trisubstituted tetrahydrofuran ring system of pachastrissamine epimer (**220**). Although the intramolecular cyclization of tetrahedral systems generally proceeds via an *exo*-cyclization pathway,[179] Sharpless has demonstrated that the relatively unstrained cyclic sulphates could permit 5-*endo* cyclization in preference to 4-*exo*-cyclization[180] (Scheme 46).

---

178 a) Bonini, C.; Righi, G. *Tetrahedron* **2002**, *58*, 4981-5021. b) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051-7091.

179 Baldwin, J. E. *J. Chem. Soc., Chem. Comm.* **1976**, 734-736.

180 Kalantar, T. H.; Sharpless, K. B. *Acta Chem. Scand.* **1993**, *47*, 307-313.

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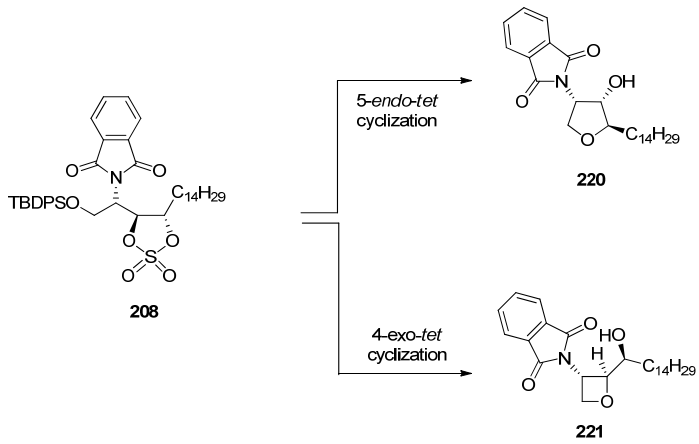
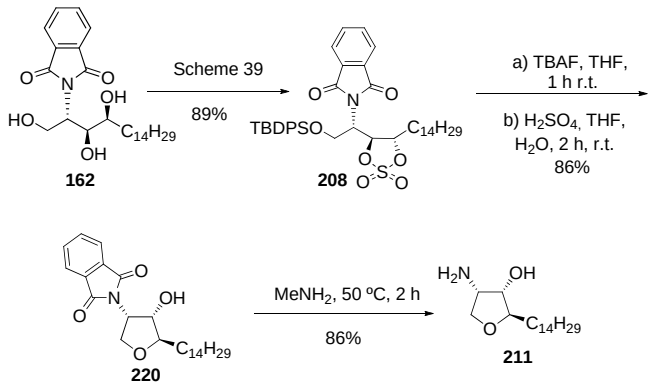


Scheme 46. Intramolecular opening pathways of cyclic sulphate **208**

Thus, treatment sulphate **208** (see section 3.2) with TBAF in THF at room temperature afforded the protected tetrahydrofuran **220** in 86% yield over two steps, via desilylative cyclization and hydrolysis of the sulfate group. The 4-*exo*-cyclization product was not detected in the reaction mixture by ^{1}H NMR, as described by Kim *et al.*[168b] After deprotection of the phthalimido group, 2-*epi*-jaspine B (**211**)[160,163a,177] was obtained in 86% yield (Scheme 47).



Scheme 47. Synthesis of *2-epi*-Jaspine B (**211**) from triol **162**

A similar strategy was followed to obtain the C-2, C-3 epimers **212** and **213** from the corresponding diastereoisomer **180** (routes c and d, Scheme 44). Thus, compound **180** was treated with TsCl in CH_2Cl_2/pyridine to directly afford the cyclization product **222** in a 60% yield. Then, the phthalimido protecting

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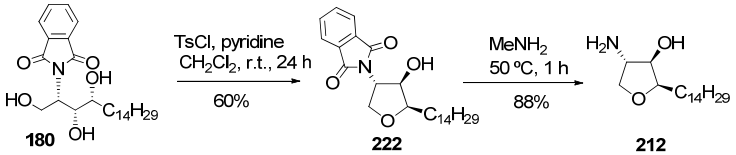
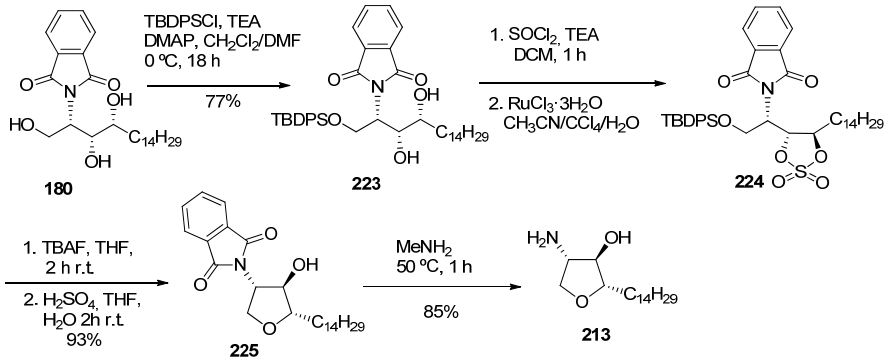
group was removed by reaction with methylamine to provide isomer **212**[160,3160,163f] in an 88% yield (Scheme 48).

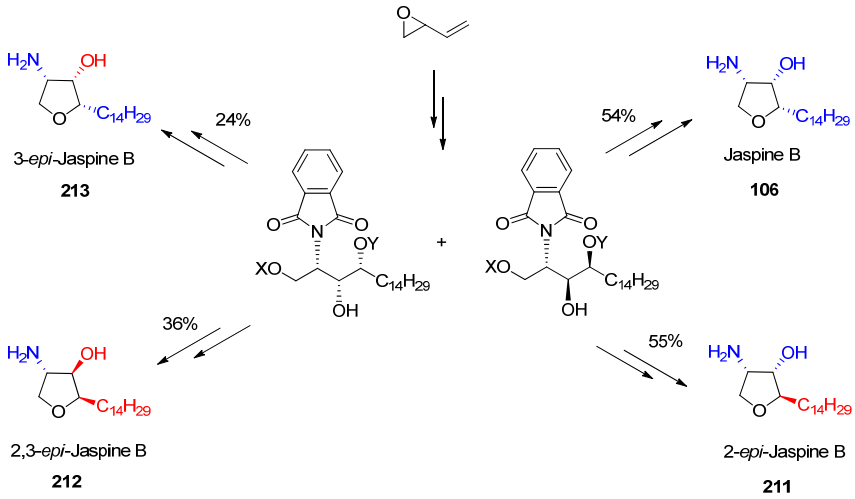


Scheme 48. Synthesis of 2,3-*epi*-Jaspine (**212**) from **180**

The synthesis of 3-*epi*-Jaspine B (**213**)[160,163f] was carried out by initial silylation of **180** to give **223**, which was then treated with $SOCl_2$ and RuO_4 to afford the cyclic sulfate **224**. Compound **224** was treated with TBAF in THF at room temperature to afford the protected tetrahydrofuran **225**, via desilylative cyclization and sulfate hydrolysis, in 93% yield over two steps. Cyclization to give the oxetane was not detected by ^{1}H NMR. Finally, the removal of the phthalimido group with methylamine afforded compound **213** in 85% yield (Scheme 49).



Scheme 49. Synthesis of 3-*epi*-Jaspine B (**213**) from **180**



Scheme 50. Summarized results in the synthesis of Jaspine B and its stereosisomers

In conclusion, we have developed a short and efficient divergent enantioselective catalytic method to synthesize the natural anhydrosphingosine, Jaspine B (Pachastrissamine) (**106**) and three of its 2-, 3-, and 2,3-isomers (**211-213**) from racemic butadiene monoepoxide. Jaspine B was synthesized in a 54% overall yield, and compounds **211**, **212** and **213**, were obtained in 55%, 36% and 24%, respectively (Scheme 50).

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Synthesis of Z-alkenes by Cross-Metathesis

CHAPTER 4

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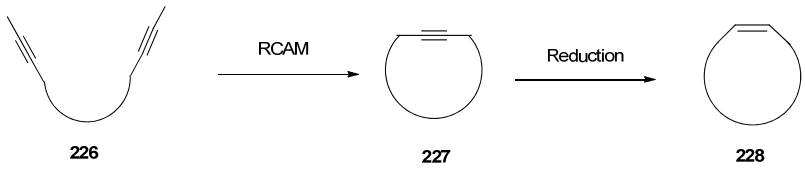
1. Background

As stated in the previous chapter developing new catalysts that could mediate highly *Z*-selective olefin cross-metathesis is a challenge in synthetic organic chemistry. In the case of ring-closing metathesis (RCM) for small or medium-sized rings, the *Z* isomer is generally formed as a consequence of minimizing ring strain. However, RCM for the formation of macrocycles and the cross-metathesis reaction do not display this high degree of selectivity. As previously mentioned, only in rare cases when one of the olefinic substrates bears an sp-hybridized substituent, such as enyne or acrylonitrile, may the *Z*-product be obtained together with the *E* isomer.[181] Fürstner and co-workers developed an efficient alkyne ring-closing metathesis (RCAM) reaction catalyzed by molybdenum. The cyclic alkyne could be reduced under H_2 or by a hydrosilylation/*proto*-desilylation sequence to obtain exclusively the *Z*-macrocycle (Scheme 51).[182] Although this route has been applied in the synthesis of several natural products, the developed Mo-catalysts have some restrictions in the cross-metathesis reaction between alkynes.[183]



Scheme 51. RCAM strategy to obtain Z-macrocycles

Hoveyda and Schrock designed, synthesized and developed an impressive new class of sterogenic-at-Mo catalyst to promote an enantioselective RCM as a key step for the synthesis of (+)-quebrachamine (Scheme 52). Chiral ruthenium-

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181 a) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162-5163. b) Randl, S.; Gesser, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430-432. c) Hansen, E. C.; Lee, D. *Org. Lett.* **2004**, *6*, 2035-2038. d) Sashuk, V.; Samojlowicz, C.; Szadkowska, A.; Grela, K. *Chem. Commun.* **2008**, 2468-2470.

182 See for example: a) Micoine, K.; Fürstner, A. *J. Am. Chem. Soc.* **2010**, *132*, 14064–14066. b) Hickmann, V.; Alcarazo, M.; Fürstner, A. *J. Am. Chem. Soc.* **2010**, *132*, 11042-11044 and references cited therein.

183 Heppekausen, J.; Stade, R.; Goddard, R.; Fürstner, A. *J. Am. Chem. Soc.* **2010**, *132*, 11045-11057.

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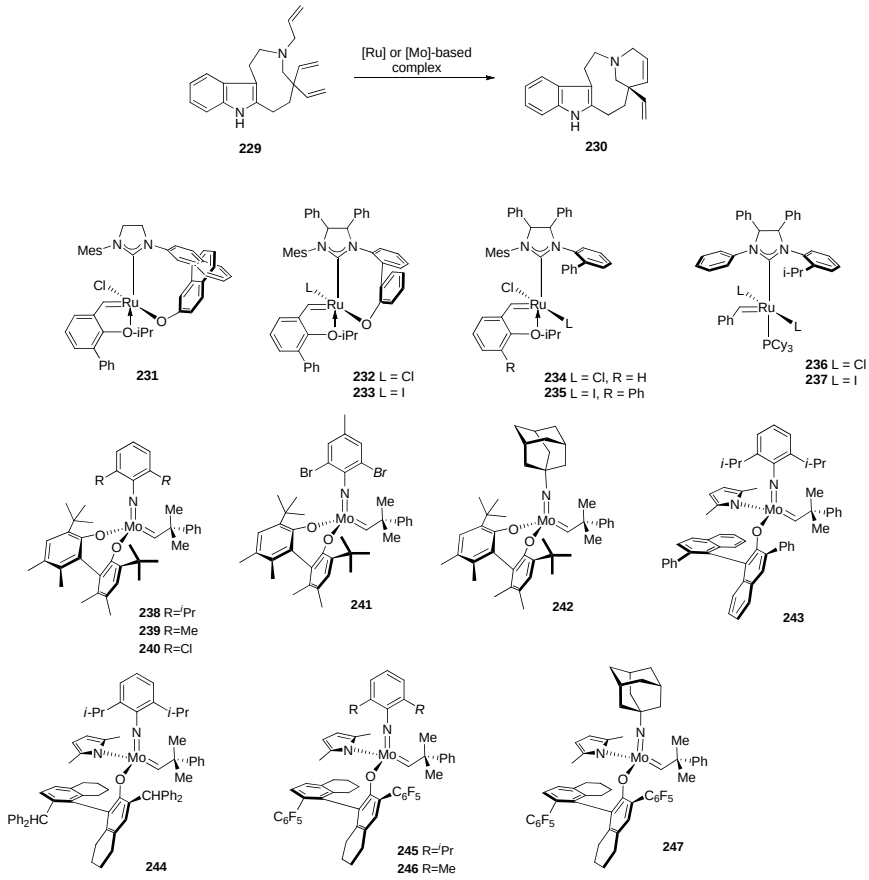
and molybdenium containing catalyst **231-237**, were tested in the study; unfortunately, the enantioselectivity obtained was very low (<10 ee). Ru catalysts were active but bidentat diolate-based Mo species were entirely ineffective in promoting the desired transformation.[184]



Scheme 52. Ru- and Mo-based chiral catalyst examined in the synthesis of compound **230** by ring-closed metathesis (RCM) of triene **229**

The achiral catalyst **248** (Scheme 53) afforded the desired product in high yield. The authors proposed that the reason for the higher activity of achiral Mo **248** (>98% of conversion), was that it bears two monodentate hexafluoro-*t*-butoxide ligands. The structural rigidity of the bidentate diolates catalysts, which

184 Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943-953.

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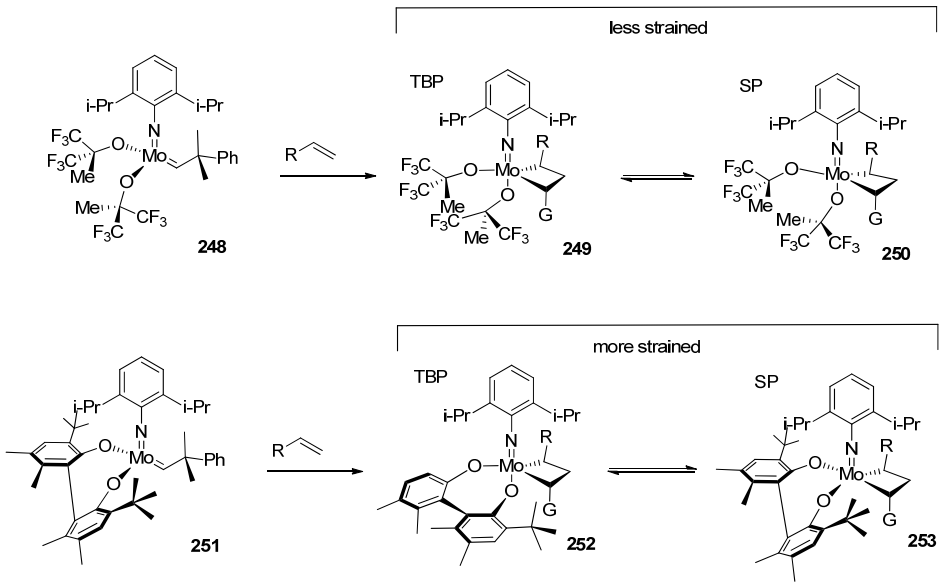
are square pyramidal (**251**) (O-Mo-O=98°)[185] and not tetrahedral as is catalyst **248** (O-Mo-O=127°),[186] increases the activation barrier for a key step of the catalytic cycle. This suggests that molybdenum catalysts bearing monodentate ligands may be more active in general (Scheme 53).[187]



Scheme 53. The relatively rigid diolate ligands in Mo-based complexes translate to high-energy metallacyclobutane intermediates

Additionally, theoretical studies by Einenstein and co-workers[188] suggested that the presence of a π-acceptor ligand (**A** in **254**, Scheme 54) is required in order to ensure that the metal centre possesses sufficient Lewis acidity to allow effective binding of an olefins substrate. Moreover, the presence of a donor ligand (**D** in **254**, Scheme 54) is favourable because it trenders the

185 Tsang, W. C. P.; Hultzsch, K. C.; Alexander, J. B.; Bonitatebus, P. J. Jr.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2003**, *125*, 2652-2666.

186 Alexander, J. B.; Schrock, R. R.; Davis, W. M.; Hultzsch, K. C.; Hoveyda, A. H.; Houser, J. H. *Organometallics* **2000**, *19*, 3700-3715.

187 Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933-937.

188 a) Poater, A.; Solans-Monfort, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2007**, *129*, 8207-8216. b) Solans-Monfort, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc*. **2005**, *127*, 14015-14025

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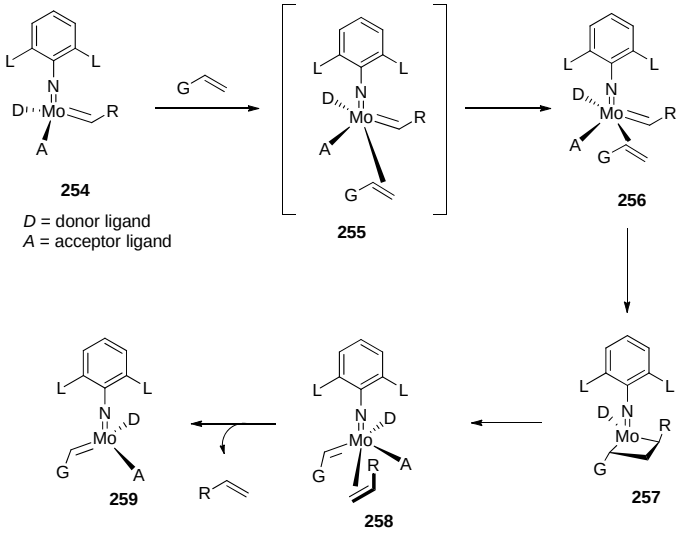
geometrically distorted intermediate **255** energetically more accessible, thus facilitating coordination of an alkene substrate. For this reason, taking into account that the substrate approaches to the catalyst in a *syn* position to the acceptor ligand, the design of an enantiomerically enriched sterogenic-Mo complex should feature acceptor ligand **A** as the source of chirality rather than the donor ligand **D**.



Scheme 54. Electronic dissymmetry at the metal facilitates olefin coordination and metallacyclobutane collapse

To summarize, high-oxidation-state complexes containing two electronically distinct ligands should be particularly effective promoters of alkene metathesis, facilitating most critical reaction steps (substrate-catalyst association and metallacyclobutane decomposition). In addition, preliminary studies have demonstrated that Mo(NR)(CHR)(pyrrolyl)(O-Rf) catalysts,[189,190] having two different acceptor and donor ligands are active metathesis catalysts.

In this context Hoveyda and co-workers prepared the aryloxy pyrrolidine complex **260** (Figure 10) that proved to be an excellent catalyst for ring-closing

[189] Blanc, F.; Berthoud, R.; Salameh, A.; Basset, J. M.; Copéret, C.; Singh, R.; Schrock, R. R. *J. Am. Chem. Soc.* **2007**, *129*, 8434-8435.

[190] Singh, R.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2007**, *129*, 12654-12655.

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metathesis transformations, and allowed the synthesis of compound **230** in high yield (>98%) and enantioselectivity (95% ee).

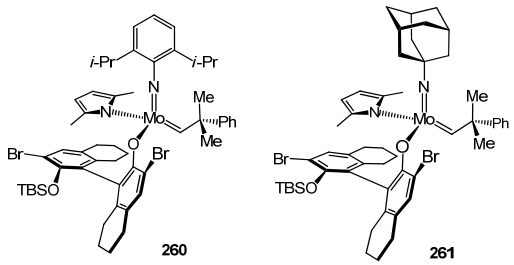
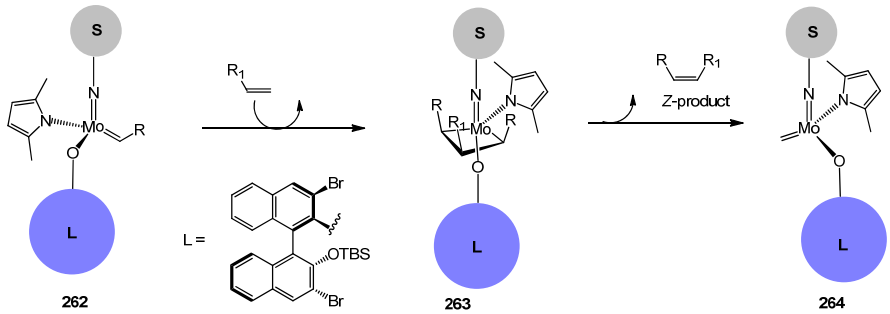


Figure 10. Stereogenic-at-Mo complexes

With this result in hand, Hoveyda, Schrock and co-workers embarked on the challenging project of developing a *Z*-selective enantioselective ROCM (ring opening cross metathesis) reaction.[191] Analogues of catalysts **260**-**261** were proposed for this purpose, in which a bulky aryloxy ligand can freely rotate around the Mo-O bond, because the substituent on the imide ligand (**S** in Scheme 55) less stericaly demanding than the aryloxy ligand. It was thought that the reaction starts with the alkylidene isomer **262** and proceeds via the all-*cis* metallacyclobutane **263** to give the *cis* olefin product.



Scheme 55. The proposed model catalyst for obtaining *Z*-selectivity

[191] Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844-3845.

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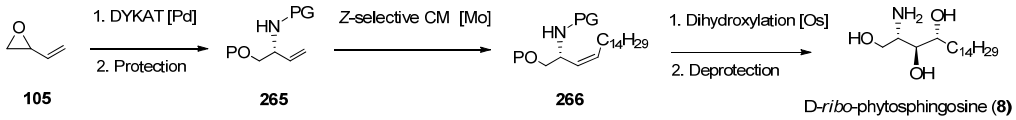
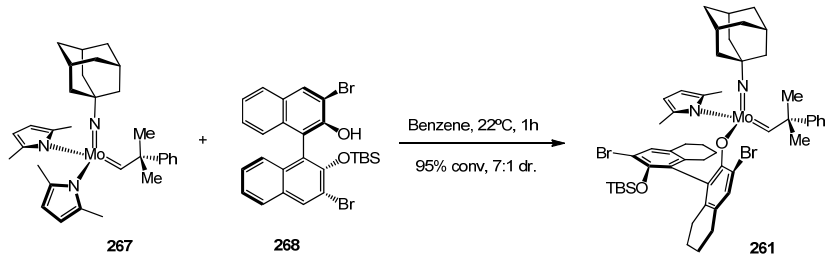
2. Results and discussion

In this context, the work was developed in the laboratory of professor Hoveyda, the excellent background for the synthesis of sphingosines by carrying out a *Z*-selective cross-metathesis. Therefore, the objective of our studies during the stage in the Hoveyda laboratory was to investigate the cross-metathesis of the allyl amine **265** and 1-hexadecene to form the *Z*-alkene product **266**. Subsequent dihydroxylation of compound **266** would afford the protected precursor of the natural product D-*ribo*-phytosphingosine (**8**). The proposed synthesis (Scheme 56) would be one the shortest and most efficient syntheses described to date.



Scheme 56. Proposed synthesis of D-*ribo*-phytosphingosine (**8**)

The catalyst **261** was synthesized by treatment of the Mo complex **267** with mono-TBS-protected diol **268** (Scheme 57). The catalyst was not isolated but used *in situ* in each catalytic test.



Scheme 57. Synthesis of mono-aryloxide pirrolidine molybdenum complex **261**

For the preliminary catalytic tests, we decided to work with the racemic substrate, which was prepared by allylic amination of vinylepoxide using a *rac*-BINAP-Pd catalyst. Further reaction with TBSCl, in dichloromethane afforded *rac*-compound **270** in 90% yield (Scheme 58).

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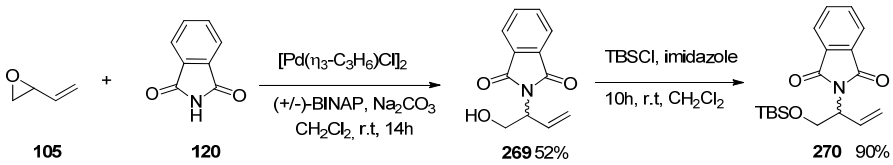

105 **120** **269** 52% **270** 90%

Scheme 58. Synthesis of compound **270**

2.1. Screening of reaction conditions

Study of the cross-metathesis began with the reaction between **270** and hexadecane in the presence of catalyst **261**. The reaction was run at 22°C for 1.5 h, 3.5 h and 12 h using 10 equivalents of 1-hexadecene and 5% catalyst loading. After 1.5 h, the conversion was 39% but, interestingly, complete stereoselectivity for the *Z* alkene was obtained (Table 8, Entry 1). When the reaction time was increased to 3.5h, the conversion also increased to 48% (Table 8, Entry 2), but the conversion did not improve when the reaction was run over 12h (Table 8, Entry 3). One reason for these moderate conversions could be the deactivation of the catalyst; for that reason, 10% catalyst loading was used, but after 3.5 h the conversion did not improve (Table 8, Entry 4). In a separate experiment, the catalyst was added in two portions over 3 h during a reaction time of 6 h, but surprisingly the conversion still did not improve (Table 8, Entry 5), suggesting that catalyst death was in fact not the reason why conversion ceased after a limited time. However, in all cases an excellent diastereoselectivity (*Z*:*E* = >98:<2) was obtained: the *E*-isomer was not detected by ^{1}H NMR spectroscopy.

At higher temperature (60°C) the conversion increased to 70% after 3.5 h, but unfortunately a low *Z*:*E* selectivity was obtained (Table 8, Entry 6). At lower temperature (40ºC) we achieved 51% conversion but the *Z*:*E* ratio obtained was 75:25 (Table 8, Entry 7). Thus, in all tested conditions, moderate conversions (c.a 50%) were obtained. An excess of one of the cross-coupling partners (20 equivalents) could displace the possible equilibrium towards product, but under these conditions the conversion was only 39% (Table 8, Entry 8).

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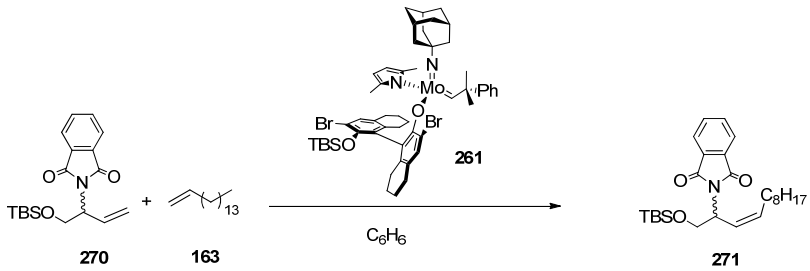
Table 8. Optimization of reaction conditions for *Z*-selective cross-metathesis[a]



Entry	Equiv of 1-hexadecene	Time (h)	Temp (ºC)	Catalyst loading (%)	Conversion(%)[b] (Yield)[c](%)	*Z:E* ratio[b]
1	10	1.5	22	5	39 (36)	>98:<2
2	10	3.5	22	5	48 (41)	>98:<2
3	10	12	22	5	47	>98:<2
4	10	3.5	22	10	38	>98:<2
5[d]	10	6	22	10	46	>98:<2
6	10	3.5	60	5	70	1.2:1
7	10	3.5	40	5	51	3:1
8	20	3.5	22	5	39	>98:<2

[a] Catalyst was prepared in situ: Mo-complex **267** and alkoxy ligand **268** were dissolved in C_6H_6 (0.1M), the mixture was stirred at 22°C for 1h. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] The catalyst was added in two portions over 3h.

Upon observing that increased catalyst loading did not improve the conversion and, although an excess of one of the cross-coupling partner made no improvement, we considered the hypothesis that an equilibrium be could controlling the product yield. Taking into account this hypothesis, the reaction was performed under vacuum to remove ethylene, which is a by-product. The reaction was run at room temperature for 3.5 hours under vacuum affording the desired compound **271** with 53% conversion (Table 9, Entry 1) and so the obtained conversion was not a significant improvement relative to the results without vacuum (48% under the same conditions, Table 8, Entry 2). However,

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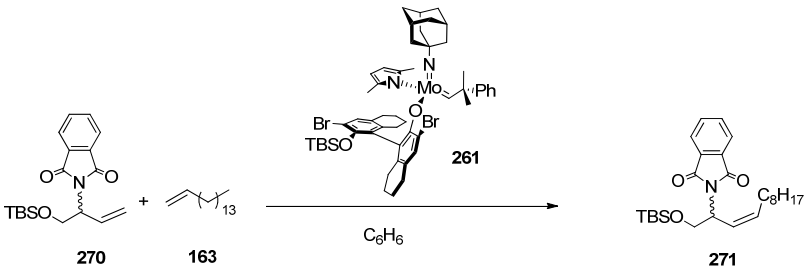
hexadecene was completely consumed in a homodimerization process, in contrast to the reaction without vacuum. This fact demonstrated that the system is more active when the reaction is run under vacuum.

Adding the catalyst in two portions over 6 h, and working under vacuum the first 3 h (Table 9, Entry 2) resulted in a conversion of 65%, with exclusively the *Z*-isomer product being isolated in 59% yield. However, adding the catalyst in 3 portions over 8h, and performing the reaction under vacuum for the first 3h did not further improve the conversion (Table 9, Entry 3). The reaction was also run using 20 equivalents of 1-hexadecene under vacuum for 3.5h to afford 39% conversion (Table 9, Entry 4) with exclusive *Z*-selectivity.

Table 9. Optimization of reaction conditions for *Z*-selective cross-metathesis under vacuum[a]



Entry	Equiv of 1-hexadecene	Time (h)	Temp (ºC)	Catalyst loading (%)	Conversion (%)[b] (Yield) (%)[c]	*Z:E*[b] ratio
1[d]	10	3.5	22	5	53	>98:<2
2[d,e]	10	6	22	10	65 (59)	>98:<2
3 [d,f]	10	8	22	10	59(51)	>98:<2
4[d]	20	3.5	22	5	39	>98:<2
5[f]	10	3.5	22	5	48	>98:<2

[a] Catalyst was prepared *in situ*: Mo-complex **267** and alkoxy ligand **268** were dissolved in C_6H_6 (0.1M), the mixture was stirred at 22°C for 1h. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] The reaction was run under vacuum. [e] The catalyst was added in two portions over 3h (5%+5%). [f] The catalyst was added in three portions over 5h (3.5%+3.5%+3%). [f] 0.4M.

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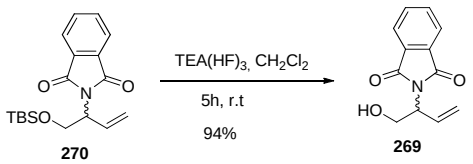
An alternative to the use of vacuum could be working at higher concentration. To test this hypothesis, the reaction was performed at 0.4 M instead 0.1 M but the results were comparable with regard to conversion and selectivity (Table 9, Entry 5 vs Entry 1).

Since the catalyst used was chiral and to be sure that a dynamic resolution was not occurring, the enantioselective ratio of starting material was systematically checked. After the cross-metathesis reaction the recovered starting material **270** was deprotected with $TEA(HF)_3$ in dichloromethane for 5h at room temperature to afford compound **269** in high yield (Scheme 59). Afterwards, it was analyzed by chiral HPLC which confirmed that no resolution process had taken place.



Scheme 59. Deprotection of starting material **270**

An experiment using racemic catalyst was also performed in order to observe if some matched diastereomeric combination exists. Thus, when the racemic catalyst was used (Table 10, Entry 1), a conversion of 43% was obtained. A longer reaction time (12h) did not appreciably affect the reaction outcome (Table 10, Entry 2). In order to confirm if the low yield was a consequence of equilibrium effects or it it was due to catalyst decomposition, the reaction was performed under vacuum but only modest improvement was observed. However, when the catalyst loading was increased (10%), being added in two portions and the reaction ran under vacuum for the first 3h, the conversion improved to 57% with complete *Z*-selectivity (Table 10, Entry 4). An excess of 1-hexadecene was added but in this case the conversion was maintained (Table 10, Entry 5). Lower catalyst loading (Table 10, Entry 6) afforded the *Z*-cross-product with comparable conversion.

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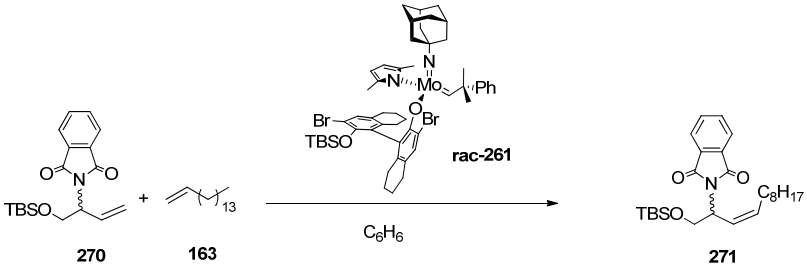
Table 10. Optimization of reaction conditions for *Z*-selective cross-metathesis using *rac* Mo-complex[a]



Entry	Equiv of 1-hexadecene	Time (h)	Temp (ºC)	Catalyst loading (%)	Conversion (%)[b] (Yield)[c] %	*Z:E*[b] ratio
1	10	4	22	5	43(38)	>98:<2
2	10	12	22	5	47 (35)	>98:<2
3[d]	10	3.5	22	5	48	>98:<2
4[d,e]	10	6	22	10	57 (50)	>98:<2
5[f]	20	3.5	22	5	50	>98:<2
6	5	3.5	22	5	48	>98:<2

[a] Catalyst was prepared in situ: Mo-complex **267** and alkoxy ligand **268** were dissolved in C_6H_6 (0.1M), the mixture was stirred at 22 °C for 1h. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] The reaction was run under vacuum. [f] Catalyst was added in 2 portions over 3h.

In conclusion, the use of racemic catalyst did not improve the conversion; however, performing the reaction under vacuum increased the conversion. Additionally, the intrinsic high activity of the process catalyst was proved by the complete homodimerization of 1-hexadecene.

2.2. Screening of catalyst

The first catalyst tested provided an excellent *Z* selectivity but the yield was moderate, and modification of the reaction conditions did not significantly improve the results. Therefore, we decided to modify the structure of the catalyst. The imido- and aryloxyde ligands bound to molybdenum metal centre can be easily tuned. It is known that replacement of the adamantylimido ligand with

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larger imido ligands (catalyst **272-275**) (Figure 11) produces a decrease in the catalyst activity as a consequence of steric hindrance, forcing the use of higher reaction temperatures. However, this modification could favour the exclusive formation of the *syn*-metallacyclobutane, and in this way avoid formation of the *trans* metallacyclobutane isomer.

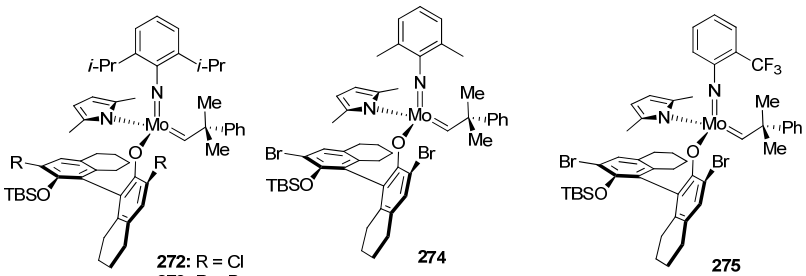

Figure 11. Aryloxide-Mo complexes (**272-275**)

Thus, the different ligands in molybdenum complexes shown in Figure 11 were studied. Complex **272** afforded the cross-coupling product with 65% conversion but, unfortunately, the stereoselectivity decreased to a ratio of 75:25 *Z*:*E* (Table 11, Entry 1). In contrast, complex **273** afforded exclusively the *Z*-product but with lower conversion (25%) (Table 11, Entry 2). When the reaction was performed at higher temperatures (60 °C) the conversion was improved to 39% (Table 11, Entry 3), and a better result was obtained with longer reaction times (15h) (47%) (Table 4, Entry 4). In both cases an excellent stereoselectivity was obtained. When the amount of 1-hexadecene was increased to 20 equivalents, using 10% catalyst loading at 60 °C for 12 h the reaction afforded exclusively the *Z*-product with comparable conversion (48%) (Table 11, Entry 5).

On the other hand, less sterically-encumbered imido complexes such as **274** afforded the *Z*-cross-product with lower conversion (Table 11, Entry 6 *versus* Entry 3). Catalyst **275** (Table 11, Entry 7) provided moderate conversion (44%) at 22 °C after 3.5 h with excellent stereoselectivity (*E*:*Z*=>98:<2); however, when the reaction time was extended to 14 h, it provided the cross-product with 69% conversion but with a ratio of *Z*:*E* 66:33 (Table 11, Entry 8). With these results in hand, we can conclude that sterically hindered complexes such as **273** afford exclusively *Z*-product even when the reaction was heated at 60ºC.

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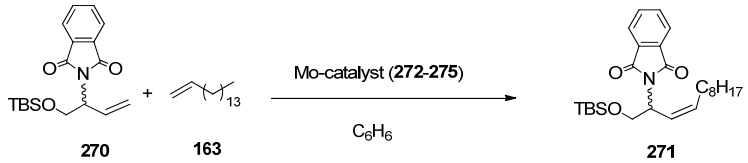
Table 11. Study of cross-metathesis reaction with catalyst **272-275**[a]



270 **163** **271**

Entry	Equiv of 1-hexadecene	Time (h)	Temp (ºC)	Catalyst	Catalyst loading	Conversion[b] (Yield)%[c]	*Z:E*[b] ratio
1	10	15	22	**272**	5	65	75:25
2	10	3.5	22	**273**	5	25	>98:<2
3	10	3.5	60	**273**	5	39	>98:<2
4	10	15	60	**273**	5	47(40)	>98:<2
5	20	12	60	**273**	10	48	>98:<2
6	10	3.5	22	**274**	5	28	>98:<2
7	10	3.5	22	**275**	5	44	>98:<2
8	10	14	22	**275**	5	69	66:33

[a] Catalyst was prepared in situ: Mo-complex **267** and alkoxy ligand were dissolved in C_6H_6, the mixture was stirred at 22 °C for 1h. (5 mol % catalyst loading) in 0.1M in benzene was used in the reaction. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield.

Next, the arylimido substituent was exchanged for another bulkier group in order to favour the *syn*-metallacyclobutane, which gives the Z-cross-product. In the proposed catalyst, the electronic and steric properties of the aryloxide ligand could be easily modulated. Thus, the effect of replacing the bromo substituent with different halogens or electron withdrawing groups (Figure 12, catalyst **276-279**) was studied.

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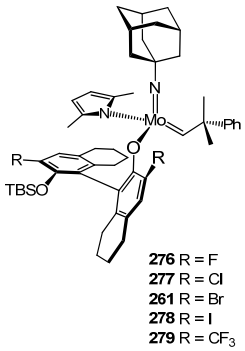

276 R = F
277 R = Cl
261 R = Br
278 R = I
279 R = CF_3

Figure 12. Mo-based catalysts with different halogens

Catalyst **276**, which incorporates a fluoride moiety in the aryloxide ligand, provides 49% conversion after 3.5h at room temperature under vacuum (Table 12, Entry 1). Chloride-containing catalyst **277** was tested under similar conditions improves the conversion to 56% (Table 12, Entry 2). When the reaction time was increased to 12 h and vacuum was applied for 3 h, the conversion was 65%, affording the product in 55% yield (Table 12, Entry 3). In all cases, at room temperature the Z-isomer was obtained exclusively. When the reaction mixture was heated at 40 °C (Table 12, Entry 4) or 60 °C (Table 12, Entry 5), conversion was 54% and 70%, respectively. In the last case the conversion was improved but in general the stereoselectivity decreased to the point where almost equimolar *E/Z* product mixtures were obtained.

Catalyst **278** bearing an iodine-substituted aryloxide ligand, gave worse conversion (29%) to Z-product (Table 12, Entry 6). When the reaction time was increased to 12 h, increased conversion was also observed (56%), maintaining the excellent diastereoselectivity obtained in the previous experiment (Table 12, Entry 7). Surprisingly, when the reaction mixture was heated at 60 °C, the mixture of both diastereomers was not observed and only the *Z*-product was obtained in 53% yield (Table 12, Entry 8). A longer reaction time (15h) at this temperature (Table 12, Entry 9), using an excess of 1-hexadecene (20 eq) and maintaining the reaction at 60 °C for 15 h resulted in a 51% yield of product. Catalyst **279**, with a trifluoromethyl group, afforded exclusively *Z*-product in comparable yield as those obtained with the brominated catalysts under the same

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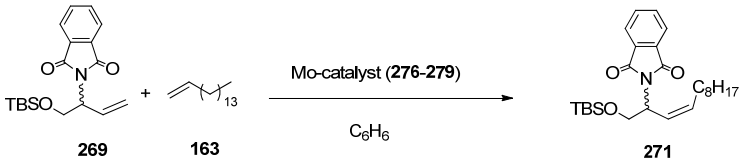
conditions (Table 12, Entry 10 *versus* 7); however, if the temperature was increased to 60ºC the diastereoselectivity dropped (Table 12, Entry 11).

Table 12. Study of cross-metathesis reaction with catalyst **276-279**[a]



269 **163** **271**

Entry	Equiv of 1-hexadecene	Time (h)	Temp (ºC)	Catalyst	Conversion[b] (Yield)[c] %	*Z:E*[b] ratio
1	10	3.5	22	**276** (F)	49	>98:<2
2	10	3.5	22	**277**(Cl)	56 (47)	>98:<2
3	10	12	22	**277** (Cl)	65(55)	>98:<2
4	10	3.5	40	**277** (Cl)	54	1.6:1
5	10	3.5	60	**277** (Cl)	70	1.2:1
6	10	3.5	22	**278** (I)	29	>98:<2
7	10	12	22	**278** (I)	56	>98:<2
8	10	3.5	60	**278** (I)	53	>98:<2
9	20	15	60	**278** (I)	52	>98:<2
10	10	15	22	**279** (CF_3)	51	>98:<2
11	10	3.5	60	**279** (CF_3)	69	2:1

[a] Catalyst was prepared in situ: Mo-comoplex **267** and alkoxy ligand were dissolved in C_6H_6, the mixture was stirred at 22ºC for 1h. 5% of catalyst prepared in situ was used, in 0.1M in benzene was used in the reaction. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield.

In the order to minimize the steric hindrance in the aryloxide ligand and provide more electron density to the Mo centre, TBSO group was replaced by MeO- in the aryloxide ligand. Catalysts **280**-**281** (Figure 13) were prepared *in situ* from the corresponding ligand and Mo-complex **267**.

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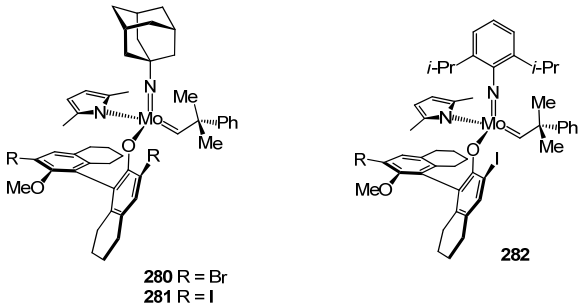

Figure 13. Mo-aryloxide ligands with OMe group (**280**-**282**)

Firstly, catalyst **280** (R=Br) was used for a reaction time of 3.5 h at 22 °C, achieving a 74% yield. However, the diastereoselectivity was very low, and in this case the *E*-isomer was the major product (Table 13, Entry 1). In order to increase steric hindrance at the metal centre, a bulkier halogen was introduced on the aryloxide ligand to favour the formation of the *syn*-metallacyclobutane Thus, iodine-substituted catalyst **281** was prepared and tested, but afforded lower conversion (48%) and also poor stereoselectivity (Table 13, Entry 2). With the same idea in mind, a more bulky imido ligand was incorporated to obtain catalyst **282**, which provided a lower conversion but a higher *Z*:*E* product ratio (Table 11, Entry 3).

The obtained results are in agreement with the proposal that sterically congested metallacyclobutane favour the formation of the *syn* intermediate. It is known that Schrock catalyst **123** provides high activity in metathesis processes,[192] in our case this catalyst afforded after 10 min the cross-product with 60% conversion as a 2:5 *Z*:*E* mixture, together with 13% of allylamine homodimer. Due to the fact that using the Schrock catalyst provided worse results than expected, we turned our attention to the modified stereogenic-at-Mo complexes **279**-**282**, where the hexafluoro-*tert*-butoxide ligand in **123** has been replaced by phenoxide.

[192] Singh, R.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2007**, *129*, 12654-12655.

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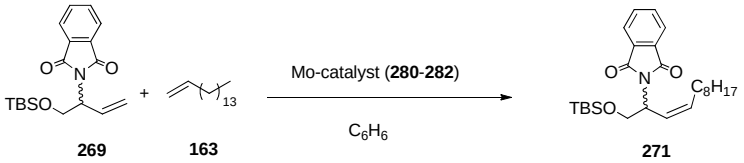
Table 13. Study of cross-metathesis reaction with catalysts **280**-**282**[a]

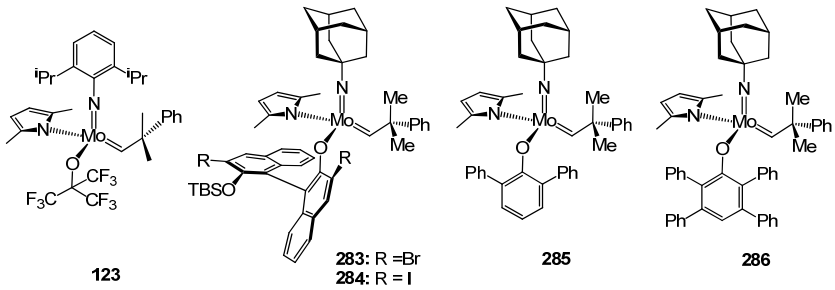


269 **163** **271**

Entry	1-hexadecene (equiv.)	Temp (ºC)	Catalyst	Catalyst loading (%)	Conversion[b] (Yield)[c] (%)	*Z*:*E*[b] ratio
1	10	22	**280**	5	80(74)	1:1.6
2	10	22	**281**	5	48	1:1
3	10	22	**282**	5	33	1.4:1

[a] Catalyst was prepared in situ: Mo-complex **267** and alkoxy ligand were dissolved in C_6H_6, the mixture was stirred at 22 °C for 1h. 5% mol *in situ* prepared catalyst, 0.1M in benzene was used in the reaction for 3.5h in all cases. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield.

The presence of a bulky aryloxide group might retard the competing intermolecular process, which leads to oligomeric products. Different bulky phenoxides (Figure 14) were studied in order to ascertain their effects in the formation of the *syn*-metallacyclobutane and thus the *Z*-cross-product.



123 **283:** R =Br **284:** R = I **285** **286**

Figure 14. Phenyloxides ligands in Mo complexes

The cross-metathesis reaction in the presence of catalyst **283** gave 33% conversion with excellent stereoselectivity (Table 14, Entry 1); similarly, catalyst **284** afforded the same conversion when the reaction time was increased to 12 h (Table 14, Entry 2). Other catalysts including 2,6-diphenylphenoxy complex **285**

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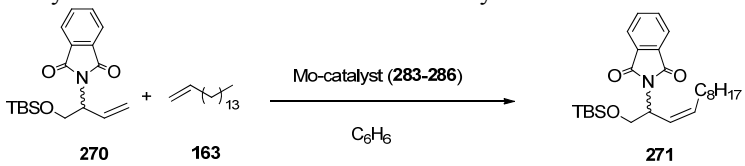
(Table 14, Entry 3), bearing a less bulky ligand, showed higher conversion (70%) but the diastereoselectivity decreased an it was even inverted (3:4 *Z*:*E* ratio). Using the 2,3,5,6-tetraphenylphenoxy complex **286** the conversion was good (60%), but a nearly 1:1 mixture of *Z* and *E* alkenes was obtained (Table 14, Entry 4).

Table 14. Study of cross-metathesis reaction with catalyst **283-286**[a]



Entry	Equiv of 1-hexadecene	Time (h)	Temp (ºC)	Catalyst	Conversion (%)[b]	*Z:E*[b]
1	10	3.5	22	**283**	33	>98:<2
2	10	12	22	**284**	35	>98:<2
3	10	12	22	**285**	70	3:4
4	10	3.5	22	**286**	60	1.1:1

[a] Catalyst was prepared in situ: Mo-complex **267** and alkoxy ligand were dissolved in C_6H_6, the mixture was stirred at 22 ºC for 1 h. 5% mol *in situ* prepared catalyst, in 0.1M in benzene was used in the reaction. [b] Determined by ^{1}H NMR spectroscopy.

2.3. Tungsten-Based catalyst

High oxidation state W-based imido alkylidene bis-alkoxyde complexes were the first well-defined olefin metathesis catalysts to be developed.[193] Among the reasons for the preference of Mo over W are relatively high stability of tungstacyclobutane intermediates toward loss of olefin, a perceived higher sensitivity of tungsten complexes to certain functional groups and the commercial availability of some Mo complexes. W-based catalysts can be dramatically more selective than Mo complexes in homocoupling of terminal olefins to generate Z internal olefins. With the aim of studying *Z*-selective cross-metathesis, tungsten

[193] Schrock, R. R. *Chem. Rev.* **2002**, *102*, 145-180.

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catalysts **287-289** (Figure 15) were also tested in the reaction of compound **270** with olefin **163**.

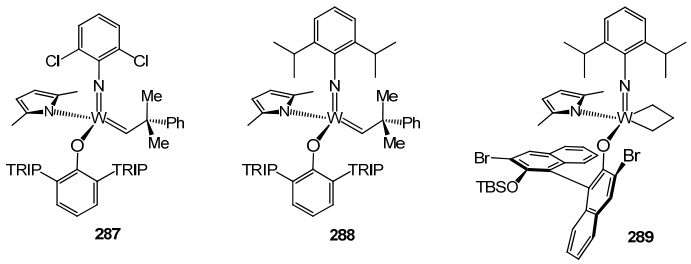

Figure 15. Tungsten-based catalysts **287-289**

When the reaction was run in the presence of catalyst **287** (Table 15, Entry 1), only starting material **270** was recovered together with 1-hexadecane and the *Z*-homocoupling product (34%). Performing, the reaction at 60 ºC, the same negative results was obtained (Table 15, Entry 2), with recovery of the starting material, hexadecane and homocoupling product of 1-hexadecene (with a 33% conversion and a lower *Z*:*E* ratio (10:1). On the other hand, in presence of catalyst **288** (Table 15, Entry 3) at room temperature the reaction afforded the product resulting from homocoupling of 1-hexadece in 15% yield and excellent *Z*:*E* ratio (>98:<2). Under these conditions no cross-metathesis product was detected by ^{1}H NMR spectroscopy.

Catalyst **289** was then tested and, fortunately, in this case the cross-product **271** was obtained, but only with 10% conversion (Table 15, Entry 4) together with 34% of hexadecane homocoupling product in a 1.6:1 *Z*:*E* ratio. When the temperature was raised, using the same catalyst **289** and a reaction time of 12 h, the conversion reached 59% (Table 15, Entry 5) with exclusive formation of the *Z*-product. The reaction was then run at 60 ºC for 9 h under vacuum, affording the desired product in a comparable conversion (55%) and selectivity (the *E* isomer was not detected by ^{1}H NMR spectroscopy). The temperature was increased to 80 ºC using toluene as solvent, but the conversion did not improve significantly (Table 15, Entry 7). Finally, an excess of 20 equivalents of 1-hexadecene was used, and the reaction run at 60 ºC for 14 h, but no improvement

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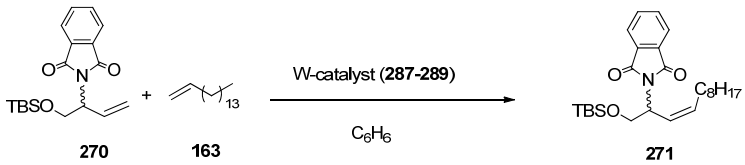
was observed and instead the cross product was generated with only 48% conversion (Table 15, Entry 8).

Table 15. Results in cross metathesis using tungsten catalyst (**287**-**289**)[a]



270 **163** **271**

Entry	Equiv of 1-hexadecene	Time (h)	Temp (ºC)	Catalyst	Conversion[b] (Yield)[c] %	*Z:E*[b]
1	10	3.5	22	**287**	<2	-
2[e]	10	3.5	60	**287**	<2	-
3	10	3.5	22	**288**	<2	-
4	10	3.5	22	**289**	10	>98:<2
5[e]	10	12	60	**289**	59	>98:<2
6[d,e]	10	9	60	**289**	55(45)	>98:<2
7[d,e]	10	14	80	**289**	64(54)	>98:<2
8[d,e]	20	14	60	**289**	48	>98:<2

[a] 5 mol % prepared catalyst, 0.1M in benzene. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] The reaction was run under vacuum. [e] The reaction was carried in toluene.

In conclusion, tungsten-based catalysts have been shown to be active in cross-metathesis of allyl amines to give exclusively *Z*-product. However, an increase of temperature and/or reaction time, an excess of one of the cross-partners or running the reaction under vacuum in order to remove ethylene did not afford any improvement in terms of conversion; however, higher temperatures or longer reaction times did not diminish the *Z:E* selectivity of the process. The enantiomeric excess of compound **270** from the cross-metathesis reaction was systematically checked and no resolution process was observed.

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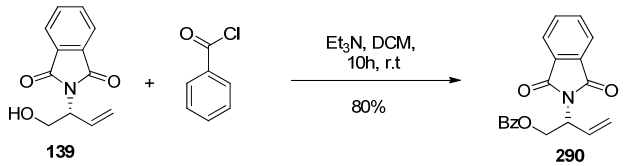
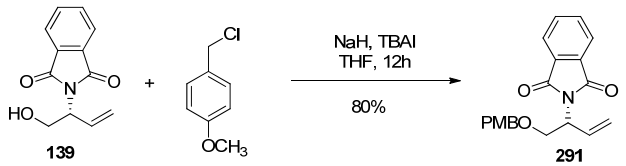
2.4. *Z-cross*-metathesis with enantiomerically pure amines

After investigation with the racemic allyl amine we decided to study the reaction with the enantiomerically pure substrate, introducing different protecting groups for the amino and hydroxyl functions in order to determine the functional groups tolerance of the process. Thus, allyl amines **290** and **291** were synthesized by protection of (2*R*)-*N*-phthalimido-3-buten-1-ol **139**, the synthesis of which is described in Chapter 3. 2-*N*-phthalimido-3-buten-1-ol **139** was treated with benzoyl chloride and triethylamine in dichloromethane to afford compound **290** in 80% yield (Scheme 60).



Scheme 60. Synthesis of allyl amine **290**

The hydroxyl group of compound **139** was protected by reating the compound with *p*-methoxybenzyl chloride and NaH in THF in presence of catalytic TBAI to afford compound **291** in 80% yield (Scheme 61).



Scheme 61. Synthesis of allyl amine **291**

Deprotection of the benzoyl group of compound **141** with LiOH in THF solvent afforded compound **142**, as it was described in Chapter 3, which was then treated with TBSCl, immidazole and catalytic DMAP to afford compound **292** in 73% yield (Scheme 62).

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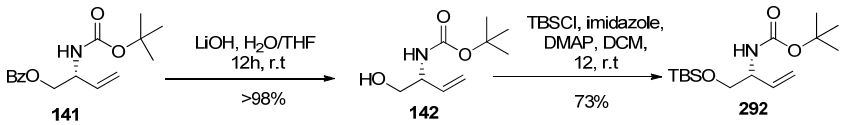
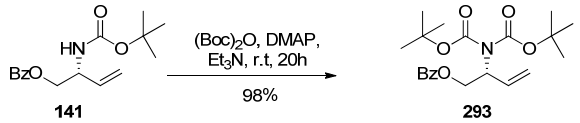


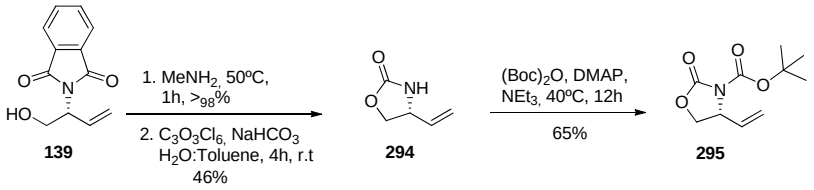
Scheme 62. Synthesis of allyl amine **292**

Compound **293** was synthesized in 98% yield by *N*-acylation of compound **141** with $(Boc)_2O$ and DMAP in Et_3N as solvent (Scheme 63).



Scheme 63. Synthesis of allyl amine **293**

The synthesis of compound **294** was carried out from compound **139** in quantitative yield by deprotection of the phthalimide group with ethylenediamine, followed by treatment with triphosgene at room temperature for 4 h (Scheme 64). Compound **295** was then synthesized from compound **294** by reaction with $(Boc)_2O$ and DMAP in triethylamine as solvent to give the product **295** in 65% yield (Scheme 64).



Scheme 64. Synthesis of compound **295**

When the cross-metathesis reaction of **290** and 1-hexadecene was carried out with catalyst **261** at room temperatureunder vacuum, compound **296** was afforded with 29% conversion, exclusively as the *Z*-product (Table 16, Entry 1). However, under the same conditions catalyst **279** was more effective, affording 35% conversion to product after 3.5 h. This conversion was increased at longer reaction times (Table 16, Entries 2-4), and the excellent *Z*-alkene product selectivity (*Z*:*E*=>98:<2) was retained under these condition.

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The carbamate protecting group was also studied, compound **292** was tested using catalyst **278** affording the desired product but with poor conversion (25%) (Table 16, Entry 5). However, using catalyst **279**, only starting material was recovered (Table 16, Entry 6). The more active catalyst **280** also did not yield any cross-product after 4h at room temperature (Table 16, Entry 7).

Replacement of the silyloxy group of substrate **292** by an ester (compound **141**) resulted exclusively in the *Z*-product with 29% conversion using catalyst **261** (Table 16, Entry 8). However, no conversion was observed in the presence of catalyst **279** at 60 ºC (Table 16, Entry 9). Using catalyst **261**, substrate **293** gave the *Z*-product with 36% conversion after 7 h (Table 16, Entry 10). At higher temperatures (60 ºC) the reaction again afforded exclusively *Z*-isomer with similar conversion (Table 16, Entry 11). The catalyst **277** proved less active, affording the product with 28% conversion at 60 ºC (Table 16, Entry 12). Catalyst **278** was also tested at 60 ºC and allowed the formation the desired product with 40% conversion (Table 16, Entry 13).

Using catalysts **261** and **278**, the *E* coupling product was never observed although the reaction was performed at 60 ºC. This may be explained by considering that the relatively bulky *di*-carbamate group could favour the formation of the *syn*-metallacyclobutane. For this reason, we decided to test the more active catalyst **280** with this substrate, which afforded the cross-product with 73% conversion (Table 9, Entry 14), although the diastereoselectivity dropped significantly (*Z*:*E*= 3.2:1).

The cross-metathesis reaction from compound **294** did not proceed when catalyst **278** was used at 60 ºC (Table 16, Entry 15). Similarly, protected compound **295** in presence of catalyst **278** did not afford the *cross*-product after 12 h (Table 16, Entry 16).

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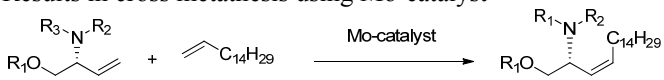
Table 16. Results in cross metathesis using Mo-catalyst[a]



(*R*)-**270**: R^1=TBS, R^2=R^3=Phth
290: R^1=Bz, R^2=R^3=Pht
292: R^1=TBS, R^2=Boc, R^3=H
141: R^1=Bz, R^2= Boc, R^3=H
293: R^1=Bz, R^2= Boc, R^3=Boc
294: R^1 R^2= R^3=H
295: R^1 R^2 = R^3=Boc

(*R*)-**271**: R^1=TBS, R^2=R^3=Phth
296: R^1=Bz, R^2=R^3=Pht
298: R^1=TBS, R^2=Boc, R^3=H
299: R^1=Bz, R^2= Boc, R^3=H
300: R^1=Bz, R^2= Boc, R^3=Boc
301: R^1 R^2= R^3=H
302: R^1 R^2 = R^3=Boc

Entry	Allyl amine	Time (h)	Temp (ºC)	Catalyst	Product	Yield (%)[c]	*Z:E*[b]
1	**290**	4	22	**261**	**296**	29	>98:<2
2	**290**	3.5	22	**279**	**296**	35	>98:<2
3	**290**	4.5	22	**279**	**296**	42	>98:<2
4	**290**	7	22	**279**	**296**	47	>98:<2
5	**292**	5	22	**278**	**298**	25	>98:<2
6	**292**	5	22	**279**	**298**	<2	-
7	**292**	4	22	**280**	**298**	<2	-
8	**141**	6	22	**261**	**299**	29	>98:<2
9	**141**	6	60	**279**	**299**	<2	-
10	**293**	7	22	**261**	**300**	36	>98:<2
11	**293**	3.5	60	**261**	**300**	35	>98:<2
12	**293**	5	60	**277**	**300**	28	>98:<2
13	**293**	7	60	**278**	**300**	40	>98:<2
14	**293**	3.5	22	**280**	**300**	73	76:24
15	**294**	12	60	**278**	**301**	<2	-
16	**295**	12	60	**278**	**302**	<2	-

[a] Catalyst was prepared in situ: Mo-complex **267** and alkoxy ligand were dissolved in C_6H_6, the mixture was stirred at 22 ºC for 1 h. 5% mol catalyst, 0.1M in benzene was used in the reaction. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield.

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Surprisingly, when the enantiomerically pure compound (***R***)-**270** was treated with 1-hexadecene in the presence of 5% catalyst **261** at room temperature, the desired product was afforded with 62% conversion (Table 17, Entry 1). This result was in disagreement with our expectation because the racemic allyl amine (±)-**270**, under the same reaction conditions, gave lower conversions, although in both cases an excellent diastereoselectivity was obtained. Surprisingly, when the reaction with compound **(*R*)-269** was run under vacuum, the *Z*-product was exclusively obtained in very good yield (86%) (Table 17, Entry 2). With this exciting result in hand, the reaction conditions were applied to compounds **290**, **291** and **293**.

Compound **290** afforded the cross-product with 59% conversion (Table 17, Entry 3); however, when the reaction was run under vacuum the conversion improved to 74% (table 17, Entry 4). Compound **291** afforded the *Z*-alkene product with 56% conversion when the reaction was run at room temperature for 6 h (Table 17, Entry 5). However, when vacuum was applied, the conversion improved to 85% (83% yield) (Table 17, Entry 6). In the case of compound **293** the *Z*-cross-product was exclusively formed with 57% conversion (Table 17, Entry 7). When ethylene was removed from the reaction mixture, the conversion increased to an excellent 95% conversion (90% yield) (Table 17, Entry 8).

These results show that a *Z*-selective cross-metathesis can be achieved with all of the homoallylic hydroxyl protecting groups tested. Phthalimide and carbamate protecting groups promote an efficient metathesis process without loss of diastereoselectivity, affording exclusively *Z*-alkenes. The use of vacuum improves the conversions, and isolated yields of the products considerably; in addition, when the reaction was carried out with enantiomerically pure allylic amines the conversion improved, resulting in the highest *Z*-alkene yields reported here. Thys, the first *Z*-selective cross-metathesis of allyl amines has been developed, which affords the desired products with high conversion and excellent diastereoselectivity.[194]

[194] Hoveyda, A. H.; Meek, S.; O´Brien, R. V.; Llaveria, J.; Schrock, R. R. PCT/2011/024100. *Efficient Method for Z- or cis-Selective cross-metathesis of enol and allylic amines.*

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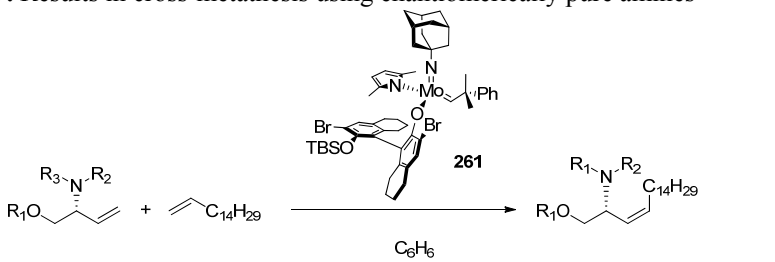
Table 17. Results in cross-metathesis using enantiomerically pure amines[a]



(*R*)-**270**: R^1=TBS, R^2=R^3=Phth
290: R^1=Bz, R^2=R^3=Pht
291: R^1=PMB, R^2=R^3=Pht
293: R^1=Bz, R^2= Boc, R^3=Boc

(*R*)-**271**: R^1=TBS, R^2=R^3=Phth
296: R^1=Bz, R^2=R^3=Pht
297: R^1=PMB, R^2=R^3=Pht
300: R^1=Bz, R^2= Boc, R^3=Boc

Entry	Substrate	Time (h)	Temp (ºC)	Product	Conversion (%)[b] (Yield %)[c]	*Z*:*E*[b]
1	(*R*)-**270**	5	22	(*R*)-**271**	62	>98:<2
2[d]	(*R*)-**270**	5	22	(*R*)-**271**	92(86)	98:2
3	**290**	5	22	**296**	59	>98:<2
4[d]	**290**	5	22	**296**	74(74)	>98:<2
5	**291**	6	22	**297**	56	>98:<2
6[d]	**291**	5	22	**297**	85(83)	>98:<2
7	**293**	5	22	**300**	57	>98:<2
8[d]	**293**	6	22	**300**	95(90)	98:2

[a] Catalyst was prepared *in situ*: Mo-complex **261** and alkoxy ligand were dissolved in C_6H_6, the mixture was stirred at 22 ºC for 1 h. 5 mol % catalyst, 0.1M in benzene was used in the reaction. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] The reaction was run under vacuum.

2.5. Application to the synthesis of D-*ribo*-phytosphingosine

In order to pursue the objective of synthesizing D-*ribo*-phytosphingosine **8**, the enantiomerically pure *Z*-alkenes obtained as discussed above were tested in the dihydroxylation reaction with the aim of studying both conversion and diastereoselectivity. In principle the diastereoselectivity of the process could be controlled by the substrate, due to the presence of a chiral C2 site in the substrate skeleton, or by double stereodifferentiation promoted by a chiral osmium complex.

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The dihydroxylation reaction performed on compound **(*R*)-271** using a catalytic amount of OsO_4 and NMO as a re-oxidant, afforded a mixture of diastereomers **304**:**305** in a 1.8:1 ratio (Table 18, Entry 1). Lower temperatures (0 ºC) did not improve the stereoselectivity of the reaction (Table 18, Entry 2). For this reason, we decided to study the dihydroxylation of compound **296**, which possessed a benzoyl moiety as a hydroxyl protecting group. The use of a benzoil substituent moderately increased the diastereoselectivity (Table 18, Entries 4 and 5) and similar diastereoselectivity results have been obtained using substrate **303** (Table 18, Entries 7 and 9). This observation is in agreement with the model proposed in Chapter 3, which justified the more stable conformation the steric interaction $A^{1,3}$ are in contrast with the $A^{1,2}$ which afford the dihydroxylation *syn* to C2 chiral group.

The results obtained indicated that the phthalimide amine protecting group was not compatible with AD-mixtures; this is in agreement with previous work wherein the reaction of *E*-allyl amines protected with phthalimide group did not afford the dihydroxylation product.[195]

However, the di-carbamate group has proved extremely effective in diastereoselective dihydroxylation reactions, directing the addition *anti* to the C-2 allyl amine.[196] With this result in mind, the diastereoselective dihydroxylation of compound **310** was performed in $^tBuOH:H_2O$ (1:1) with OsO_4 and NMO, (Table 18, Entry 10) affording the desired product with high selectivity (ratio *anti:syn* 20:1). Taking into account the previously reported results, we tested the dihydroxylation with compound **310** in OsO_4 and NMO in dichloromethane affording the product in 89% yield (*anti*:*syn* 24:1) as a result of an attack *anti* (Table 18, Entry 10).

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195 Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Lett.* **2009**, *11*, 205.

196 Jeon, J.; Shin, M.; Yoo, J. M.; Oh, J. B.; Bae, J. G.; Jung, S. H.; Kim, G. Y. *Tetrahedron Lett.* **2007**, *48*, 1105-1108.

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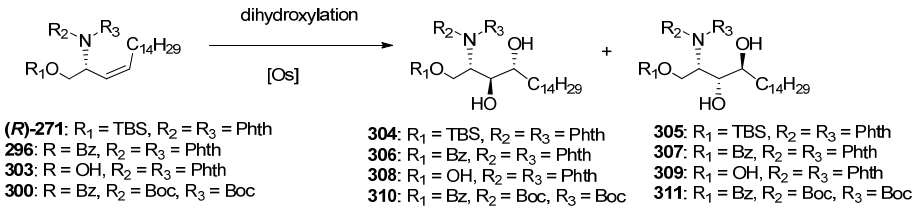
Table 18. Study of dihydroxylation of **(*R*)-271**, **296** and **303**



(*R*)-271: R_1 = TBS, R_2 = R_3 = Phth
296: R = Bz, R_2 = R_3 = Phth
303: R = OH, R_2 = R_3 = Phth
300: R = Bz, R_2 = Boc, R_3 = Boc

304: R_1 = TBS, R_2 = R_3 = Phth
306: R_1 = Bz, R_2 = R_3 = Phth
308: R_1 = OH, R_2 = R_3 = Phth
310: R_1 = Bz, R_2 = Boc, R_3 = Boc

305: R_1 = TBS, R_2 = R_3 = Phth
307: R_1 = Bz, R_2 = R_3 = Phth
309: R_1 = OH, R_2 = R_3 = Phth
311: R_1 = Bz, R_2 = Boc, R_3 = Boc

Entry	Substrate	Reagents	Product	Conversion (%)[f]	Diastereoselectivity *anti:syn*[f]
1[a]	**(*R*)-271**	OsO_4/NMO[e]	**304:405**	>99	1.8:1
2[b]	**(*R*)-271**	OsO_4/NMO[e]	**304:405**	>99	2:1
3[a]	**(*R*)-271**	AD-mix β[e]	**304:405**	<2[c]	-
4[a]	**296**	OsO_4/NMO[e]	**306:307**	>99	2.5:1
5[a]	**296**	OsO_4/NMO[d]	**306:307**	>99	2.8:1
6[a]	**296**	AD-mixβ[e]	**306:307**	<2	-
7[a]	**303**	OSO_4/NMO[e]	**308:309**	>99	3:1
8[a]	**303**	AD-mixβ[e]	**308:309**	<2	-
9[a]	**303**	OsO_4/NMO[d]	**308:309**	>99	2.8:1
10[a]	**300**	OsO_4/NMO[e]	**310:311**	>99	20:1
11[a]	**300**	OsO_4/NMO[d]	**310:311**	>99	24:1

[a] Room temperature, 5% mol catalyst. [b] 0ºC, 14h. 2.5% mol catalysts. [c] The starting material was recovered after 2d. [d] DCM was used as a solvent. [e] ^{t}BuOH:H_2O (1:1) were used as a solvent. [f] Determined by ^{1}H NMR.

The high diastereoselectivity obtained in compound **310** can be rationalized by noting that the H-eclipsed conformer is energetically favoured relative to the *N*-outside conformer (Scheme 65), in that conformer the attack of OsO_4 will take place preferentially from the bottom face of the alkene.

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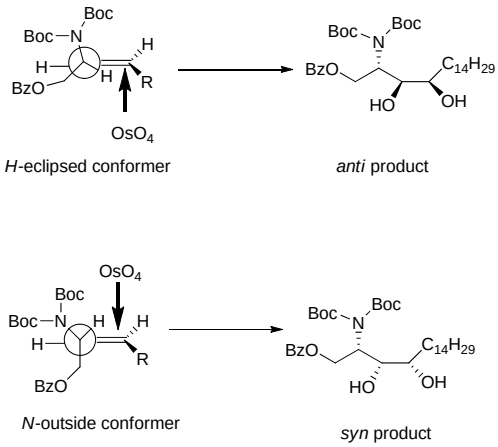
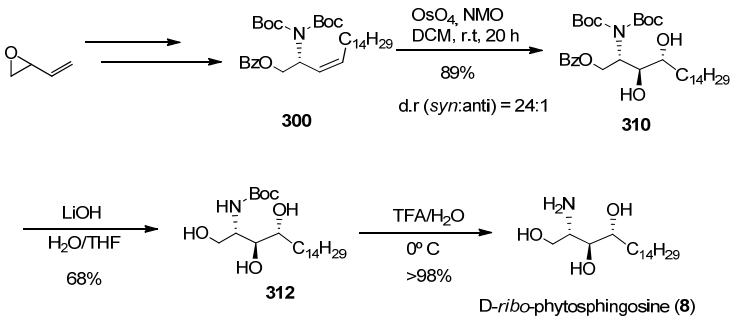


Scheme 65. Proposed conformers in dihydroxylation reaction

Once the dihydroxylated product was obtained, we proceeded with the total synthesis. Thus, the benzoyl-protected hydroxyl group was deprotected with LiOH to afford the reported compound **312**,[197] in 68% yield. Finally, the deprotection of the carbamate-protected amino group was carried out with TFA/H_2O to give D-*ribo*-phytosphingosine **(8)** in quantitative yield (Scheme 66).



Scheme 66. Synthetic sequence to afford D-*ribo*-phytosphingosine (**8**)

In summary, we have developed an efficient method for obtaining exclusively *Z*-allylic amines by Mo-catalyzed cross-metathesis. The good functional-group tolerance of the Mo-catalysts allowed compound **310** to be isolated in excellent yield and with exquisite diastereoselectivity. Compound **310** was dihydroxylated to give the desired product in 85% yield, with the

[197] Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657-10670.

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diastereoselectivity being controlled by the substrate. Unmasking amino alcohol by removal of the protecting benzoyl and carbamate groups afforded D-*ribo*-phytosphingosine (**8**) was afforded in 45% overall yield for the six steps. All spectroscopic and physical properties of the obtained compound are in agreement with those reported for the natural product.

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Aziridination of Dienes

CHAPTER 5

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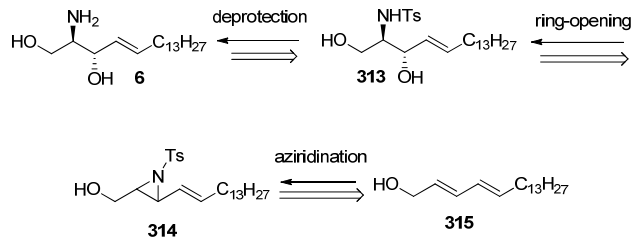
1. Retrosynthetic Scheme

Looking for new and efficient methods for synthesizing sphingoid bases, specially D-*erythro*-sphingosine (**6**), we proposed a synthetic route based in the regio- and stereoselective synthesis of the vinylaziridine **314**, which by a ring-opening reaction could afford the 1,2-aminodiol **313**, a precursor of the target compound (Scheme 67).

To achieve this objective, we decided to study the aziridination of non-symmetric 2,4-diene-1-ols using nitrene transfer protocols. Regio- and stereoselective procedures for this reaction have not been reported. Besides, the aziridination with an unprotected hydroxyl group has neither been explored. Our methodology involves first, the aziridination of the dienes with a hydroxyl group at allylic position; second, the regioselective ring-opening reaction in order to obtain 2-amino-1,3-diols and subsequent deprotection to obtain D-*erythro*-sphingosine.



Scheme 67. Proposed retrosynthetic sequence for obtaining D-*erythro*-sphingosine **(6**) via aziridination

2. Background

Aziridines, saturated three-membered heterocycles containing one nitrogen atom, are among the most fascinating intermediates in organic synthesis, acting as precursors of many interesting products. The strain in their skeletons enables easy cleavage of the C-N bond. So, aziridines allow the construction of

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several compounds such as amines, amino acids, β-aminosulfonic acids, amino alcohols, alkaloids and β-lactams.[198]

Aziridines have an inherent *in vivo* potency due to their ability to act as DNA cross-linking agents via nucleophilic ring opening, giving biological properties as antibiotic and antitumor agents.[199] For instance, Mitomycin C and aziridine-containing analogs (Figure 16) have a broad activity against a range of tumours.[200]

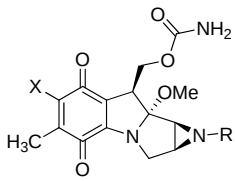

Figure 16. Mitomycin C

Because of the biological and chemical activities of aziridines, new methods for the direct and selective C-N bond formation have been developed. The main approaches to the synthesis of aziridines can be classified as i) addition to alkenes, ii) addition to imines, iii) addition to azirines and iv) intramolecular cyclization.[201]

i) Nitrogen-atom transfer to alkenes is a particularly appealing strategy for the generation of aziridines because of the ready availability of olefinic starting materials and the direct nature of such process. There are two general methods for the addition of nitrene to alkenes (Scheme 68), involving one- or two-step mechanism: a) Gabriel-Cromwell method, and b) aziridination to alkenes.

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201 Aires-de-Sousa, J.; Prabhakar, S.; Lobo, A. M.; Rosa, A. M.; Gomes, M. J. S.; Corvo, M. C.; Williams, D. J.; White, A. J. P. *Tetrahedron: Asymmetry* **2001**, *12*, 3349-3365.

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a) The Gabriel-Cromwell aziridine synthesis involves a nucleophilic addition of amine to a 2-haloacrylate or similar reagent. Thus, there is an initial Michael addition followed by ring closure.

b) The aziridination of olefins is typically accomplished by using a nitrene-transfer reagent. The nitrene can be generated by using different methodologies from a variety of nitrogen sources such as PhINTs (N-tosyliminophenyliodinane), Chloramine T, Bromamine T and azides.[202] The most successful methods use metal complexes such as copper,[203] silver,[204] gold,[205] rhodium,[206] iron,[207] palladium,[208] ruthenium,[209] cobalt[210] and manganese.[211]

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202 Dauban. P.; Dodd, R. H. *Synlett* **2003**, *11*, 1571-1586.

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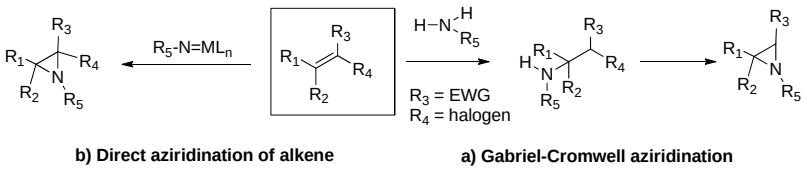

Scheme 68. Addition of nitrenes to alkenes

ii) A widely explored methodology for achieving aziridines is the addition to imines, which can be divided into three conceptual categories involving the reaction with: a) α-haloenolates, b) carbenes and c) ylides (Scheme 69).

a) The aza-Darzens reaction involves the reaction of imines with stabilized anions bearing α-leaving groups. The mechanism has two distinct steps: initial nucleophilic attack to the C=N bond followed by cyclization of the intermediate.[212]
b) The addition of carbenes to imines comprises an increasingly useful method for aziridination.[213]
c) The reaction between an ylide and imine forms a betaine. The ring closing to form an aziridine takes place through elimination of the heteroatom-contained leaving group originated from the ylide.[214]

Whereas methods a) and b) are employed to prepare aziridines bearing electron-withdrawing groups such as esters or amides, the ylide methodology provides a route to aryl, alkyl, vinyl and terminal aziridines, as well as ester-or amide-substituted aziridines.

212 a) Sweeney, J. *Eur. J. Org. Chem.* **2009**, 4911-4919. b) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341-2372.

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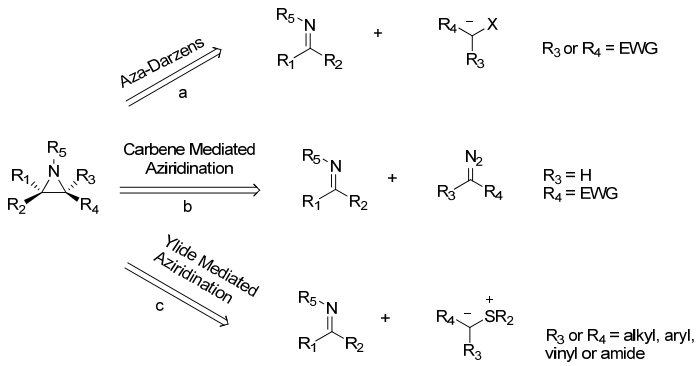

Scheme 69. Aziridination methods from imines.

iii) Azirines, three-membered cyclic imines, are versatile compounds and have been used for the preparation of various substituted aziridines by nucleophilic addition (Scheme 70).[215]

Scheme 70. Aziridination through addition to azirines

iv) Aziridines can be also readily formed by ring closure of appropriately substituted amines, the SN_2-type cyclization of 1,2-amino alcohols, 1,2-amino halides, 1,2-azido alcohols, 1,2-amino sulfides, 1,2-amino selenides or epoxides.

We focus our study in nitrene transfer to alkenes catalyzed by metals to afford vinylaziridines, which are versatile and useful and powerful intermediates building blocks for stereoselective synthesis of biologically and synthetically

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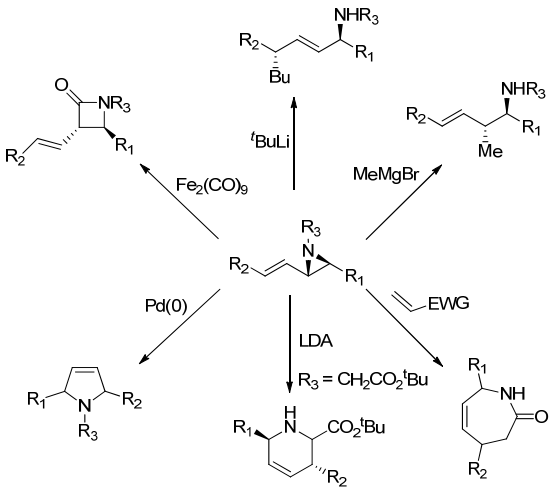
important compounds.[216] In particular, vinylaziridines can be regio- and stereoselectively opened by different nucleophiles making them very useful precursors for the synthesis of functionalized amines. Moreover, appropriately functionalized vinylaziridines allow an easy access to a wide range of interesting products such as allyl amines,[217] homoallyl amines,[218] β-lactams,[219] pyrrolidines,[220] pyperidines[221] and azepines[222] (Scheme 71).



Scheme 71. Synthetic application of vinylaziridines

In fact, vinylaziridines are commonly synthesized by stoichiometric procedures based on nucleophilic intramolecular substitution. Thus, Darzens-type

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216 Aziridines and Epoxides in Organic Synthesis; Yudin, A. K., Ed.; Wiley-VCH; Weinheim, Germany, **2006**.

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reaction (Scheme 72 a) is one of the oldest and most flexible methods for preparation of functional aziridines including vinylaziridines.[223] The reaction between an allylic ylide and imines or sulfinimines[224] also provides a facile way of synthesis as it involves the regioselective construction of vinylaziridine (Scheme 72b). Both methods have usually led to the thermodynamically stable *cis*-aziridines.[225] *trans*-Aziridines were obtained with high stereoselectivity by the ylide route driving the reaction under steric and kinetic control conditions.[224j] Vinylaziridines were also prepared from vinyl epoxides by ring opening with azides[226] or ammonia[227] (Scheme 72 e), from 1,2-amino halides (Scheme 72 c),[228] or by conjugate addition.[229] The aforementioned nitrene addition to dienes

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223 a) Sweeney, J. *Eur. J. Org. Chem.* **2009**, 4911-4919. b) Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612-1613. c) Akiyama, T.; Suzuki, T.; Mori, K. *Org. Lett.* **2009**, *11*, 2445-2447. d) Concellón, J. M.; Rodriguez-Solla, H.; Simal, C. *Org. Lett.* **2008**, *10*, 4457-4460. e) Concellón, J. M.; Rodríguez-Solla, Bernad, P. L.; Simal, C. *J. Org. Chem.* **2009**, *74*, 2452-2459.

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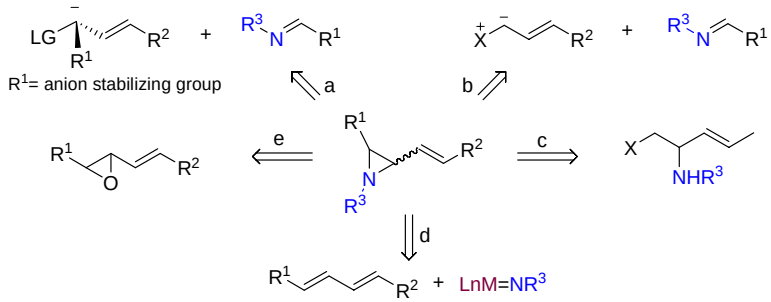
229 Armstrong, A.; Pullin, R. D. C.; Jenner, C. R.; Scutt, J. N. *J. Org. Chem.* **2010**, *75*, 3499-3502.

(Scheme 72 d) has been described,[230] but it can even be considered far away from success in terms of regio- and stereoselectivity.



Scheme 72. Methods to synthesize vinylaziridines

A large number of reports related to the alkene aziridination have been published,[231,232] but only a few have dealt with conjugated dienes as the substrate. Copper-,[230] manganese- or ruthenium based catalysts[209b,230c] have provided good yields of vinylaziridines formed by the exclusive aziridination of one C=C bond of the diene. Even so, the reported methods employed only symmetric dienes and

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230 a) Ma, L.; Du, D.-M.; Xu, J. *Chirality* **2006**, *18*, 575-580. b) Sureshkumar, D.; Maity, S. ; Chandrasekaran, S. *J. Org. Chem.* **2006**, *71*, 1653-1657. c) Knight, J. G. ; Muldowney, M. P. *Synlett* **1995**, 949-951. d) Piangiolino, C. ; Gallo, E.; Caselli, A.; Fantauzzi, S.; Ragaini, F.; Cenini, S. *Eur. J. Org. Chem.* **2007**, 743-750. e) M. Nishimura, S. Minakata, S. Thongchant, I. Ryu, M. Komatsu, *Tetrahedron Lett.* **2000**, *41*, 7089-7092.

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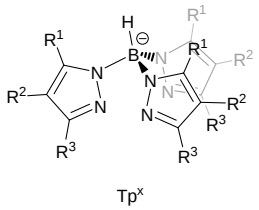
the selectivity, understood as *cis/trans* (or *trans/cis*) ratio, was low. The before mentioned drawbacks do not allow the synthetic application of this methodology.

3. Results and discussion

In this context, we planned to develop a catalytic system capable of inducing the formation of vinylaziridines to achieve the following goals: (a) tolerance to other functional groups, (b) use of non-symmetric dienes, (c) control of the regioselectivity (given an asymmetric diene) and (d) control of the stereoselectivity (to obtain either *cis* or *trans* vinylaziridines). P. Pérez et al reported that $Tp^xCu(NCMe)$ (Tp^x = homoscorpionate ligand,[233] Figure 17) complexes were effective catalyst for aziridination of simple alkenes through the nitrene-transfer reaction,[234] using PhI=NTs as nitrene source. These catalysts were excellent candidates for exploring the aziridination of more complex molecules such as the showed in the retrosynthesis, and the following work was developed in collaboration.



Tp^x

Tp^x	R^1	R^2	R^3
Tp^*	Me	H	Me
Tp^{Br3}	Br	Br	Br
$Tp^{*,Br}$	Me	Br	Me
$Tp^{Ph,4Et}$	H	Et	Ph
$Tp^{pClPh,Br2}$	Br	Br	p-ClC_6H_4

Figure 17. Tp ligands

3.1. Study of tolerance to functional groups

In order to drive our work to the above goals, and because the β-aminoalcohol moiety is found in a wide variety of biologically active

233 a) Trofimenko, S. *Scorpionates, The Coordination Chemistry of Polypyrazolylborate Ligands*; Imperial College Press: London, **1999;** b) Pettinari, C. *Scorpionates II: Chelating Borate Ligands*; Imperial College Press: London, **2008**.

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compounds,[235] first we planned to study the effect of the influence of hydroxyl group in the reaction (Figure 18). The commercially available allylic alcohol (**316**), was selected as a model substrate, and was protected as a benzyl ether (**317**), silyl ether (**318**), carbamate (**319**), methyl ether (**320**) and ester (**321**) by standard procedures to study the tolerance of functional groups.

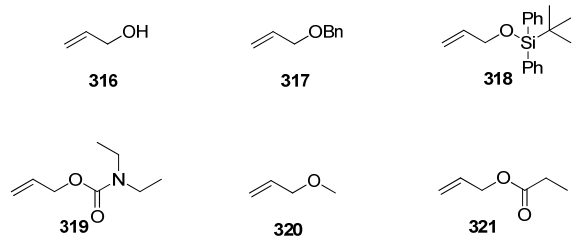
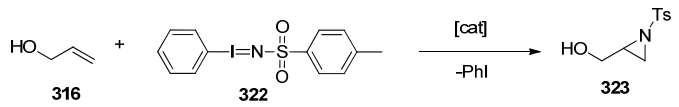


Figure 18. Allylic protected substrates

In previous reported studies of the aziridination reaction a large excess of alkene was used or it was directly used as a solvent. With the aim of optimizing the reaction, different ratios alkene:PhINTs were tried in the aziridination of allylic alcohol (**316**), using in all cases a 5% of $Tp^{Br3}Cu(NCCH_3)$ (Scheme 73).



Scheme 73. Aziridination of allylic alcohol with PhINTs

Firstly, when a 10:1 ratio alkene:nitrene source (Table 19, Entry 1) was used, the desired aziridine was obtained in a 55% yield. PhINTs was completely consumed and only tosyl amine and aziridine were observed by ^{1}H NMR in the reaction mixture. Decreasing the ratio between alkene and PhINTs did not improve the obtained conversion (Table 19, Entries 2-5). Meanwhile using an equimolar relation between the two reagents the conversion only decrease c.a. 5% (Table 19, Entry 5). When an excess (2 eq) of nitrene source was used, the conversion was again maintained (Table 19, Entry 6). All these attemps were

235 a) Castejón, P.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1996**, *52*, 7063-7086. b) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431-432 and references cited therein.

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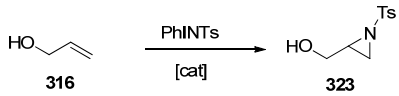
performed adding nitrene source in one portion, however, when PhINTs was added in four portions an increase of conversion was observed (Table 19, Entry 7). Finally, nitrene source was added in more portions, but unfortunately in this case the conversion did not increase.

Table 19. Optimization of the aziridination reaction with allylic alcohol[a]



316 323

Entry	alkene/PhINTs ratio	Yield (%)[b]
1	10:1	55
2	8:1	53
3	4:1	52
4	2:1	57
5	1:1	50
6	1:2	52
7[c]	1:1	68

[a] [Tp]:[**316**]=1:20, referred to a 0.0125 mmol of catalyst, 5% $Tp^{Br3}Cu$, 5 mL of DCM, 7h at room temperature. [b] Isolated yield. [c] The nitrene source was added in 4 portions over 4h, then the reaction was stirred 3h.

Compounds **317-321** were tested using a relation alkene:PhINTs (4:1). All compounds **317-321** led the corresponding aziridine, despite the fact that yields were lower than the obtained for allylic alcohol.

Compound **317,** was aziridinated affording compound **324** in a 29% yield (Table 20, Entry 1), although a mixture of compounds was also observed in the reaction crude by ^{1}H NMR. Nitrene addition to silyl derivative **318** afforded only a 36% of compound **325**. The reaction using carbamate **319** gave a complex mixture and the aziridine **326** was obtained in an 18% (Table 20, Entry 3). Methoxy compound **320** and the ester **321** were also tested in the standard conditions but the corresponding aziridines **327** and **328**, respectively, were not detected in both substrates. (Table 20, Entries 4 and 5).

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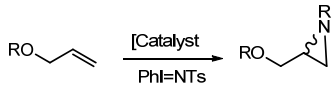
Table 20. Study of the tolerance of functional groups towards aziridination reaction[a]



317: R=Bn
318: R=^{t}BuPh$_2$Si
319: R=C(O)NEt$_2$
320: R=Me
321: R=C(O)CH$_3$

324 : R=Bn
325 : R=^{t}BuPh$_2$Si
326: R=C(O)NEt$_2$
327: R=Me
328: R=C(O)CH$_3$

Entry	Substrate	Product	Yield (%)[b]
1	**317**	**324**	29
2	**318**	**325**	36
3	**319**	**326**	18
4	**320**	**327**	<2%
5	**321**	**328**	<2%

[a] [Tp^{Br3}Cu(NCCH$_3$)]:[PhINTs]:[alkene]=1:20:80 referred to 0.0125 mmol of catalyst, 5% catalyst, 7h, room temperature. TsNH$_2$ accounted for 100% initial PhINTs not converted into aziridines. [b] Determined by ^{1}H NMR.

Unprotected allyl alcohol affords the corresponding aziridine in higher conversion than when the alcohol was protected. For this reason, allyl alcohol was chosen as model substrate for cheking copper or silver catalysts containing different Tp ligands. Initially, Tp^{Ph}Cu(NCCH$_3$) (Table 21, Entry 1), Tp^{Br3}Ag(NCCH$_3$) (Table 21, Entry 4) and Tp^{*,Br}Ag(NCCH$_3$) (Table 21, Entry 5) were tested observing that all of them catalyzed the reaction affording the aziridine in similar yields. However, Tp*Cu(NCCH$_3$) (Table 21, Entry 2), Tp^{*,Br}Cu(NCCH$_3$) (Table 21, Entry 3) and Tp*Ag(NCCH$_3$) (Table 21, Entry 6) resulted less efficient catalysts in that process and afforded the aziridine in a 28, 22 and 23% yield, respectively.

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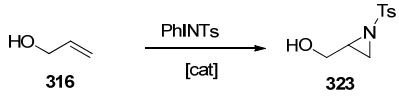
Table 21. Study of different Tp complexes in the aziridination of allylic alcohol[a]



316 323

Entry	Catalyst	Yield (%)[b]
1	$Tp^{Ph}Cu(NCCH_3)$	56
2	$Tp^{*}Cu(NCCH_3)$	28
3	$Tp^{*,Br}Cu(NCCH_3)$	22
4	$Tp^{Br3}Ag(NCCH_3)$	51
5	$Tp^{*,Br}Ag(NCCH_3)$	55
6	$Tp^{*}Ag(NCCH_3)$	23

[a] [TpM]:[PhINTs]:[alkene]=1:20:80 referred to 0.0125 mmol of catalyst, 5% mol catalyst, 7h, room temperature. PhINTs was added in 4 portions over 4h. $TsNH_2$ accounted for 100% initial PhINTs not converted into aziridines. [b] Determined by ^1H NMR.

Other nitrene source such as Cloramine-T and TsN_3 were also tested in presence of 5% $Tp^{*,Br}Ag$ or $Tp^{Br3}Cu$. In all cases, the conversion to aziridine was lower than 15%, in dichloromethane and dichloroethane as solvents at room temperature and under reflux. After these results, we continued our study using PhINTs as a nitrene precursor.

Different catalytic systems were also used to study the asymmetric aziridination of allylic alcohol. In this sense, bisoxazolines are common useful ligands in copper catalyzed aziridination reaction.[236] For this reason, we decided to test bisoxazoline-copper or silver (**329**-**332**) ligands as a catalysts in the aziridination of allylic alcohol. The copper complexes, which were prepared by stirring at room temperature $[Cu(OTf)]_2 \cdot C_6H_6$ and the corresponding bisoxazoline in dichloromethane using 2:1 ratio ligand:metal, were detected by HRMS. The

[236] a) Kwong, H.-L.; Liu, D.; Chan, K.-Y.; Lee, C.-S.; Huang, K.-H.; Che, C.-M. *Tetrahedron* **2004**, *45*, 3965-3968. b) Ma, L.; Jiao, P.; Zhang, Q.; Xu, J. *Tetrahedron:Asymmetry* **2005**, *16*, 3718-3734.

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desired aziridine was obtained in all cases with copper-bisoxazoline catalysts; however, when silver was used as a metal, no aziridination was observed and only the starting material was recovered. Moreover, we do not have any evidence about the formation of the silver complex because it was not detected by HRMS.

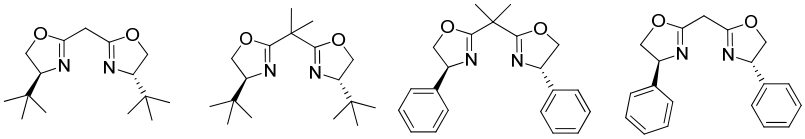
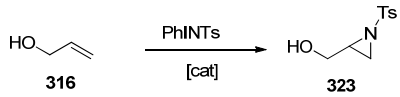


Figure 19. Bisoxazolines used in the aziridnation reaction of allylic alcohol

All bisoxazoline-copper complexes prepared afforded the desired product in comparable conversion than $Tp^{Br3}Cu$ complex.

Table 22. Study of the aziridination of allylic alcohol using Cu-bisoxazolines[a]



316 323

Entry	Ligand	Ligand/Cu	Yield (%)[b]	e.e. (%)[c]
1	**329**	2:1	56	1
2	**330**	2:1	46	3
3	**331**	2:1	45	-5
4	**332**	2:1	59	7

[a] [CuOTf·$(PhH)_2$]:oxazoline:PhINTS:alkene=1:2:20:80 referred to 0.0125 mmol of catalyst, 7h at room temperature, 5mL of DCM, PhINTs was added in 4 portions over 4 h. $TsNH_2$ accounted for 100% initial PhINTs not converted into aziridines. [b] Isolated yield. [c] enantiomeric excess was determined by HPLC (Chiralcel OD column, 5% 2-propanol in hexane, 1.0 ml/min, λ= 225 nm. t_R= 35.7 y 38.0).

Methylene connection between the two oxazoline rings (**329** and **332**) lead a more active complex (56 and 59% yield, respectively, Table 22, Entries 1 and 4) than when an isopropylidene framework was present (**330** and **331**) (46

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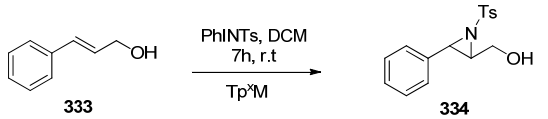
and 45%, respectively, Table 22, Entries 2 and 3). Unfortunately, no enantioselectivity was observed in all cases.

Other substituted allylic alcohols were aziridinated in presence of $Tp^{Br3}Cu$ or $Tp^{*,Br}Ag$, as the most efficient catalysts. Thus, substrate **333** was treated with PhINTS (Scheme 74) under the optimized conditions and aziridine **334** was obtained in a 56% yield using $Tp^{Br3}Cu$ and in a 57% using $Tp^{*,Br}Ag$. Although, higher conversion were observed in relation to allyl alcohol (76 and 77% respectively), the corresponding oxidation product (cinnamaldehyde) was also detected in both cases (c.a. 20%).



333 **334**

$Tp^{Br3}Cu$: 76 conv., 56% yield
$Tp^{*,Br}Ag$: 77conv., 57% yield

Scheme 74. Results of aziridination of compounds **333**

Although aziridines **323** and **334** were obtained in moderate yields, there were not reports describing the aziridination of allylic alcohols by a direct nitrene addition method. Moreover, the configuration *E* of the alkene **333** was maintained to obtain exclusively *trans* aziridine **334** with an excellent stereoselectivity (>98%). Compounds analogues to **334** are usually prepared by Sharpless epoxidation followed by a ring-opening to afford 1,2-aminodiol which was then cyclised to afford the aziridine.[237]

3.2. Study of the aziridination reaction of non-symmetric dienes

The preliminary study showed that TpCu and TpAg complexes were good catalysts for the aziridination of allyl alcohols. Next, we explored the aziridination reaction by using a non-symmetric diene containing a hydroxyl group. Thus, we selected *trans,trans*-2,4-hexadiene-1-ol (**335**) as model substrate. The reaction of **335** with PhI=NTs in the presence of the appropriate $Tp^{x}M$

[237] a) Choi, J. Y.; Borch, R. F. *Org. Lett.* **2007**, *9*, 215-218. b) Sehgal, R. K.; Almassian, B.; Rosenbaum, D. P.; Zadrozny, R.; Sengupta, S. K. *J. Med. Chem.* **1987**, *30*, 1626-1631. c) Xu, J. *Tetrahedron: Asymmetry* **2002**, *13*, 1129-1134.

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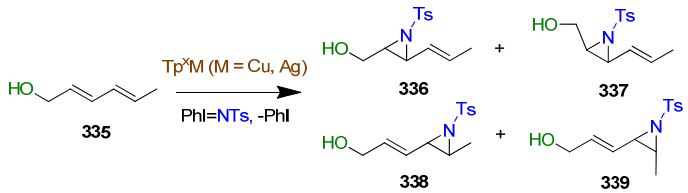
catalyst might afford two different aziridines from a regioselective point of view, each of them with a *cis* or *trans* geometry (compounds **336-337**, **338-339**) (Scheme 75). Aziridines **336** and **337** could be formed by nitrene addition to the double bond neigbouring to the hydroxyl group, whereas aziridines **338** and **339** would result from the addition to the double bond close to the methyl group.



Scheme 75. Possible products resulting from aziridination of *trans,trans*-2,4-hexadiene-1-ol with Tp^xM catalysts (M = Cu, Ag) using PhI=NTs as the nitrene source.

In a first series of experiments, several Tp^xCu complexes were employed as catalysts in the reaction of the diene with PhI=NTs. The results are shown in Table 23. $Tp^{Ph,4Et}Cu$ (Table 23, Entry 1), $Tp^{ClPh,Br2}Cu$ complex (Table 23, Entry 2) and Tp*Cu (Table 23, Entry 3) showed less activity in the aziridination of alcohol **335** than $Tp^{Br3}Cu$ (Table 23, Entry 4), which afforded full conversion. So, the four tested copper complexes afforded variable conversions into aziridines in the range 60-99% (based in initial PhINTs) without the observation of diaziridination products. In agreement with the obtained results in the aziridination of allylic alcohol, the most active catalyst was $Tp^{Br3}Cu$. However, the diene tested was more reactive than simple alkenes giving quantitative conversion and aziridines were exclusively formed.

In all cases, regioselection towards the internal aziridine (**336**+**337**) was high (81-86%). Unfortunately, the copper catalysts induce also a certain degree of inversion of the initial *E* configuration of the olefin, leading to final *trans:cis* mixtures in the interval from 1:1 to 2:1. This is in agreement with previous studies in which it is proposed that the aziridination reaction may occur throughout step-wise or concerted mechanisms (Scheme 76).[238] If it takes place via concerted

[238] a) Vedernikov, A. N.; Caulton, K. G. *Org. Lett.* **2003**, *5*, 2591-2594. b) Brandt, P.; Södergren, M. J.; Andersson, P. G.; Norrby, P.-O. *J. Am. Chem. Soc.* **2000**, *122*, 8013-8020. c) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem Soc.* **1995**, *117*, 5889-5890.

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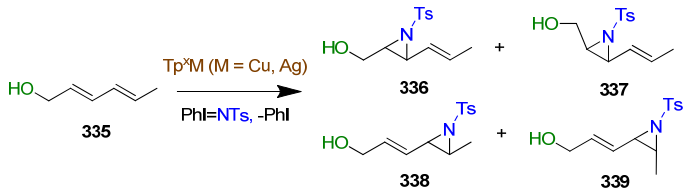
mechanism, retention of the configuration of alkene will be observed in that process.

Table 23. Conversions and selectivities of the reaction of *trans,trans*-2,4-hexadiene-1-ol with Tp^xCu catalysts using PhI=NTs as nitrene source[a]



Entry	Catalyst	Conv. (%)[b]	Regiosel.[b] (336+337):(338+339)	Ratio[b] 336:337
1	$Tp^{Ph,4Et}Cu$	60	83:17	60:40
2	$Tp^{ClPh,Br2}Cu$	80	81:19	51:49
3	$Tp^{*}Cu$	67	82:18	66:34
4	$Tp^{Br3}Cu$	>99	86:14	66:34

[a] [cat]:[PhINTs]:[**325**] = 1:20:30, referred to 0.0125 mmol of catalyst, 5% mol catalyst loading. Reaction time 8h in all cases. $TsNH_2$ accounted for 100% initial PhINTs not converted into aziridines. [b] Determined by ^1H NMR.

On the contrary, if the mechanism works through radical intermediates, the cyclization step could occur without losing the initial configuration of alkene or by a rotation process, which involves the formation of the product with the contrary configuration of the starting material. The problem of the formation of *cis*-vinylaziridines could be explained due to the fact that *cis*-vinylaziridines are thermodynamically more stable than *trans*-vinylaziridines. The problem of the formation of *cis*- and *trans*-vinylaziridines mixtures had been solved by isomerisation with Pd-catalyst to afford the *cis*-vinylaziridines.[239]

[239] a) Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 999-1015. b) Ibuka, T.; Mimura, N.; Ohno, H.; Nakai, K.; Akaji, M.; Habashita, H.; Tamamura, H.; Miwa, Y.; Taga, T.; Fujii, N. ; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2982-2991.

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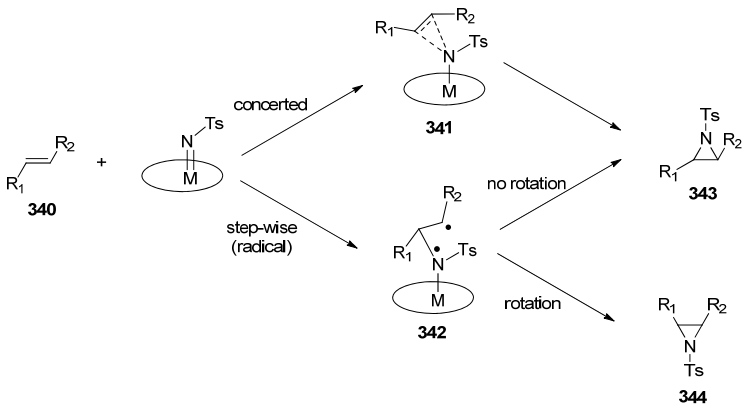

Scheme 76. Proposed mechanisms for the aziridination reaction.[240]

However, it is worth mentioning that in spite of the low selectivities obtained, the nitrene moiety was exclusively added to the double bonds, remaining the hydroxyl group undisturbed along the process.

In order to prove the possible formation of radical species the reaction was carried out in the presence of different amounts of BHT. However, in all cases (from 0.25 to 1 eq. of the BHT) the stereoselectivity was identical to the observed without using BHT; although the formation of non-desired and non-identified products was observed.

Then, $Tp^{x}Ag$ catalysts were tested under the same conditions tested for the copper catalyts.[204] Interestingly, when the aziridination reaction was carried out using silver catalyst, $Tp^{*,Br}$ and Tp^{*}, only *trans* aziridines were observed and they gave nearly quantitative conversions (Table 24, Entries 1,2). However, unexpectedly, initial experiments with the complex bearing the Tp^{Br3} ligand provided very low yields in aziridines (Table 24, Entry 3).

The first three attemps showed in Table 24 were performed using a 5% of catalyst. An increase in catalyst (7%) led no variation in the regioselectivity, and excellent stereoselectivity was also obtained (Table 24, Entry 4). The catalyst loading was then decreasd to 2.5 and 1.25% and the same results in terms of

[240] Proposed mechanism based on: Simonato, J.-P.; Pécaut, J.; Scheidt, W.R; Marchon, J.-C. *Chem Commun* **1999**, 989-990.

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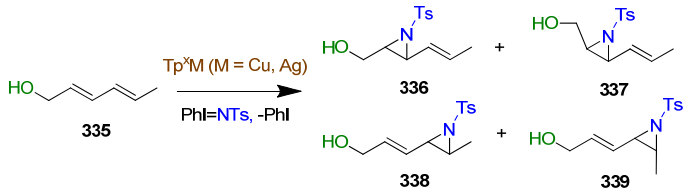
regio- and stereoselectivity were obtained (Table 24, Entries 5 and 6, respectively). The excellent performance of the $Tp^{*,Br}$-based silver catalyst allowed to decrease the relative amount of catalyst to 0.5% without loss of activity (Table 24, Entry 7).

Table 24. Conversions and selectivities of the reaction of *trans,trans*-2,4-hexadiene-1-ol with $Tp^{x}M$ catalysts using PhI=NTs as nitrene source[a]



Entry	Catalyst	Catalyst loading	Conv. (%)[b]	Regioselectivity[b] (336+337)/(338+339)	*trans*:*cis* ratio (336 :337) [b]
1	Tp*Ag	5	>95	90:10	>98:<2[c]
2	$Tp^{*,Br}$Ag	5	>99	90:10	>98:<2[c]
3	Tp^{Br3}Ag	5	<5	--	--
4	$Tp^{*,Br}$Ag	7	>99	90:10	>98:<2[c]
5	$Tp^{*,Br}$Ag	2.5	>99	89:11	>98:<2[c]
6	$Tp^{*,Br}$Ag	1.25	>99	88:12	>98:<2[c]
7	$Tp^{*,Br}$Ag	0.5	>99	89:11	>98:<2[c]
8	$Tp^{*,Br}$Ag	0.1	80	89:11	>98:<2[c]
9	$Tp^{*,Br}$Ag[d]	0.5	>99	88:12	>98:<2[c]

[a] [cat]:[PhINTs]:[**335**] = 1:20:30, referred to 0.0125 mmol of catalyst, 8h, room temperature. $TsNH_2$ accounted for 100% initial PhINTs not converted into aziridines. [b] Determined by ^1H NMR. [c] *cis* isomer not detected. [d] [cat]:[PhINTs]:[**335**] = 1:200:200, referred to 0.00125 mmol of catalyst, 0.5% catalyst loading, ratio diene:PhINTs = 1:1.

Only when a 0.1% of catalyst was employed, the conversion dropped to 80% (Table 24, Entry 8). All these results were obtained with PhINTs:diene initial mixtures of 1:1.5. Remarkably, the use of a 0.5% of catalyst loading (Table 24, Entry 9) provided quantitative formation of aziridines, and a ca. 9:1 mixture of

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regioisomers (**336**:**338**) and complete retention of stereochemistry. This is important since usually an excess of the olefin with respect to the nitrene precursor was employed with this methodology, a drawback when applying the procedure to more elaborated unsaturated substrates.

In conclusion, diene **335** was aziridinated to afford vinyl aziridine **336** with excellent regio- and stereoselectivity and in a quantitative way by using 0.5% catalyst loading of $Tp^{*,Br}Ag$, and avoiding the use of an excess of the nitrene source.

3.3. Study of the effect of hydroxyl protecting groups in the regioselectivity of the aziridination of dienes

It is known that the presence of a hydroxyl group in the substrate can direct the stereoselectivity of functionalizing alkenes for reactions such as epoxidation, dihydroxylation or cyclopropanation.[241] In this sense, we were interested to confirm if the hydroxyl group was the responsible of the high regioselectivity observed in the aziridination of diene **335**. With this purpose we prepare *O*-protected dienes **345** and **346** bearing acetyl or benzyl groups, respectively (Table 25).

The obtained results indicated that these substrates gave aziridines in lower conversions and, more interestingly, with a substantial decrease in the regioselectivity. Thus, aziridination of the acetyl derivative **345** afforded a mixture of aziridines in a 77% of conversion using $Tp^{Br3}Cu$. The regioselectivity as (**347**+**349**)/(**351**+**353**) ratio was 78:22 and the stereoselectivity *trans:cis* in the major regioisomer was 62:38 (Table 25, Entry 1). Starting from benzyl ether **346** the mixture of aziridines was obtained in an 80% of conversion and the regioselectivity, **348+350** *versus* **352+354**, decreased to 65:35 (Table 25, Entry 3) observing a similar ratio between *trans* and *cis* aziridines. Therefore, the protection of the hydroxyl group led to significant decrease of regioselectivity, and the stereoselectivity was in agreement with the isomerisation of initial configuration observed previously when copper catalyst were used.

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[241] Hoveyda, A. H.; Evans, D. E.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370 and references cited therein.

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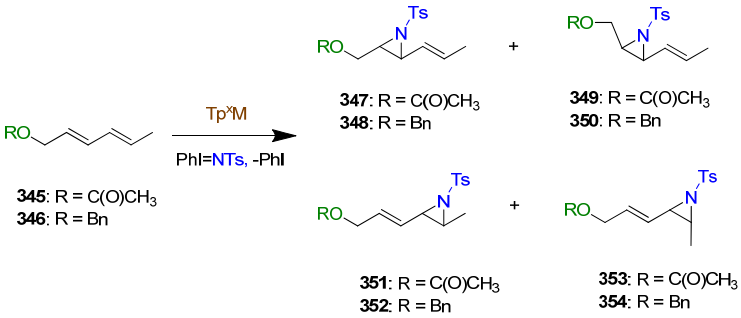
When Tp*,^{Br}Ag was used in the aziridination of acetyl derivate **245** a mixture of the aziridines was also formed with a 70:30 regioselectivity and a 60% of conversion (Table 25, Entry 2). Aziridination of benzylic ether **346** afforded the mixture of aziridines with a 60:40 ratio between the two regioisomers (Table 25, Entry 4). It is important to underline that in both cases silver catalyst showed an excellent stereoselectivity because only *trans* aziridines were observed (Table 25, Entries 2 and 4).

Table 25. Conversions and selectivities of the reaction of 1-*O*-protected-*trans,trans*-2,4-hexadiene with Tp^{x}Ag catalysts using PhI=NTs as nitrene source[a]

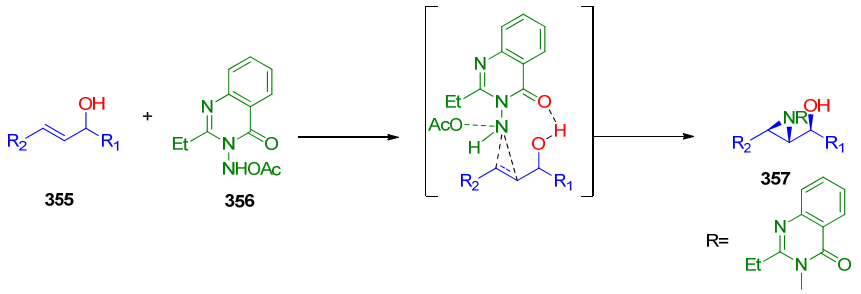


Entry	Catalyst	Substrate	Conv. (%)[b]	Regioselectivity[b]	*trans*:*cis* ratio[b]
1	Tp^{Br3}Cu	**345**	77	78:22[c]	62:38[e]
2	Tp*,^{Br}Ag	**345**	60	70:30[c]	>98:<2[e,f]
3	Tp^{Br3}Cu	**346**	80	65:35[d]	58:42[g]
4	Tp*,^{Br}Ag	**346**	66	60:40[d]	>98:<2[f,g]

[a] [cat]:[PhINTs]:[alkene] = 1:20:30, referred to 0.0125 mmol of catalyst, 5% catalyst loading. Reaction time is 8h in all cases. $TsNH_2$ accounted for 100% initial PhINTs not converted into aziridines. [b] Determined by ^{1}H NMR. [c] As (**347**+**349**):(**351**+**353**) [d] As (**348**+**350**):(**352**+**354**). [e] As **347**:**349**. [f] *cis* isomer was not detected. [g] As **348**:**350**.

Atkinson has documented that in the aziridination of allyl alcohols with (3-(acetoxyamino)-2-ethylquinazolin-4(3H)-one (**356**) the aziridine *syn* to the alcohol is obtained with a highly stereoselectivity (Scheme 77). The director effect exerted by the hydroxyl group is more important than the observed in the

epoxidation reaction using *m*CPBA.[242] These studies, together with more recent studies[243] justify the high stereoselectivity by the coordination in the transition state of the hydroxyl to the electron-rich carbonyl group, which directs the stereoselectivity of the process.[244]



Scheme 77. Transition-state for the hydroxyl directed aziridination proposed by Atkinson[242]

In our case, we propose that the regiocontrol exerted by substrate is a consequence of the interaction between the hydroxyl group and the sulfonyl group from the nitrene source (Scheme 78). This interaction could stabilize the transition state providing a preferred pathway to the regioisomers **336-337**). Theoretical calculations in order to explain these results are currently under study by F. Maseras (ICIQ).

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242 a) Atkinson, R. S.; Kelly, B. *J. Chem. Soc., Chem. Commun.* **1988**, 624-625. b) Atkinson, R. S.; Kelly, B. J.; McNicolas, C. *J. Chem. Soc., Chem. Commun.* **1989**, 562-564.

243 a) Atkinson, R. S.; Williams, P. J. *J. Chem. Soc., Perkin. Trans. 1* **1996**, 1951-1959. b) Atkinson, R. S.; Ulukanli, S.; Williams, P. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2121-2128. c) Cakici, M.; Karabuga, S.; Kilic, H.; Ulukanli, S.; Sahin, E.; Sevin, F. *J. Org. Chem.* **2009**, *74*, 9452-9459. d) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519-1559. d) Atkinson, R. S.; Fawcett, J.; Russell, D. R.; Williams, P. J. *J. Chem. Soc., Chem. Commun.* **1994**, 2031-2032.

244 a) Coote, S. C. ; O'Brien, P. ; Whitwood, A. C. *Org. Biomol. Chem.* **2008**, *6*, 4299-4314. b) Caine, D.; O'Brien, P.; Rosser, C. M. *Org. Lett.* **2002**, *4*, 1923-1926.

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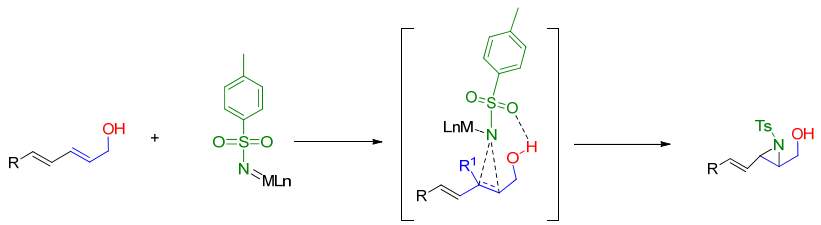


Scheme 78. Proposed intermediate to explain the regioselectivity observed in aziridination of dienes

3.4. Scope of the reaction

Given this unprecedented result for a metal-catalyzed diene aziridination reaction, we decided to investigate the scope of this process, using different dienes **358-363** and **315** shown in Figure 20. These substrates could inform us about the effect of the substitution (products **358**, **359**, **360**, **361** and **315**); the Z configuration (**362**) or the alcohol location (**363**) in the diene framework on the actitivity, regioselectivity and stereocontrol in the aziridination process.

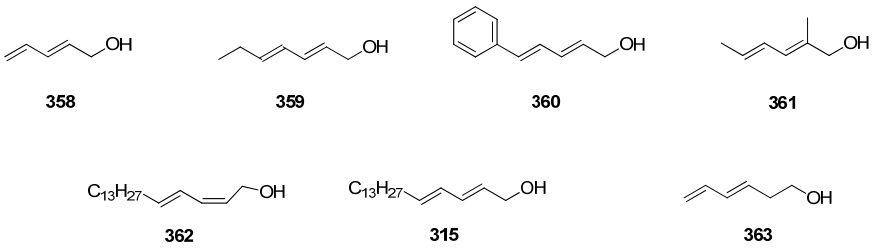
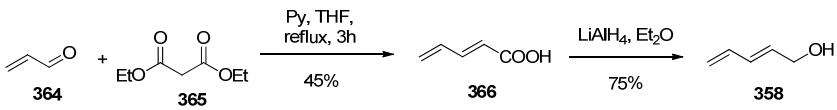


Figure 20. Dienes studied in the aziridination with the catalyst $Tp^{*,Br}Ag$

Compound **358** was prepared from a condensation between acroleine (**364**) and diethylmalonate (**365**), followed by decarboxylation to give compound **366** in a low yield (45%). Subsequent reduction with $LiAlH_4$ afforded the desired product **358** in a 75% yield (Scheme 79).[245]



Scheme 79. Preparation of compound **358**

[245] Linder, J.; Blake, A. J.; Moody, C. *Org. Biomol. Chem*, **2008**, *6*, 3908-3916.

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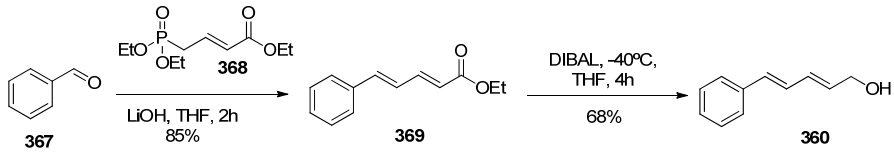
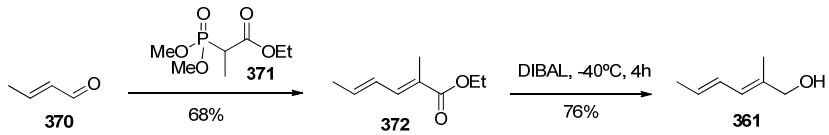
Wittig-Horner olefination of benzaldehyde **367** with stabilized phosphonate **368** in the presence of LiOH gave unsaturated ester **369** in a 85% yield. The ester was reduced to 2,4-dienen-1-ol **360** with DIBAL at -40ºC in a 68% yield (Scheme 80).[246]



Scheme 80. Preparation of compound **360**

Branched diene **361** was obtained in a 76% yield from the reduction of the corresponding ester **372**, which was prepared by an olefination reaction between aldehyde **370** and methylphosphonate **371** (Scheme 81).



Scheme 81. Synthesis of branched diene **361**

Hydrozirconation of alkyne **373** followed by treatment with iodine gave vinyl iodide **374** in a 86% yield. Sonogashira coupling between the vinyl iodide **374** and propargyl alcohol gave the enyne **375**, which was reduced under hydrogen with Lindlar-quinoline poisoned catalyst to afford diene **362** in a 84% yield (Scheme 82).

[246] Kim, D. D.; Lee, S. J.; Beak, P. *J. Org. Chem.* **2005**, *70*, 5376-5386.

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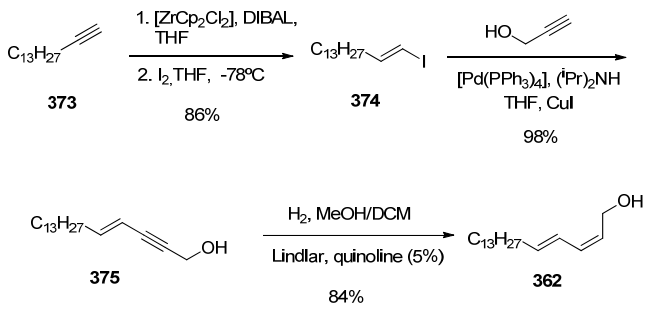
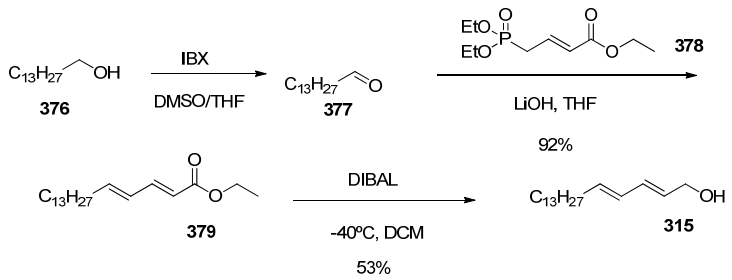


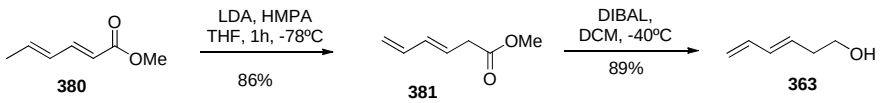
Scheme 82. Synthesis of diene **362**

1-tetradecanol (**376**) was reacted with IBX in DMSO/THF at room temperature to afford tetradecanal (**377**), which was reacted with the Wittig reagent **378** in presence of LiOH to provide ester **379** in a 92% yield. Reduction of **379** with DIBAL at -40ºC affords the desired diene **315** (Scheme 83).[247]



Scheme 83. Synthesis of diene **315**

Homoallylic diene **363** was synthesized in 89% yield by a reduction of the ester **382** with DIBAL at -20ºC for 2h. Ester **381**, in turn, was obtained in a 86% yield by rearrangement in basic conditions of the ester **380** (Scheme 84).[248]



Scheme 84. Synthesis of compound **363**

The aziridination of **358-362** and **315** was studied in the presence of silver-based catalysts, with a 5% catalyst loading and with equimolar mixtures of

[247] a) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514-2517.
[248] Taber, D. F.; Guo, P.; Guo. N. *J. Am. Chem. Soc.* **2010**, *132*, 1179-11182.

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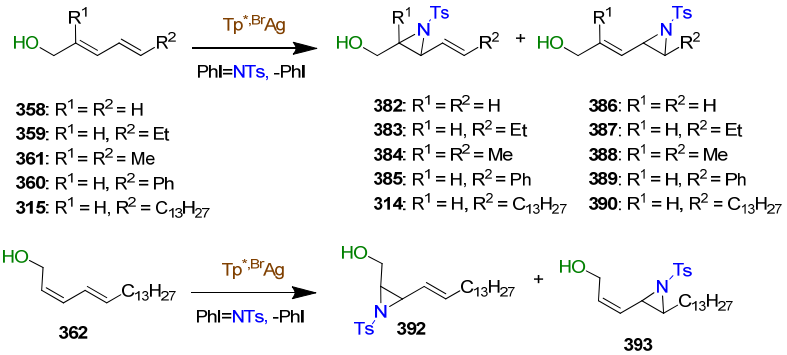
the dienes and PhINTs. The results are summarized in Table 26. In summary, products **358-362** and **315** afforded preferently the aziridination towards the hydroxyl terminal. The effect of the substituient affected slightly the regioselectivity, observing that the presence of the more hindered phenyl group at the terminal position improve it. In all cases the diastereoselectivity was excellent when silver was used, obtaining in all cases a *trans*:*cis* ratio = >98:<2.

Table 26. Scope of the diene aziridination reaction using substrates **3586-362** and **315** using Tp*,^{Br}Ag as catalyst.[a]



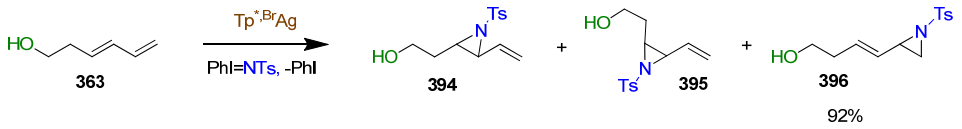
Entry	Diene	Product	Conv (%)[b]	Regioselectivity[b]	*trans*:*cis* ratio (%)[b,c]
1	R^1=R^2=H (**358**)	**382/386**	>99	88:12	>98:<2[d]
2	R^1=H, R^2=Et (**359**)	**383/387**	>99	85:15	>98:<2[d]
3	R^1=R^2=Me (**361**)	**384/388**	>99	86:14	>98:<2[d]
4	R^1=H, R^2=Ph (**360**)	**385/389**	>99	93:7	>98:<2[d]
5	R^1=H, R^2=$C_{13}H_{27}$ (**315**)	**314/390**	>99	86:14	>98:<2[d]
6	**362**	**392/393**	>99	90:10	<2:>98[e]

[a] [cat]:[PhINTs]:[diene] = 1:20:20, referred to 0.0125 mmol of catalyst, 4h, room temperature. $TsNH_2$ accounted for 100% initial PhINTs not converted into aziridines. [b] Determined by ^{1}H NMR. [c] Ratio *trans:cis* for the major aziridine. [d] *cis* isomer not detected. [e] *trans* isomer not detected.

(2*Z*,4*E*)-octa-2,4-dien-1-ol (**362**) afforded exclusively the *cis* aziridine without isomerisation of the initial configuration of the alkene. This result is in agreement with the fact that c*is*-vinylaziridines are more stable compound than *trans*-vinylaziridines. Both, Cu- or Ag-based systems provide exclusively the expected *cis*-vinylaziridine.

The results are in agreement with those obtained with **335**, and can be summarized as follows: (i) quantitative conversions into aziridines were obtained in all cases, even with the sterically hindered diene **361** (ii) the product derived from the aziridination of the double bond vicinal to the hydroxyl group was preferred in all cases, regioselection being within the interval 85:15 to 93:7; (iii) complete retention of configuration appeared as a constant in all the experiments. It is worth mentioning that when the *cis:trans* diene **362** was employed, aziridination of the internal *cis* double bond was preferred (due to its vicinity to the OH group), and such geometry was maintained in the resulting aziridine, a fact that indicates that the reaction is stereospecific.

Excepcionally, the aziridination of (*E*)-hexa-3,5-dien-1-ol (**363**), as an exemple of homoallylic diene-1-ol afforded exclusively the aziridination of the terminal double bond in a high regioselectivity (>98:<2), obtaining compound **396** in a 92% yield. This result shows that the excellent regioselectivity obtained in allylic alcohols cannot extended to homoallylic alcohols. In this case, the major aziridine is the result of the reaction at the less hindered position.



Scheme 85. Aziridination of **363**

Substrate-directed reaction is a well-known procedure; but the number of examples related to aziridination reactions is scarce. We have proposed that the mentioned effect could explain the high regiocontrol in diene aziridination. In addition, this effect would be studied in alkenes which contain one double bond in allylic position and another double bond with the same substitution non conjugated and far away from the hydroxyl group. To study this effect we used

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terpenes (Figure 21) such as geraniol (**397**) and nerol (**398**) which have been extensively studied in epoxidation processes but not in the reaction of aziridination.

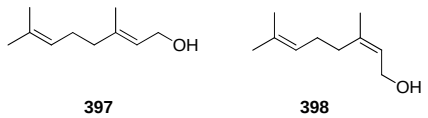
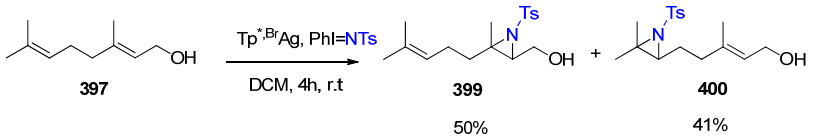


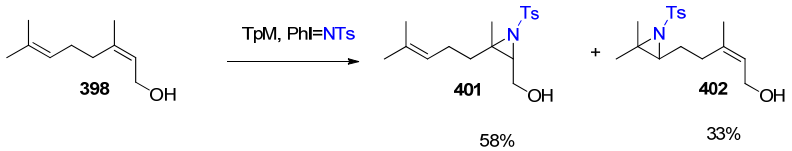
Figure 21. Structure of geraniol (**397**) and nerol (**398**)

The aziridination reaction from geraniol (Scheme 86) gave quantitative conversion (>99%) using $Tp^{*,Br}Ag$ and maintaining the reaction for 4h. But, unexpectedly, aziridines **399** and **400** were obtained in poor regioselectivity 1.1:1 (**399**:**400** ratio) in a 50% and 41% yield, respectively.



Scheme 86. Aziridination of geraniol

Nerol **398** (Scheme 87), an isomer of geraniol with Z-configuration, was used as a substrate and also a quantitative conversion (>99%) was obtained. Compounds **401** and **402** were isolated in a 58% and 33% yield, respectively.



Scheme 87. Aziridination of nerol

In order to test the effect of a protected hydroxyl group, the reaction was performed using geranyl acetate **402** as a substrate (Scheme 88). The aziridination using PhINTs as a nitrene source in dichloromethane using $Tp^{*,Br}Ag$ afforded after 5h compound **405** in a 83% yield with an excellent regioselectivity (ratio **404:405** = <2:>98).

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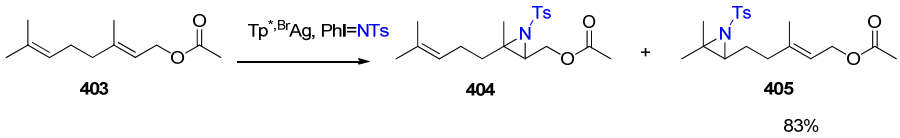
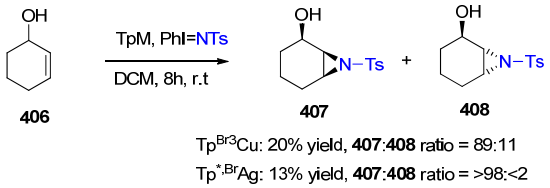


Scheme 88. Aziridination of geranyl acetate

These results confirm that the hydroxyl group partially direct the aziridination reaction, but the effect it is not strong enough to reverse the selectivity. This effect is stronger when allylic conjugated dienes were employed as substrates.

$Tp^{Br3}Cu$ and $Tp^{*,Br}Ag$ catalysts were also used in the aziridination of 3-cyclohexen-1-ol **406** (Scheme 89). The conversion in both cases was low and provided the aziridination product in a 20 and 13% yield, respectively. The *syn*:*anti* ratio was 89:11 when $Tp^{Br3}Cu$ was used, meanwhile $Tp^{*,Br}Ag$ afforded exclusively the *syn* isomer and the *anti* isomer was not detected by ^{1}H NMR (*syn:anti* >98:<2) . These results also support that hydroxyl group directs the aziridination.



Scheme 89. Aziridination of 2-cyclohexenol **406**

3.5. Ring opening reaction of vinylaziridines. Application to the synthesis of (+/-)-Sphingosine

Regiocontrolled ring-opening reaction of C-substituted aziridines constitutes a useful synthetic tool for the preparation of a large variety of biologically important compounds.[249] Aziridine ring are commonly opened using

[249] a) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, 107, 2080-2135. b) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194-206. c) Tanner, D. *Pure Appl. Chem.* **1993**, *65*, 1319-1328. d) Wipf, P.; Uto, Y. *Tetrahedron Lett.* **1999**, *40*, 5165-5169. e) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701-2743. f) Hodgson, D. M.; Gibbes, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361.

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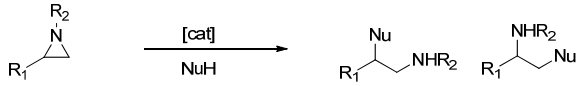
Lewis acids such as $Cu(OTf)_2$, $CeCl_3$, $LiClO_4$, $ZnCl_2$, $Sn(OTf)_2$ or $BF_3{\cdot}OEt_2$ (Scheme 90). [250] The reactions are dominated by the electrophilic nature of these heterocycles, and include a wide range of nucleophiles to give β-substituted amines.[251] Nucleophiles such as N_3, ROH, RSH, amines and halides have been commonly used, whereas the use of carbon based nucleophiles remains quite limited.[252]



Scheme 90. Ring opening aziridines

Vinyl aziridines are increasingly being exploited as versatile building blocks for the synthesis of biological and synthetically important compounds, thanks to their high reactivity and ability to function as carbon electrophiles. Elaboration through rearrangement, including ring-expansion, isomerization and cycloadditions have been studied providing direct access to structural motifs in synthesis. Meanwhile, ring-opening reactions of vinylaziridines[253] can produce a variety of functionalized amine derivatives[254] such as sphingosines,[255] allyl amines,[256] and (*E*)-alkene dipeptide isosteres.[257] Vinyl aziridines can be opened through S_N2 process by the attack of the nuclophile at the allylic position, or by a S_N2' process (Scheme 91).[258] Transition metal catalyzed openings have been reported to afford commonly the S_N2' product. Thus, borylative opening using Ni[259] and Pd[260] has been reported to afford the corresponding borane derivatives

250 Ghorai, M. K.; Das, K.; Shukla, D. *J. Org. Chem.* **2007**, *72*, 5859-5862.

251 Hu, X. E. *Tetrahedron* **2004**, *60*, 2701-2743.

252 Pineschi, M. *Eur. J. Org. Chem.* **2006**, 4979-4988.

253 Cantrill, A. A.; Jarvis, A. N.; Osborn, H. M. I.; Ouadi, A.; Sweeney, J. B. *Synlett* **1996**, 847-849.

254 Harada, S.; Kowase, N.; Tabuchi, N.; Taguchi, T.; Dobashi, Y.; Dobashi, A.; Hanzawa, Y. *Tetrahedron* **1998**, *54*, 753-766.

255 a) Olofsson, B.; Khamrai, U.; Somfai, P. *Org. Lett.* **2000**, *2*, 4087-4089. b) Olofsson, B.; Somfai, P. J. *Org. Chem.* **2002**, *67*, 8574-8583.

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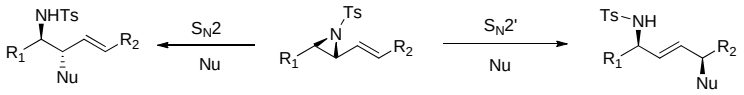
($X=BR_2$) and copper-alkylation have also been described.[261] The selective opening at the allylic position will afford to a series of compounds that can be converted into sphingosine or modified sphingosine at position 3. Both S_N2 and S_N2' process afford a set of products that can be transformed in highly functionalized synthons by functionalization of the double bond.



Scheme 91. Ring-opening to vinylaziridines

Vinylaziridines are difficult to purify by flash chromatography and we explored the ring opening aziridine **336** *in situ* using different S, N and O nucleophiles. Firstly, we explored the use of *O*-nucleophiles under acid conditions. Thus, the reaction was performed by using H_2O or MeOH with catalytic amounts of CAN, $CeCl_3$, $CuCl_2$, Amberlist-15, $BF_3{\cdot}OEt$, $Sn(OTf)_2$, montmorillonite and TFA as acids. In all cases a complex mixture of products was obtained probably because SN and SN' took simultaneously place. Other O-nucleophiles with acid properties such as PhOH and BzOH were tested but also a mixture of products was observed.

Then, we decided to open the vinylaziridine under basic conditions using strong nucleophiles (Scheme 92). Thus, vinylaziridine **336** was treated with KOH affording the amino diol **409** in a 68% yield over two steps (aziridination and ring opening). Other nucleophiles like NH_3 and PhSNa were also used achieving the respective 1,2-diamino **410** or 1,2-tioamino alcohol **411** in 64% and 46% yield, respectively. On the contrary, when NaN_3 was used as a nucleophile the only isolated product was the result of the ring-opening by S_N2' to afford **412** in a 62% yield.

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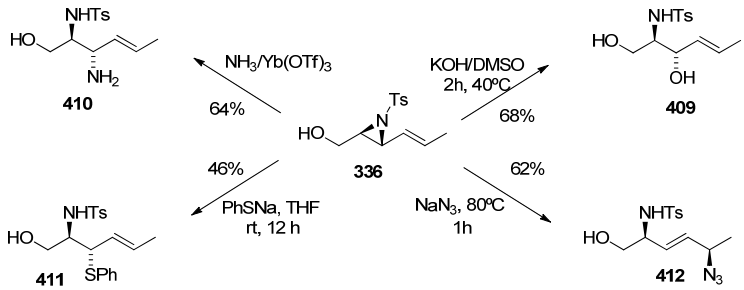
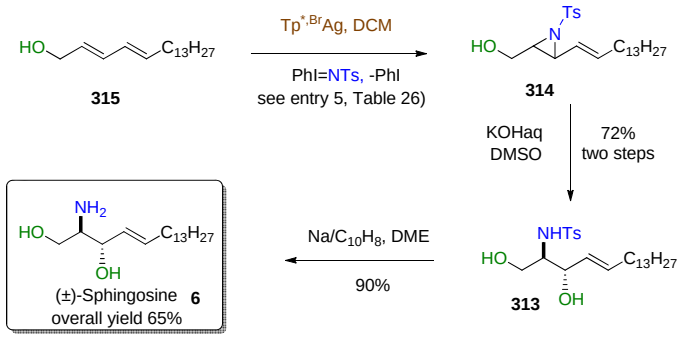


Scheme 92. Ring-opening reaction of aziridine **336**

Drived by our interest in developing new methods for the synthesis of aminoalcohols of biological interest,[262] we applied this methodology to the synthesis of (±)-sphingosine.[263] As shown in Scheme 93, diene **315** was employed as starting material for such purpose. Aziridination with PhINTs gave a mixture of aziridines in 86:14 ratio, being the major isomer that resulting from the reaction on double bond vicinal to the OH group. The final reaction mixture of aziridines was treated with KOH to induce ring opening and thus, the formation of the N-protected aminoalcohol **313** that was isolated and characterized. Further treatment of **313** with Na/naphthalene provided the targeted (±)-sphingosine in 65% isolated yield based on the starting diene **315**.



Scheme 93. Application of the diene aziridination methodology to the synthesis of (±)-sphingosine

262 a) Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Lett.* **2009**, *11*, 205-208; b) Morales-Serna, J. A.; Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Biomol. Chem.* **2008**, *6*, 4502-4504.

263 For a review about the synthesis of sphingosines see: Morales-Serna, J. A.; Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Curr. Org. Chem.* **2010**, *14*, 2483-2521.

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As conclusion, we have found that several complexes containing the $Tp^{x}M$ fragment (M = Cu, Ag) catalyze the aziridination of conjugated dienes bearing an allylic OH group, affording vinyl aziridines with a low catalyst loading and using stoichiometric mixtures of reactants (the diene and PhI=NTs as the nitrene source). The $Tp^{*,Br}Ag$ catalyst was found to be highly regioselective toward the aziridination of the double bond vicinal to the hydroxyl end as well as highly stereospecific with an array of dienes, including a precursor of (±)-sphingosine. The results presented herein makes of the silver-catalyzed aziridination of dienes a promising synthetic tool in organic synthesis. Work directed to understand the mechanism that governs this transformation as well as to develop the asymmetric version of this catalytic system is currently underway in our laboratories.

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Conclusions

CHAPTER 6

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The present work aimed to develop new synthetic procedures for obtaining sphingoid bases. Two main synthetic procedures have been explored: a) an enantioselective synthesis of sphingoid bases, which is based in three main synthetic procedures, i) enantioselective allylic amination of butadiene monoepoxide, ii) stereoselective cross-metathesis, and iii) stereoselective dihydroxylation; and b) a procedure based on a regio- and stereoselective aziridination of conjugated dienes, followed by regioselective ring-opening of the resulting vinylaziridine. More detailed conclusions follows:

Procedure a: Enantioselective synthesis of sphingoid bases

The three key steps of this methodology have been optimized:

i) the Pd-catalyzed DYKAT process from butadiene monoepoxide was carried out following the Trost procedure.

ii) cross-metathesis using a second generation Grubbs catalyst afforded the *E*-alkene in excellent yield and stereoselectivity.

iii) the dihydroxylation reaction was optimized and it was found that the catalytic system OsO_4/$(DHQ)_2PYR$ provided a full conversion and a high diastereoselectivity.

The resulting compounds from the dihydroxylation were effectively transformed into the following natural products of biological interest:

i) D-*erytrho*-sphingosine.

ii) D-*ribo*-phytosphingosine, and their 4-mercapto and 4-azido analogues.

iii) the natural anhydrosphingosine Jaspine B and its 2-, 3-, and 2,3-stereoisomers.

In order to get D-*ribo*-phytosphingosine with the configuration of the natural product, it was necessary to invert the configuration at C-4 of the product resulting from the dihydroxylation. This process required three additional synthetic steps that would not be necessary if the cross-metathesis reaction would afford the alkene of *Z* configuration.

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In this way, an efficient method for preparing exclusively *Z*-1,2-disubstituted allyl amines using Z-selective cross-metathesis catalyzed by Mo-catalyst has been studied. Several modifications in the catalyst and the process were studied, finding that the Mo-adamantyl-tetrahydroaryloxide is the most efficient catalyst for that purpose. The presence of vacuum to remove ethylene is necessary to obtain high conversions. This methodology is completely new and opens up interesting possibilities in organic synthesis. The methodology was applied to the synthesis of D-*ribo*-phytosphingosine affording the shortest enantioselective method described until now to afford the target compound.

Procedure b: Regio- and stereoselective aziridination of non-symmetric dienes.

An efficient, regioselective and stereospecific method of aziridination of dienes affording vinyl aziridines has been developed. The main characteristics of this method are the following:

i) $[Tp^{*,Br}Ag]$ resulted to be the more active catalysts providing exclusively aziridines *trans* from *E*-alkenes, and aziridines *cis* from *Z*-alkenes, which indicates that the reaction is stereospecific.

ii) The regioselectivity was driven by the OH group, the aziridine resulting from aziridination of the double bond close to the OH being mainly obtained.

iii) The process is highly regioselective for conjugated dienes and for homoallylic alcohols, but the regioselectivity decreases when the dienes are not conjugated.

iv) catalyst loading as low as 0.5% can be used to obtain quantitative conversions.

v) stoichiometric mixtures of diene and PhINTS (the nitrene source) were used.

Vinylaziridines were regioselectively opened by S_N2 process, by attack at the allylic position. Selective S_N2' processes have been also observed using azide as a nucleophiles. This procedure has also been applied to the synthesis of racemic sphingosine.

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Experimental Section

CHAPTER 7

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1. General Methods

All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and dimethylformamide (DMF) were dried using a solvent purification system (Pure SOLV system-4®). Toluene was purified using standard procedure.[264]

^1H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 (400 MHz and 100.6 MHz respectively) or Varian 400-MR spectrometer in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm ^1H, 77.23 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program (Varian®). ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Optical rotations were measured at room temperature in a Perkin-Elmer® 241 MC apparatus with 10 cm cells. Elemental analysis (C, H, N, S) were performed on a Carlo Erba® EA 1108 Analyser in the Servei de Recursos Científics (SRCiT-URV). IR spectra were recorded on a JASCO FT/IR-600 plus Fourier Transform Infrared Spectrometer ATR Specac Golden Gate. Melting points, determined with Reichert apparatus, are uncorrected.

Reactions were monitored by TLC carried out on 0.25 mm E. Merck® silica gel 60 F_{254} glass or aluminium plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in ethanol/H_2SO_4 (15:1) and basic solution of potassium permanganate. Flash column chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh). Radial chromatography was performed on 1 or 2 mm plates of Kieselgel 60 PF_{254} silica gel, depending on the amount of product. Flash column chromatography (FCC) was performed using flash silica gel (32–63 μm) and using a solvent polarity correlated with TLC mobility.

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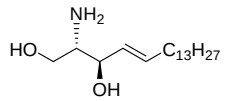
2. Compound characterization

(*2S,3R*)-*(4E)*-*2*-aminooctadec-4-ene-1,3-diol (*D-erythro-sphingosine*) **(6)**



6

Method A (Enantioselective procedure, Chapter 3): Compound **209** (0.240 g, 0.36 mmols) was disolved in THF (2 mL) and a solution of TBAF (0.5 mL, 0.47 mmols) in THF was added under argon. The mixture was stirred at rt for 2 hours. The crude was filtered on Celite and the solvent was evapored, then the crude was dissolved in methanol (2 mL), hidrazine (0.54 mL, 0.54 mmol) was added, and the resulting solution was refluxed under argon for 6 hours. The reaction crude was concentrated, dissolved in $CHCl_3$, and filtered over Celite, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography ($CHCl_3$, MeOH, NH_4OH, 66:12:2). The obtained solid was dissolved in $CHCl_3$ and filtered through a pad of Celite to remove the residual silica. The filtrate was concentrated to give sphingosine **6** (0.087 g, 87 %) as a white solid.

Method B (Diastereoselective procedure, Chapter 5): Naphtalene (0.2 mmol, 1.5 mmol) was dissolved in dry DME (2 mL) and Na (0.03 mg, 1.1 mmol) was added under argon. The green solution was stirred at room temperature for 2 hours. Then, a solution of compound **313** (23 mg, 0.05 mmol) in DME (2 mL) was added at -78 ºC. The mixture was warmed gradually to -10ºC and it was stirred for 3 hours. It was diluted with water, the crude was extracted with diethyl ether and the combined organic layers were washed with NH_4Cl aqueous solution, water and brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude was purified by a short silica gel chromatography using dichloromethane:methanol:NH_4OH (94:6:1) to afford 10 mg of compound **6** (70%) as a white solid and 4 mg of compound **313** was recovered. The yield was 90 % based on consumed **313**.

$[\alpha]_D^{25}$= −1.6 (*c* 0.7, $CHCl_3$). **NMR ^{1}H** (400 MHz, $CDCl_3$): δ= 5.77 (dtd, 1H, *J* = 15.4, 6.8, 1.2 Hz), 5.48 (ddt, 1H, *J* = 15.4, 7.2, 1.6 Hz), 4.04 (t, 1H, *J* = 7.2 Hz),

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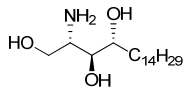
3.69 (dd, 1H, *J* = 10.4, 4.8 Hz), 3.62 (dd, 1H, *J* = 10.4, 5.8 Hz), 2.88 (td, 1H, *J* = 5.8, 4.8 Hz), 2.05 (dt, 2H, *J* = 7.2, 6.4 Hz), 1.74 (br s, 4H), 1.37 (t, 2H, *J* = 7.2 Hz), 1.32-1.26 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ= 135.2, 129.4, 76.9, 75.9, 64.6, 56.3, 32.6, 32.1, 29.9, 29.9, 29.9, 29.8, 29.7, 29.6, 29.4, 29.3, 22.9, 14.4. **ESI-HMRS** calcd for $C_{18}H_{28}NO_2$: 300.2903, found: 300.3106.

(*2S,3S,4R*)-*2*-aminooctadecane-1,3,4-triol (*D-ribo-phytosphingosine*) **(8)**



8

Method A (Chapter 3): Compound **210** (0.122 g, 0.18 mmols) was disolved in THF (2 ml) and a solution of TBAF in THF (0.3 mL, 0.28 mmols) was added. The resulting solution was stirred at rt for 2 hours. The reaction mixture was filtered over Celite and the solvent was removed under reduced pressure. The crude was dissolved in methanol (2 mL), hidrazine (0.54 mL, 0.27 mmols) was added and the mixture was refluxed under argon for 7 hours. The reaction mixture was concentrated and the residue was dissolved in $CHCl_3$, filtered and the organic layer was concentrated in vacuo. The solvent was evaporated and the residue was purified by column chromatography (CH_2Cl_2, MeOH, NH_4OH, 18:6:1). The obtained solid was dissolved in $CHCl_3$ and filtered through a pad of Celite to remove the residual silica. The filtrate was concentrated to give phytosphingosine (0.048 g, 89 %) as a white solid.

Method B (Chapter 4). Triol **312** (418 mg, 1.0 mmol) was dissolved in TFA/H_2O (20:2) and the solution was stirred at room temperature for 30 minutes. The solution was diluted with dichloromethane (10 ml) and then it was neutralized with saturated aqueous $NaHCO_3$ solution. The white solid was filtered and washed with H_2O to give phytosphingosine **8** as a white solid, which was recristlyzed with acetonitrile to afford 300 mg.

Mp = 81-83 ºC. **$[\alpha]_D^{25}$**= +9.2 (*c* 0.9, pyridine). **^{1}H NMR** (400 MHz, CD_3OD): δ= 3.75 (dd, 1H, *J* =10.8, 4.0 Hz), 3.53 (m, 2H), 3.34 (d, 1H, *J* = 6.0 Hz), 2.94 (d, 1H, *J* = 4.4 Hz), 1.74 (m, 1H), 1.55 (m, 1H), 1.36-1.28 (m, 24H), 0.90 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100.6 MHz, CD_3OD): δ= 76.6, 74.6, 64.3, 55.9, 34.9, 33.2,

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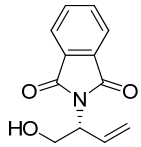
31.1, 31.0, 31.0, 30.9, 30.7, 26.8, 23.9, 14.6. **ESI-HMRS** [M+1] calcd for $C_{18}H_{40}O_3$: 318.3003, found: 318.3148.

2-(*R*)-*N*-phthalimido-3-bueten-1-ol (139)[98]



139

In a 250 mL flamed-dried flask, Na_2CO_3 (53 mg, 0.05 mmol), phthalimide (**120**) (1.47 g, 10 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (14.6 mg, 0.04 mmol) and *S*,*S* ligand **118** (94.6 mg, 0.12 mmol) were added under argon being the flask purged three times with argon. Then dry dichloromethane (80 mL) was added to the mixture and the solution was stirred 15 min at rt. Butadiene monoepoxide (810 μl, 10 mmol) was added in one portion and the resulting mixture was stirred at rt for 14h. The resulting mixture was concentrated and purified by flash chromatography, using 1:1 hexanes:ethyl acetate as a solvent, to afford 2.16 g of compound **139** (99%) as a white solid. An enantiomeric excess of 99% ee was determined by chiral HPLC (chiralpack OD, heptane:^{i}PrOH 90:10, 1 mlmin^{-1}, t_R(R) = 14.1 min and t_R(S) = 16.9 min).

$[\alpha]_D^{25}$ +65.9 (*c* 1, $CHCl_3$). **Mp** 60-63 ºC. **IR** (neat): 3527, 1763, 1702, 1656, 1609, 1467 and 1388 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.73 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.62 (dd, 2H, *J* = 5.6, 3.2 Hz), 6.06 (ddd, 1H, *J* = 17.6, 10.4, 7.2 Hz), 5.19 (ddd, 1H, *J* = 17.6, 1.2, 1.2 Hz), 5.18 (ddd, 1H, *J* = 10.0, 1.2, 1.2 Hz), 4.84 (m, 1H), 4.07 (ddd, 1H, *J* = 11.4, 8.4, 8.0 Hz), 3.86 (ddd, 1H, *J* = 11.4, 7.6, 4.6 Hz), 2.98 (dd, 1H, *J* = 8.0, 4.6). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.7, 134.3, 132.1, 131.9, 123.5, 119.0, 62.8, 56.1. **ESI-HRMS** [M+1] calcd for $C_{12}H_{12}NO_3$: 218.0817, found: 218.0813.

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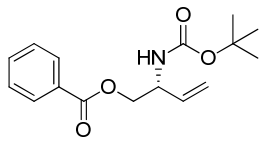
(*R*)-*tert*-Butyl-1-benzoyloxybut-3-ene-2-ylcarbamate (141)



141

Benzoylisocianate (0.13mL, 1mmol) was dissolved in *t*BuOH (1mL) and the mixture was stirred for 15 h at room temperature before the solvent was removed under vacuum to give a white solid (210mg, 95%) which was used without any further purification.

In a 25 mL flamed-dried flask under vacuum, benzoylimido carboxylate (0.6 g, 2.8 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (18.6 mg, 0.05 mmol) and *S*,*S* ligand **118** (118.6 mg, 0.15 mmol) were added under argon and the flask was purged three times with argon. Then dry dichloromethane (60 mL) was added to the mixture and the solution was stirred 30 min at rt. Butadiene monoepoxide (810 μl, 10 mmol) was added in one portion and the resulting mixture was stirred at 35 °C for 18h. The resulting mixture was concentrated and purified by flash chromatography using 87:13 hexanes:ethyl acetate as a solvent to afford 574 mg of compound **141** as a white solid (75%). The enantiomeric excess was 90% ee determined by chiral HPLC (chiralpack OD, heptane:^{i}PrOH 90:10, 1 mlmin^{-1}, $t_R(R) = 8.3$ min and $t_R(S) = 9.2$ min).

$[\alpha]_D^{25}$ +37.2 (*c* 1, $CHCl_3$). **Mp** 79-80 ºC. **IR** (neat): 3349, 1717, 1687, 1524, 1349, 1286, 1249, 1158, 1128, 1071, 708 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (d, 2H, *J* = 7.6 Hz), 7.57 (tt, 1H, *J* = 7.6, 0.8 Hz), 7.44 (dd, 2H, *J* = 7.6, 7.6 Hz), 5.88 (ddd, 1H, *J* = 17.2, 10.4, 5.2 Hz), 5.33 (ddd, 1H, *J* = 17.2, 1.6, 0.8 Hz), 5.25 (ddd, 1H, *J* = 10.4, 1.6, 0.8 Hz), 4.78 (brs, 1H), 4.61 (brs, 1H), 4.37 (d, 2H, *J* = 5.2 Hz), 1.43 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.6, 155.4, 135.0, 133.4, 130.0, 129.9, 128.6, 116.9, 79.9, 66.6, 52.0, 28.5. **ESI-HRMS** [M+23] calcd for $C_{16}H_{21}NO_4Na$: 314.1368, found: 314.1363.

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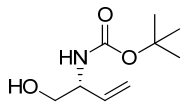
(*R*)-*tert*-Butyl-1-hydroxybut-3-en-2-ylcarbamate (142)

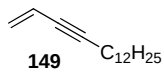


142

An aqueous solution of LiOH (0.4 mL, 0.6 mmol, 1M) and compound **141** (150 mg, 0.5 mmol) in THF (2 mL) was stirred at room temperature for 20 h. The crude was diluted with water, and it was extracted with dichloromethane. The combined organic layers were washed with brine, dried over ahydrous $MgSO_4$, filtered and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using 3:1 hexanes:ethyl acetate as a solvent to afford 93 mg of compound **142** as a colorless oil (99%).

$[\alpha]_D^{25}$ +21.6 (*c* 1, $CHCl_3$). **IR** (neat): 3329, 2978, 2931, 1687, 1456, 1392, 1367, 1167, 1071, 1051, 922 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.79 (ddd, 1H, *J* = 16.4, 10.4, 5.6 Hz), 5.25-5.17 (m, 2H), 5.06 (brs, 1H), 4.19 (brs, 1H), 3.66 (dd, 1H, *J* = 11.2, 4.4 Hz), 3.58 (dd, 1H, *J* = 11.2, 5.6 Hz), 2.96 (brs, 1H), 1.42 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.3, 135.8, 116.5, 80.0, 65.2, 54.8, 28.5. **ESI-HRMS** [M+1] calcd for $C_9H_{18}NO_3$: 188.1287, found: 388.1283.

1-Hexadecen-3-yn (149)



149

Method A (Elimination reaction from compound **157**). Compound **157** was added to a solution of BuLi (0.1 ml, 0.130 mmol, 1.6 M) in THF (2 ml) at 0ºC. The mixture was stirred for 14 h and then the solution was warmed at room temperature before it was quenched with ethyl acetate. Then water was added and the layers were separated. The aqueous phase was extracted with ethyl acetate and the combiend organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed, the residue was purified by flash chromatography using petroleum ether to give a colorless oil (73%).

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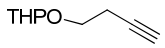
Method B (Sonogashira Coupling). Vinyl bromide (**158**) (4 ml, 4 mmol, 1M) was disolved in THF (20 mL) and CuI (0.04 g, 5 %) and $Pd(PPh_3)_2Cl_2$ (0.3 g, 10 %) were successively added, then freshly distilled Et_3N (6 ml) was added and the solution was stirred for 30 minutes at room temperature before 1-tetradecyn (**159**) (1.2 ml, 3.16 mmol) was added. The solution was stirred at room temperature for 8h before it was quenched with saturated NH_4Cl aqueous solution (10 mL). The aqueous phase was extracted with ethyl acetate (2 x 40 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was purified by flash chromatography using petroleum ether to give 0.81 g of compound **149** as beige oil (92 %).

IR (neat): 3202, 2920, 2855, 1610, 1455, 1380, 1330, 970, 910, 720 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ= 5.79 (ddt, 1H, *J* = 17.2, 10.6, 2.4 Hz), 5.55 (dd, 1H, *J* = 17.2, 2.1 Hz), 5.35 (dd, 1H, *J* = 10.6, 2.1 Hz), 2.29 (t, 2H, *J* = 7.2 Hz), 1.53 (m, 2H), 1.38 (m, 2H), 2.27 (m, 16 H), 0.87 (t, 3H, *J* = 6.3 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 125.5, 117.9, 91.4, 79.5, 32.2, 29.9, 29.8, 28.6, 29.6, 29.4, 28.9, 22.9, 22.9, 19.5, 19.4, 13.3. **ESI-HRMS** [M+23] calcd for $C_{15}H_{28}Na$: 243.2089, found: 243.2095.

1-[(2-tetrahydropyranyl)oxy]-3-butyn (154)



154

3,4-Dihydro-(*2H*)-pyrane (4 ml, 594 mmol) and 3-butyn-1-ol (**153**) (15 ml, 198 mmol) were disolved in anhydrous CH_2Cl_2 (150 ml), then camphorsulphonic acid (2.25 g, 9.9 mmol) was added and the solution was stirred at room temperatura for 4 h before the reaction was quenched with water (75 ml). The phases were separated and the aqueous phase was extracted with ^{t}BuOMe (2 x 100 ml). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using hexanes:ethyl acetate (5:1) to give 27.9 g of **154** as a colorless oil (80%).

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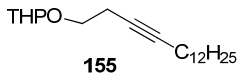
IR (neat): 3292, 2942, 2875, 1733, 1120, 1059, 1030, 981, 636 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ= 4.64 (dd, 1H, *J* = 6.3, 2.8 Hz), 3.87 (m, 2H), 3.83 (t, 2H, *J* = 6.8 Hz), 2.48 (td, 2H, *J* = 6.8 Hz, 2.4 Hz), 1.97 (t, 1H, *J* = 2.4 Hz), 1.47-1.56 (m, 2H), 1.70 (m, 2H), 1.82 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ= 98.9, 82.2, 69.7, 65.7, 62.4, 30.7, 25.6, 20.1, 19.6. **ESI-HRMS** [M+1] calcd for $C_9H_{15}O_2$: 155.1072, found: 155.1081.

1-[(2-tetrahydropiranyl)oxy]-3-hexadecyne (155)



155

Method A. $NaNH_2$ (0.3 g, 7.20 mmol) was added to a solution of compound **154** (1 g, 6.49 mmol) at 0ºC in THF (3 ml). The solution was stirred at that temperature for 1h and then a solution of 1-bromodecane (1.7 ml, 7.21 mmol) in DMSO (3.5 mL) was slowly added dropwise. The mixture was stirred at room temperature for 12h before the reaction was quenched with water (3 ml). The crude was extracted with ^{t}BuOMe and then, the aqueous phase was extracted with ^{t}BuOMe (3 x 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and they were concentrated under reduced pressure. The residue was purified by flash chromatography using pretoleum ether:^{t}BuOMe (from 1:0 to 10:1) to give 0.35 g of product **155** as a yellow oil (18 %).

Method B. CuCl (0.64 g, 6.5 mmol) was dissolved in ammonia (1ml, 16 M), and the solution was stirred over 20 minutes at room temperature before the crude was filtered. The obtained solid was added to a solution of compound **154** (0.5 g, 3.3 mmol) in methanol (40 ml). After stirring 1h at room temperature, the mixture was filtered under argon and the precipitate was wahed with methanol to give a yellow solid. The precipitate was dried under vacuum and it was added to a solution of 1-bromodecane (0.3 ml, 1.22 mmol) in DMF (3 mL). The mixture was stirred 5 h at room temperature before quenching it with aqueous saturated NH_4Cl solution. The crude was diluted with ^{t}BuOMe and the layers were separated. The aqueous layer was extracted with ^{t}BuOMe (3 x 50 ml). The combiend organic layers were washed with brine and then dried over anydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified with flash

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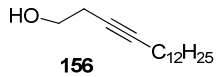
chromatography using petroleum ether:^{t}BuOMe (10:1) to give 0.70 g of compound **155** as a beige oil (36 %).

IR (neat): 2922, 2852, 1234, 1463, 648 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ= 4.61 (dd, 1H, *J* = 6.8, 2.8 Hz), 3.84 (m, 2H), 3.51 (t, 2H, *J* = 7.0 Hz), 2.45 (t, 2H, *J* = 7.0 Hz), 1.98-1.48 (m, 28 H), 0.88 (t, 3H, *J* = 6.7 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 98.8, 81.5, 69.3, 65.6, 62.3, 60.0, 32.0, 30.6, 30.3, 29.8, 29.6, 25.5, 22.1, 19.5, 14.3. **ESI-HMRS** [M+23] calcd for $C_{21}H_{38}O_2Na$: 345.2770, found: 345.2800.

3-Hexadecyn-1-ol (156)



156

Compound **155** (0.143 g, 0.5 mmol) was added to a solution of *p*-TsOH (0.04 g, 0.2 mmols) in diethyl ether:metanol (10 mL, 1:1) and the mixture was stirred 2 h at room temperature before adding water (25 ml). ^{t}BuOMe (25 ml) was added and the phases were separated, the aqueous solution was extracted with ^{t}BuOMe (2 x 100 ml). The combined organic layers were dried over anydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using petroleoum ether to give 68 mg of product **156** as a white solid (62 %).

Mp = 89-91 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ=3.72 (t, 2H, *J* = 6.1 Hz), 2.43 (t, 2H, *J* = 6.1 Hz), 2.16 (t, 2H, *J* = 7.2 Hz), 1.72 (brs, 1H, OH), 1.25-1.57 (m, 20H), 0.88 (t, 3H, *J* = 6.5 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ= 79.8, 78.7, 61.5, 31.9, 29.7, 28.4, 28.2, 22.1, 19.2, 14.1. **ESI-HMRS** [M+23] calcd for $C_{16}H_{30}ONa$: 261.2194, found: 261.2209.

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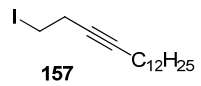
1-Iodohexadec-3-yne (157)

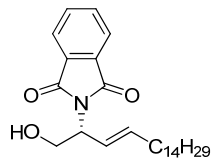


157

Compound **156** (68 mg, 0.27 mmol), triphenylphosphine (0.09 g, 0.324 mmol), imidazole (0.04 g, 0.59 mmol) and iodine (0.08 g, 0.3 mmol) were disolved in THF (4 ml). The mixture was stirred at room temperature for 2h and then, it was quenched with saturated aquoeous NH_4Cl solution. The biphasic solution was separated and the aqueous phase was extracted with petroleum ether. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using petroleum ether to give 73 mg of compound **157** as a beige oil (92 %).

IR (neat): 2925, 2850, 1695, 1460, 1375, 1300, 1240, 1170, 970, 720 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ= 3.32 (t, 2H, *J* = 7.3 Hz), 2.74 (t, 2H, *J* = 7.3 Hz), 2.15 (t, 2H, *J* = 6.9 Hz), 1.27-1.8 (m, 20 H), 0.88 (t, 3H, *J* = 6.7 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$): δ=79.1, 78.2, 29.9, 29.6, 28.8, 24.1, 22.9, 22.8, 19.2, 14.3, 7.2. **ESI-HRMS** [M+23] calcd for $C_{16}H_{29}INa$: 371.1212, found: 371.1230.

(2*R*)-(3*E*)-2-*N*-phthalimido-3-octadecen-1-ol (161)



161

Compound **139** (0.5 g, 2.3 mmol) and 1-hexadecene (2.1 g, 9.3 mmol) were dissolved in CH_2Cl_2 (25 mL) at room temperature. Second generation Grubbs catalyst (5%) was added to the solution and then the reaction mixture was refluxed under argon for 12 h. After cooling the reaction mixture it was concentrated and purified by column chromatography with hexane:ethyl acetate (4:1) to afford compound **161** (0.99 g, 99%) as a white solid.

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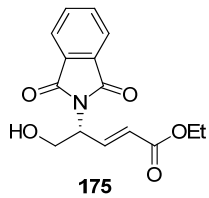
Mp = 37-39 ºC. $[\alpha]_D^{25}$= +19.5 (*c* 1.1, CH_2Cl_2). **IR** (neat): 3525, 3069, 2956, 2918, 2848, 1773, 1694, 1467, 1391, 1367 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ= 7.83-7.78 (m, 2H), 7.71-7.66 (m, 2H), 5.77 (m, 2H), 4.87 (dt, 1H, *J* = 8.0, 4.8 Hz), 4.07 (m, 1H), 3.89 (dd, 1H, *J* = 12.4, 4.8 Hz), 2.64 (br s, 1H), 1.99 (td, 2H, *J* = 7.6, 6.4 Hz), 1.20-1.10 (m, 24H) 0.84 (t, 3H, *J* = 6.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ=168.6, 136.5, 134.0, 131.9, 123.3, 123.3, 63.2, 55.8, 32.3, 32.0, 29.7, 29.6, 29.5, 29.4, 29.2, 28.9, 22.8, 14.2. **ESI-HMRS** [M+Na] calcd for $C_{26}H_{39}NO_3Na$: 436.2828, found: 436.2819. **Elemental Analysis** calcd: C, 66.35; H, 5.10; N, 6.45, found: C, 66.33; H, 5.18; N, 6.43.

Ethyl (4*R*)-(2*E*)-4-*N*-phthalimido-5-hydroxypent-2-enoate (175)



175

Compound **139** (50 mg, 0.23 mmol) and compound **170** (0.1 mL, 0.92 mmol) were dissolved in dichloromethane (25 mL) at room temperature. Second generation Grubbs catalyst (5%) was added to the solution and then the reaction mixture was refluxed under argon for 12h. After cooling the reaction mixture it was concentrated under vacuum and purified by flash chromatography using petroleum ether: ethyl acetate (3:2) to give compound **175** as a colorless oil (40 mg, 71%).

IR (neat): 3470, 3102, 3083, 2924, 2854, 1774, 1703, 1384, 1314, 1273, 1180, 1027, 719 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ= 7.92-7.85 (m, 2H), 7.79-7.71 (m, 2H), 7.12 (dd, 1H, *J* = 15.9, 6.0 Hz), 5.92 (d, 1H, *J* = 15.9 Hz) 5.09 (m, 1H), 4.19 (q, 2H, *J* = 6.9 Hz), 4.05 (m, 2H), 3.00 (brs, 1H), 1.27 (t, 3H, *J* = 6.9 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 168.4, 165.7, 141.2, 134.7, 131.7, 124.2, 123.8, 62.6, 61.0, 54.2, 14.4.

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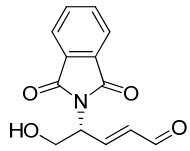
(4*R*)-(2*E*)-4-*N*-phthalimido-5-hydroxy-pent-2-em-1-al (176)

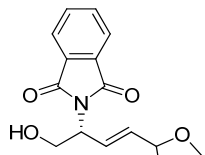


176

Compound **139** (50 mg, 0.23 mmol) was dissolved in dichloromethane (15 mL) at reflux. Hoveyda-Grubbs catalyst (8 mg, 0.012mmol, 5%) was added to the solution and then the reaction mixture was stirred under argon. Acrolein (0.05 mL, 0.7 mmol) was added at that temperature over 2h by slowly addition. After 11h the crude was cooled and it was concentrated under vacuum and purified by flash chromatography using hexanes: ethyl acetate (2:1) to give compound **176** as an yellow oil (50 mg, 78%).

IR (neat): 3462, 2926, 2706, 1772, 1707, 1467, 1383, 1063, 877, 796, 718 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.54 (d, 1H, *J* = 8.0 Hz), 7.83 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.72 (dd, 2H, *J* = 5.2, 3.6 Hz), 7.03 (dd, 1H, *J* = 16.0, 4.0 Hz), 6.12 (dd, 1H, *J* = 16.0, 8.0 Hz), 5.17 (m, 1H), 4.18 (m, 1H), 4.09-4.04 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 193.1, 168.2, 149.9, 134.7, 133.8, 131.8, 62.1, 60.6, 54.1, 21.2, 14. 3.

(2*R*)-(3*E*)-2-*N*-phthalimido-4-(1,3-dioxalan-2-yl)but-3-en-1-ol (177)



177

Compound **139** (50 mg, 0.23 mmol) was dissolved in dichloromethane (25 mL) at room temperature. Second generation Grubbs catalyst (5%) was added to the solution and then the reaction mixture was refluxed under argon. Compound **172** (0.1mL, 0.92 mmol) was added at that temperature over 2 h by slowly addition. After 10 h the crude was cooled and it was concentrated under

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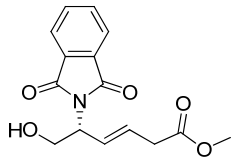
vacuum and purified by flash chromatography using hexanes: ethyl acetate (3:1) to give compound **177** as an yellow oil (57mg, 81%).

$[\alpha]_D^{25}$= +34.0 (*c* 2.7, CH_2Cl_2). **IR** (neat): 3471, 2924, 2854, 1774, 1703, 1466, 1382, 1312, 1273, 1180, 1123, 1029, 719 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.85-7.81 (m, 2H), 7.77-7.72 (m, 2H), 6.28 (dd, 1H, *J* =16.0, 6.8 Hz), 5.72 (dd, 1H, *J* = 16.0, 5.8 Hz), 5.25 (d, 1H, *J* = 5.8 Hz), 4.95 (m, 1H), 4.12 (m, 1H), 3.67 (m, 2H), 3.87 (m, 1H), 3.74 (m, 1H), 3.6 (m, 1H), 3.01 (brs, 1H, OH). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 168.6, 134.4, 131.9, 131.2, 129.9, 123.6, 102.9, 72.5, 65.2, 62.8, 54.6. **ESI-HMRS** [M+1] calcd for $C_{15}H_{46}NO_5$: 290.1028, found: 290.1009.

Methyl (2*R*)-(2*E*)-5-*N*-phthalimido-6-hydroxyhex-3-enoate (179)



179

Compound **139** (50 mg, 0.23 mmol) and compound **174** (0.1 mL, 0.92 mmol) were dissolved in dichloromethane (2 mL) at room temperature. Second generation Grubbs catalyst (5%) was added to the solution and then the reaction mixture was refluxed under argon for 12 h. After cooling the reaction mixture it was concentrated under vacuum and purified by flash chromatography using petroleum ether: ethyl acetate (from 4:1 to 2:1) to give compound **179** as a colorless oil (50 mg, 65%).

IR (neat): 3405, 2926, 1772, 1705, 1386, 1058, 721 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.88-7.81 (m, 2H), 7.75-7.72 (m, 2H), 6.01 (dtd, 1H, *J* = 15.6, 7.4, 0.8 Hz), 5.89 (dd, 1H, *J* = 15.6, 8.0 Hz), 4.94 (m, 1H), 4.10 (m, 1H), 3.95 (dd, 1H, *J* = 11.0, 4.0 Hz), 3.68 (s, 3H), 3.11 (d, 2H, *J* = 7.4 Hz), 2.60 (brs, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 171.8, 168.8, 134.4, 132.0, 127.9, 127.5, 123.7, 63.3, 55.3, 52.2, 37.6.

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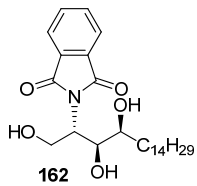
Dihydroxylation reaction of compound 161

Method A. In a 10 ml round bottomed flask NMO (0.04 g, 0.329 mmol) was dissolved in water (0.2 mL), OsO_4 (0.004 g, 0.015 mmols), acetone (0.3 mL) and ^tBuOH (0.3 ml) were added. The mixture was stirred for 5 minutes at 0 ºC and then, a solution of compound **161** (50 mg, 0.121 mmols) in acetone (0.2 mL) was added in one portion. The mixture was stirred for 20 hours at room temperature until the starting material was not observed by TLC. When the reaction had finished a solution of Na_2SO_3 was added and the resulting clear mixture was stirred for 15 minutes. The reaction mixture was diluted with ethyl acetate and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The reaction mixture was purified by column chromatography with hexane:ethyl acetate (2:1 to 1:1) to obtain **162** (0.039 g, 76 %) as a white solid.

Method B. OsO_4 (36 mg, 0.14 mmol) was dissolved in dichloromethane (1 mL) at -78ºC and a solution of alkene (50 mg, 0.12 mmol) in dichloromethane (4 mL) was added via cannula. Then, TMEDA or TEMEN (0.14 mmol) was added at -78ºC and the mixture was stirred for 12 h a -78ºC quenching the reaction with saturated aqueous citric acid solution (4 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 x 5mL). The combined organic layers were consecutively washed with saturated solutions of $NaHCO_3$, NaCl and $Na_2S_2O_3$. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude was purified by radial chromatography using hexanes: ethyl acetate (1:1).

(*2S,3S,4R*)-2-*N*-phthalimido-1,3,4-octadecane-1,3,4-triol (162)



162

$[\alpha]_D^{25}$= – 22.9 (*c* 0.51, CH_2Cl_2). **IR** (neat): 3457, 3183, 3059, 2720, 1772, 1710, 1604, 1487, 1366, 1305, 1287, 1051 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.89-7.85 (m, 2H), 7.78-7.74 (m, 2H), 4.59 (m, 1H), 4.08-4.00 (m, 2H), 3.97 (m,

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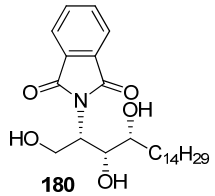
1H), 3.66 (br s, 1H), 3.45 (d, 1H, *J* = 9.2 Hz), 3.10 (br s, 1H), 2.64 (br s, 1H), 1.51 (m, 2H), 1.27 (m, 24H), 0.88 (t, 3H, *J* = 6.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.1, 134.6, 131.8, 123.9, 72.7, 71.6, 61.9, 55.7, 33.9, 32.1, 29.9, 29.7, 29.6, 25.7, 22.9, 14.3. **ESI-HMRS** [M+Na] calcd for $C_{26}H_{41}NO_5Na$: 470.2882, found: 470.2892. **Elemental Analysis** calcd: C, 69.77; H, 9.23; N, 3.13, found C, 69.59; H, 9.28; N, 3.15.

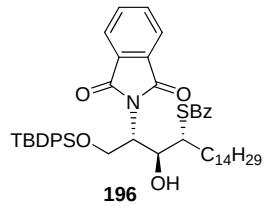
(*2S,3R,4R*)-2-*N*-phthalimidooctadecane-1,3,4-triol (180)



180

[α]$_D^{25}$= – 3.1 (*c* 1.5, CH_2Cl_2). **^{1}H RMN** (300 MHz, $CDCl_3$): δ= 7.86-7.82 (m, 2H), 7.77-7.72 (m, 2H), 4.43 (dd, 1H, *J* = 6.8 6.0 Hz), 4.19 (dd, 1H, *J* =10.3, 6.6 Hz), 4.17 (d, 1H, *J* = 10.3 Hz), 4.08 (m, 1H), 3.98 (dt, 1H, *J* = 6.0, 4.2 Hz), 3.47 (brs, 2H), 3.35 (brs, 1H), 1.52 (m, 2H), 1.33 (m, 2H), 1.27 (m, 21H), 0.88 (t, 3H, *J* = 6.6 Hz). **^{13}C RMN** ($CDCl_3$, 75.4 MHz, δ en ppm): δ = 170.1, 134.8, 131.8, 124.0, 72.7, 71.3, 61.9, 55.1, 33.9, 32.1, 29.9, 29.7, 28.3, 14.0.

(*2R,3S,4R*)-1-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-2-*N*-phthalimido-octadecan-4-yl thiobenzoate (196)



196

To a solution of sulfate **208** (0.19 mmol) in DMF (1 mL) acid thiobenzoic (38μL, 0.323 mmol) and Cs_2CO_3 (0.093 g, 0.078 mmol) were added. This mixture was stirred for 8 hours and H_2SO_4 (1.1 μL), H_2O (1.2 μL) and THF (20 μL) were added. The stirring was continued at room temperature for 3 hours and then the

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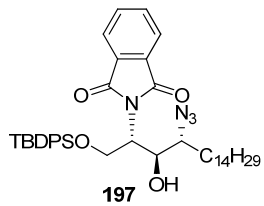
reaction mixture was diluted with ethyl acetate and it was washed with a solution of $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and it was concentrated. The mixture was purified by radial chromatography with hexane:ethyl acetate (4:1) to obtain compound **196** (0.13 g, 87 %) as a colorless oil.

$[\alpha]_D^{25}$= – 11.7 (*c* 1.3, CH_2Cl_2). **IR** (neat): 3402, 3070, 2923, 2853, 1774, 1699, 1663, 1467, 1399, 1368, 1209, 1112, 747, 701 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.75-7.60 (m, 6H), 7.60-7.58 (m, 3H), 7.48-7.44 (m, 3H), 7.41-7.36 (m, 3H), 7.38-7.31 (m, 3H), 7.32 (t, 1H, *J* = 7.2 Hz), 4.98 (td, 1H, *J* = 8.8, 4.4 Hz), 4.58 (d, 1H, *J* = 10.8 Hz), 4.10 (t, 1H, *J* = 9.2 Hz), 4.07 (t, 1H, *J* = 8.8 Hz), 4.00 (td, 1H, *J* = 10.8, 5.2 Hz), 3.67 (td, 1H, *J* = 10.0, 3.2 Hz), 2.01-2.06 (m, 2H), 1.44-1.39 (m, 2H), 1.26-1.20 (m, 22 H), 0.87-0.86 (m, 12H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ =190.8, 136.6, 135.8, 135.6, 135.4, 134.1, 133.3, 133.0, 132.8, 132.0, 129.7, 129.6, 128.8, 128.8, 128.5, 128.4, 127.7, 127.7, 127.6, 127.2, 123.3, 72.5, 62.3, 55.7, 46.2, 31.9, 31.3, 29.7, 29.6, 29.5, 29.4, 29.4, 26.6, 26.3, 22.7, 19.2, 18.9, 14.1. **ESI-HMRS** [M+23] calcld for $C_{49}H_{63}NO_5SSiNa$: 828.4028, found: 828.4076. **Elemental Analysis** calcd: C, 70.98; H, 7.66; N, 1.69; S, 3.87, found: C, 71.01; H, 7.66, N, 1.73; S, 3.85.

(*2R,3S,4R*)-4-azido-1-(*tert*-butyldiphenylsilyloxy)-2-*N*-phthalimido-octadecan-3-ol (197)



197

To solution of sulfate **208** (0.19 mmol) in DMF (1 mL), NaN_3 (38 mg, 0.57 mmol) and a catalytic amount of 15-crown-5 (20%) were added. The mixture was heated at 80 ºC under argon for 1.5 hours and then H_2SO_4 (1 μL), H_2O (1 μL) and THF (20 μL) were added. The reaction mixture was stirred at room temperature for 3 hours, it was diluted with ethyl acetate and it was washed with $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and it

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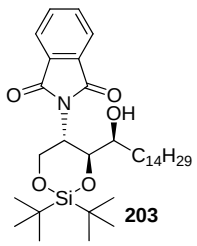
was concentrated. The mixture was purified by radial chromatography with hexane:ethyl acetate (8:1) to obtain compound **197** (0.124 g, 98 %) as a colorless oil.

$[\alpha]_D^{25}$= – 21.3 (*c* 3.5, CH_2Cl_2). **IR** (neat): 3415, 3071, 3049, 2925, 2854, 2103, 1775, 1703, 1467, 1428, 1367, 1263, 1111, 704 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.88-7.86 (m, 2H), 7.77-7.76 (m, 2H), 7.59 (dd, 2H, *J* = 8.0, 1.2 Hz), 7.48 (dd, 2H, *J* = 8.4, 1.6 Hz), 7.41-7.32 (m, 4H), 7.27 (t, 2H, *J* = 6.0 Hz), 4.81 (ddd, 1H, *J* = 8.8, 5.2, 4.8 Hz), 4.62 (d, 1H, *J* = 10.4 Hz), 4.12 (dd, 1H, *J* = 10.8, 9.6 Hz), 3.96 (dd, 1H, *J* = 10.8, 5.6 Hz), 3.79 (ddd, 1H, *J* = 10.8, 7.2, 3.6 Hz), 3.18 (td, 1H, *J* = 11.2, 3.6 Hz), 1.74 (m, 2H), 1.46 (m, 2H), 1.26-1.22 (m, 22 H), 0.89 (s, 9H), 0.86 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 135.8, 135.6, 135.0, 134.6, 133.0, 133.0, 130.0, 129.9, 129.9, 127.9, 127.9, 127.8, 123.9, 72.2, 65.8, 61.9, 54.9, 29.9, 29.9, 29.9, 29.8, 29.7, 29.7, 29.6, 29.6, 26.7, 26.8, 26.4, 22.9, 19.1, 14.3. **ESI-HMRS** [M+23] calcd for $C_{42}H_{58}N_4O_4Si$: 733.4125, found: 733.4125. **Elemental Analysis** calcd: N, 7.63; C, 68.73; H, 7.63, found N, 7.76; C, 69.01; H, 7.72.

(2*S*, 3*S*, 4*S*)-1,3-di*tert*butydisilyloxy)-2-*N*-phthalimido-3-octadecan-3-ol (203)



203

Pyridine (60µl, 0.75mmol) was added to a solution of compound **162** (100 mg, 0.23 mmol) in anhydrous acetonitrile (5 mL). The solution was cooled at -20ºC and then, $Si(^tBu)_2(OTf)_2$ was added. After stirring the crude for 6 h the reaction was quenched with aqueous HCl solution (10%). The phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum before the crude was purified by

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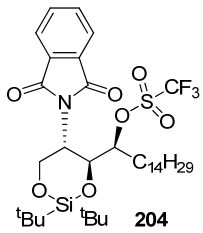
flash chromatography using hexanes: ethyl acetate (2:1) to give the compound **203** as colorless oil (140 mg, 81%).

$[\alpha]_D^{25}$= +8.0 (*c* 1.0, CH_2Cl_2). **^{1}H RMN** (400 MHz, $CDCl_3$): δ = 7.82 (dd, 2H, *J* = 5.6, 3.4 Hz), 7.71 (dd, 2H, *J* = 5.6, 3.2 Hz), 4.72 (t, 1H, *J* = 10.0 Hz) 4.68 (td, 1H, *J* = 10.0, 1.6 Hz), 4.42 (td, 1H, *J* = 6.8, 2.4 Hz), 4.17 (ddd, 1H, *J* = 10.0, 10.0, 2.0 Hz), 3.86 (d, 1H, *J* = 10.0 Hz), 1.90 (d, 1H, *J* = 10.0 Hz), 1.76-1.67 (m, 2H), 1.33-1.25 (m, 23H), 1.11 (s, 9H), 1.09 (s, 9H), 0.87 (t, 3H, *J* = 6.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 168.4, 134.3, 132.0, 123.6, 74.0, 73.6, 65.2, 57.9, 33.2, 32.1, 30.0, 29.9, 29.8, 29.7, 29.6, 28.3, 28.2, 26.0, 22.9, 22.7, 20.7, 14.3.

(2*S*, 3*S*, 4*S*)-1,3-di*tert*butydisilyloxy)-2-*N*-phthalimido-4-O-triflyloctadecane (204)



204

Pyridine (15 µl, 0.2 mmol) was added to a solution of compound **203** (11 mg, 0.02 mmol) in dichloromethane (1 ml). The solution was cooled at 0ºC and then, Tf_2O (5µl, 0.04mmol) was added. The solution was warmed at room temperature and diluted with ethyl acetate (10 mL). The solution was washed with HCl solution (10%), saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was used in the following step without any further purification.

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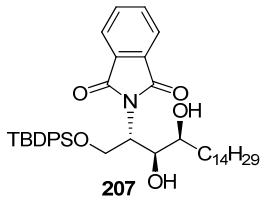
(*2R,3S,4S*)-1-(*tert*-butyldiphenylsilyloxy)-2-*N*-phtalimido-octadecane-3,4-diol (207)



207

To a solution of **162** (0.200 g, 0.45 mmol) in CH_2Cl_2 (2.5 mL) and DMF (0.5 mL), triethylamine (0.16 mL, 1.1. mmol) and DMAP (2.7 mg, 0.05 mmol) were added. The solution was cooled at 0ºC, TBDPSCl (0.14 mL, 0.54 mmol) was added and the mixture was stirred at this temperature for 18 h until the starting material was not observed by TLC. The reaction mixture was stirred for 5 minutes at room temperature and it was diluted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexane:ethyl acetate 3:1) to obtain diol **207** (150 mg, 89 %) as a colorless oil.

$[\alpha]_D^{25}$= +19.5 (*c* 0.9, CH_2Cl_2). **IR** (neat): 3447, 3182, 3055, 2925, 2854, 1773, 1703, 1468, 1428, 1391, 1112 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ= 7.83-7.82 (m, 2H), 7.74-7.72 (m, 2H), 7.60 (dd, 2H, *J* = 8.0, 1.0 Hz), 7.50 (dd, 2H, *J* = 8.0, 1.6 Hz), 7.32-7.41 (m, 4H), 7.27 (t, 2H, *J* = 8.0 Hz), 4.66 (dt, 1H, *J* = 8.4, 5.2 Hz), 4.14 (m, 1H), 4.02 (dd, 1H, *J* = 10.6, 5.2 Hz), 3.97 (d, 1H, *J* = 6.0 Hz), 3.74 (dt, 1H, *J* = 10.6, 5.2 Hz), 3.38 (m, 1H), 2.47 (d, 1H, *J* = 3.6 Hz), 1.43 (m, 2H), 1.31-1.21 (m, 23H), 0.92 (m, 9 H), 0.88 (t, 3H, *J* = 6.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ=170.1, 135.8, 135.6, 133.0, 132.9, 131.9, 131.9, 130.0, 129.9, 127.9, 127.9, 123.7, 73.1, 72.3, 61.9, 55.7, 33.1, 32.1, 29.9(2), 29.8(2), 29.7, 29.6, 26.8, 25.4, 22.9, 19.1, 14.3. **ESI-HRMS** [M+23] calcd for $C_{42}H_{59}NO_5Na$: 708.4060, found: 708,4052. **Elemental Analysis** calcd: C, 73.53, H, 8.67; N, 2.04, found C, 73.74; H, 8.72; N, 2.11.

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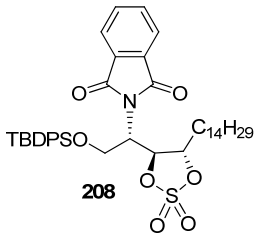
(*2S*,3*S*,4*S*)-1-(*tert*-butyldiphenylsilyloxy)-2-*N*-phtalimido-3,4-*O*-sulfuryl-octadecane (208)



208

To a solution of diol **207** (0.16 g, 0.23 mmol) in CH_2Cl_2 (2 mL), triethylamine (90 μL, 0.68 mmol) and thionyl chloride (20 μl, 0.27 mmol) were added at 0ºC. After 40 minutes under stirring the reaction mixture was poured into brine and extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vaccuo. The crude was dried in vaccuo for one night and then it was dissolved in $CCl_4/CH_3CN/H_2O$ (1mL:1mL:1mL). $RuCl_3 \cdot 3H_2O$ (6 mg, 0.011 mmol) and $NaIO_4$ (0.14 g, 0.68 mmol) were added. After 2.5 hours no starting material was observed by TLC. The reaction mixture was diluted with AcOEt, washed with a saturated solution of Na_2SO_3 and the organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford compound **208** as beige oil, which was not purified and was directly used in the next reaction.

NMR ^{1}H (400 MHz, $CDCl_3$): δ= 7.86-7.84 (m, 2H), 7.76-7.74 (m, 2H), 7.63-7.58 (m, 4H), 7.44-7.42 (m, 2H), 7.40-7.36 (m, 4H), 5.2 (t, 1H, *J* = 6.4 Hz) 4.75 (m, 1H), 4.62 (dt, 1H, *J* = 7.6, 6.4 Hz), 4.24 (dd, 1H, *J* = 10.8, 7.6 Hz), 4.10 (m, 1H), 1.49 (m, 2H), 1.28-1.21 (m, 24H), 1.02 (s, 9H), 0.88 (t, 3H, *J* = 6.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 167.9, 135.6, 135.6, 134.6, 132.3, 132.3, 131.5, 130.4, 130.3, 128.2, 128.2, 123.9, 84.9, 83.5, 61.0, 53.4, 32.8, 32.1, 29.9(3), 29.8, 29.7, 29.6(2), 29.5, 29.2, 26.9, 25.2, 22.9, 19.2, 14.4. **ESI-HMRS** [M+23] calcd for $C_{42}H_{57}NO_7SSiNa$: 770.3523, found: 770.3289.

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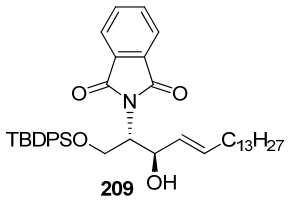
(*2R*,*3R*)-(4*E*)-1-(*tert*-butyldiphenylsilyloxy)-2-*N*-phtalimido-octadec-4-en-3-ol (209)



209

The cyclic sulphate **208** (0.075 mmol) was dissolved in toluene (2 mL) and Bu_4NI (0.03 g, 0.08 mmol) and DBU (17 μL, 0.11 mmol) were added. The reaction mixture was heated to reflux for 3 hours. Then it was cooled at room temperature and H_2SO_4 (1.4 μL), H_2O (1.2 μL) and THF (20 μL) were added. Stirring continued for 2 hours at room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$ solution and brine and finally it was dried over anhydrous $MgSO_4$. The crude was concentrated and it was purified by radial chromatography using hexane:ethyl acetate (3:1) as eluent yielding compound **209** (0.041 g, 82 %) as a colorless oil.

$[\alpha]_D^{25}$= + 21.7 (*c* 1.7, CH_2Cl_2). **IR** (neat): 3428, 3190, 3064, 2924, 2853, 1773, 1708, 1641, 1467, 1428, 1389, 1112 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ= 7.85-7.82 (m, 2H), 7.75-7.73 (m, 2H), 7.62-7.60 (m, 2H), 7.52-7.50 (m, 2H), 7.41-7.33 (m, 4H), 7.28-7.26 (m, 2H), 5.70 (dt, 1H, *J* = 16.0, 6.8 Hz), 5.30 (dd, 1H, *J* = 16.0, 4.8 Hz), 4.56 (m, 2H), 4.16 (t, 1H, *J* = 10.8 Hz), 4.01 (dd, 1H, *J* = 10.8, 4.8 Hz), 3.53 (br s, 1H), 1.90 (m, 2H), 1.26-1.13 (m, 22H), 0.92 (s, 9H), 0.88 (t, 3H, *J* = 6.6 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 167.9, 135.8, 135.7, 134.3, 133.4, 133.2, 133.2, 129.9, 129.8, 129.2, 129.0, 127.9, 127.8, 123.6, 70.8, 61.5, 58.6, 32.2, 32.1, 29.9(3), 29.7, 29.6, 29.2, 29.1, 26.8, 22.9, 19.2, 14.3. **ESI-HMRS** [M+23] calcd for $C_{42}H_{57}NO_4SiNa$) *m/z* $(M+Na+H)^+$: 691.4033, found: 691.4026. **Elemental Analysis** calcd: C, 75.52; H, 8.60; N, 2.10, found: C, 75.42; H, 8.72; N, 2.19.

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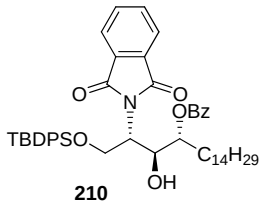
(*2R,3S,4R*)-1-(*tert*-butyldiphenylsilyloxy)-2-*N*-phthalimido-3-hydroxy-octadecan-4-yl benzoate (210).



210

To a solution of sulfate **196** (0.052 mmol) in DMF (1 mL), benzoic acid (0.01 g, 0.08 mmol) and Cs_2CO_3 (0.025 g, 0.078 mmol) were added. The resulting mixture was stirred for 7.5 hours and H_2SO_4 (1.4 μL), H_2O (1.5 μL) and THF (20 μL) were added. Then, stirring was continued at room temperature for 3 hours. The reaction mixture was diluted with ethyl acetate, and it was washed with a solution of $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and it was concentrated. The remaining crude was purified by radial chromatography with hexane:ethyl acetate (2:1) to obtain compound **211** (0.049 g, 91%) as a colorless oil.

$[\alpha]_D^{25}$= – 2.9 (*c* 1.5, CH_2Cl_2). **IR** (neat): 3410, 3069, 2925, 2854, 1774, 1698, 1604, 1465, 1428, 1397, 1368, 1268, 1108, 706 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ=7.88-7.86 (dd, 2H, *J* = 8.4, 1.2 Hz), 7.81-7.78 (m, 2H), 7.76-7.72 (m, 4H), 7.60 (dd, 2H, *J* = 8.0, 1.6 Hz), 7.47 (dd, 2H, *J* = 8.0, 1.6 Hz), 7.42-7.31 (m, 6H), 7.24 (t, 1H, *J* = 6.8 Hz), 5.04 (td, 1H, *J* = 8.4, 3.4 Hz), 4.78, (dt, 1H, *J* = 9.2, 5.2 Hz), 4.61 (d, 1H, *J* = 10.8 Hz), 4.15 (t, 1H, *J* = 9.2 Hz), 4.08 (dd, 1H, *J* = 8.4, 3.4 Hz), 4.03 (dd, 1H, *J* = 10.8, 5.2 Hz), 1.92 (br s, 1H), 1.75-1.66 (m, 2H), 1.27-1.19 (m, 24H), 1.08 (s, 12 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 166.2, 135.8, 135.7, 135.4, 135.0, 134.5, 133.1, 133.1, 133.0, 130.4, 130.0, 129.9, 129.8, 129.7, 128.4, 127.9, 127.9, 127.9. 127.8, 123.7, 74.2, 71.7, 61.9, 54.6, 32.1, 31.5, 29.9(2), 29.8(2), 29.7, 29.6(2), 26.8(2), 25.0, 22.9, 19.2, 19.1, 14.3. **ESI-HMRS** [M+23] calcd for $C_{49}H_{63}NO_6SiNa$: 797.4548, found: 797.4542. **Elemental Analysis** calcd: C, 77.58; H, 8.20; N, 1.81; found: C, 77.55; H, 8.27 N, 1.80.

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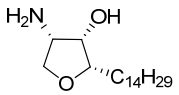
(2*S*, 3*S*, 4*S*)-4-amino-2-tetradecyltetrahydrofuran-3-ol (Jaspine B) (106)

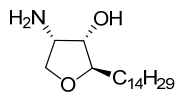


106

Compound **219** (23 mg, 0.051 mmol) was dissolved in aqueous solution of $MeNH_2$ (0.15 mmol, 15 μL 40%) and the resulting mixture was stirred in an open flask for 1 h at 50 ºC. The reaction is allowed to cool at room temperature and methylamine is removed, first by bubbling argon through the reaction for 30 minutes and then under vacuum for 1 hour. The crude was purified by silica gel chromatography using 96:3:1 (CH_2Cl_2, MeOH, NH_4OH) as a eluent to afford a 13 mg of compound **106** as a white solid (93%).

$[\alpha]_D^{25}$ = +7.7 (*c* 0.6, $CHCl_3$). Lit $[\alpha]_D^{25}$ = + 8.7 (*c* 1.1, CH_3Cl),[160] $[\alpha]_D^{25}$ = + 9.0 (*c* 1.5, CH_3Cl),[169a] $[\alpha]_D^{25}$ = + 7.0 (*c* 0.1, CH_3Cl).[154] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.86 (dd, 1H, *J* = 8.5, 7.2 Hz), 3.80 (dd, 1H, *J* = 4.8, 3.4 Hz), 3.66 (td, 1H, *J* = 7.2, 3.4 Hz), 3.60 (dt, 1H, *J* = 7.2, 4.8 Hz), 3.45 (dd, 1H, *J* = 8.5, 7.2 Hz), 1.80 (brs, 3H), 1.65–1.52 (m, 2H), 1.38–1.18 (m, 24 H), 0.81 (t, 3H, *J* = 6.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 83.4, 72.5, 71.9, 54.4, 32.1, 30.0, 29.9, 29.8, 29.6, 26.5, 26.5, 22.9, 14.5 ppm. **ESI–HMRS** [M+1] calcd for $C_{18}H_{38}NO_2$: 300.2903, found: 300.3000.

(2*R*, 3*S*, 4*S*)-4-amino-2-tetradecyltetrahydrofuran-3-ol (2-*epi*-Jaspine) (211)



211

Compound **220** (25 mg, 0.055 mmol) was dissolved in aqueous solution of $MeNH_2$ (0.2 mmol, 0.2 mL, 40%) and the resulting mixture was stirred in an open flask for 1.5 h at 50 ºC. The reaction is allowed to cool at room temperature and methylamine is removed, first by bubbling argon through the reaction for 30 minutes and then under vacuum for 1 hour. The crude was purified by silica gel

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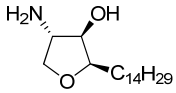
chromatography using 96:3:1 (CH_2Cl_2, MeOH, NH_4OH) as a eluent to afford a 13 mg of compound **211** as a white solid (86%).

$[\alpha]_D^{25}$ = + 9.1 (c 0.1, $CHCl_3$). Lit $[\alpha]_D^{25}$ = +9.6 (c 0.11, CH_3Cl),[163a] $[\alpha]_D^{25}$ = + 11.7 (c 0.65, CH_3Cl),[177a] $[\alpha]_D^{25}$ = + 14.8 (c 0.97, CH_3Cl).[160] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.12 (dd, 1H, *J* = 9.1, 6.8 Hz) 3.61 (m, 2H), 3.45 (m, 1H), 3.40 (dd, 1H, *J* = 9.1, 6.8 Hz), 2.10–1.49 (m, 5H), 1.34–1.25 (m, 24H), 0.86 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 85.5, 74.5, 73.4, 52.7, 32.1, 30.0, 29.9, 29.8, 29.6, 26.5, 22.9, 14.4 ppm. **ESI–HMRS** [M+1] calcd for $C_{18}H_{38}NO_2$: 300.2903, found: 300.2910.

(2*R*, 3*R*, 4*S*)-4-amino-2-tetradecyltetrahydrofuran-3-ol (212)



212

Compound **222** was dissolved in aqueous solution of $MeNH_2$ (0.17 mmol, 15 ml, 40%) and the resulting mixture was stirred in an open flask for 1h at 50ºC. The reaction is allowed to cool at room temperature and methylamine is romoved, first by bubbling argon through the reaction for 30 minutes and then under vacuum for 1 hour. The crude was purified by silica gel chromatography using 96:4:1 (DCM, MeOH, NH_4OH) as a eluent to afford a 17 mg of compound **212** as a white solid (88%).

$[\alpha]_D^{25}$ = - 0.7 (*c* 1.0, CH_3Cl). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 4.22 (dd, 1H, *J* = 9.4, 5.6 Hz), 3.89 (td, 1H, *J* = 7.2, 3.2 Hz), 3.49-3.47 (m, 1H), 3.38 (dd, 1H, *J* = 9.4, 3.6 Hz), 1.62-1.52 (m, 5H), 1.33-1.25 (m, 24H), 0.87 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 80.9, 80.0, 74.0, 60.1, 32.1, 30.0, 29.9, 29.8, 29.7, 29.6, 28.7, 26.6, 22.9, 14.4. **ESI-HMRS** [M+23] calcd for $C_{18}H_{37}NO_2Na$: 322.2722, found: 322.2720.

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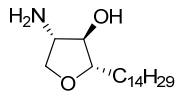
(2*S*, 3*R*, 4*S*)-4-amino-2-tetradecyltetrahydrofuran-3-ol. (3)-*epi*-Jaspine B (213)

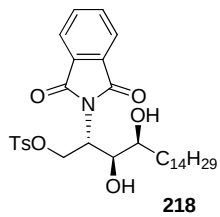


213

Compound **225** (36 mg, 0.085 mol) was dissolved in aqueous solution of $MeNH_2$ (0.20 mmol, 0.25 ml, 40%) and the resulting mixture was stirred in an open flask for 1h at 50 ºC. The reaction is allowed to cool at room temperature and methylamine is removed, first by bubbling argon through the reaction for 30 minutes and then under vacuum for 1 hour. The crude was purified by silica gel chromatography using 96:4:1 (DCM, MeOH, NH_4OH) as a solvent to offord a 30 mg of compound **213** as a white solid (85%).

$[\alpha]_D^{25}$ = -1.8 (*c* 0.8, $CHCl_3$). **^{1}H NMR** (400 MHz,$CDCl_3$): δ = 4.00 (dd, 1H, *J* = 9.2, 6.0 Hz), 3.59-3.56 (m, 3H), 3.29 (ddd, 1H, *J* = 8.0, 4.4, 3.6 Hz), 1.94 (brs, 3H), 1.68-1.57 (m, 2H), 1.49-1.14 (m, 24), 0.87 (t, 3H, J = 6.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 85.1, 83.7, 73.7, 60.4, 34.0, 31.9, 29.7, 29.6, 29.5, 29.4, 26.1, 22.7, 14.1. **ESI-HMRS** [M+1] calcd for $C_{18}H_{38}NO_2$: 300.2903, found: 300.2906.

(2*S*, 3*R*, 4*S*)-2-*N*-phtalimido-1-*p*-toluenesulphonyl-3,4-octadecandiol (218)



218

Compound **162** (450 mg, 1 mmol) was dissolved in anhydrous dichloromethane and triethylamine (0.7 mL, 5 mmol). Then, DMAP and tosyl chloride (573 mg, 3 mmol) were added and the mixture was stirred for 1 h at 0ºC and then 4 h at room temperature. The crude was acidified with HCl aqueous solution (10%) and then the organic layer was washed with saturated aqueous

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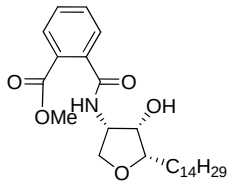
solution of $NaHCO_3$ and brine. The solvent was removed under vacuum and the crude was purified by radial chromatography using 8:2 to 7:3 hexanes:ethyl acetate as an eluent to afford 238 mg of compound **218** as a white solid (42%).

$[\alpha]_D^{25}$ = - 2.0 (*c* 1.5, CH_2Cl_2). **IR** (neat): 3512, 3063, 2922, 2852, 2361, 2337, 1775, 1710, 1465, 1383, 1361, 1190, 1176, 977, 812, 720 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 (dd, 2H, *J* = 5.6, 2.6 Hz), 7.75 (dd, 2H, *J* = 5.6, 4.8 Hz), 7.65 (d, 2H, *J* = 8.2 Hz), 7.18 (d, 2H, *J* = 8.2 Hz), 4.81 (dd, 1H, *J* = 11.0, 10.0 Hz), 4.61 (dd, 1H, *J* = 11.0, 3.2 Hz), 4.56 (ddd, 1H, *J* = 10.0, 8.0, 3.2 Hz), 3.90 (ddd, 1H, *J* = 8.4, 8.0, 1.6 Hz), 3.41 (brs, 1H), 3.03 (d, 1H, *J* = 8.4 Hz), 2.4 (s, 3H), 2.34 (brs, 1H), 1.53-1.44 (m, 2H), 1.35-1.19 (m, 23H), 0.86 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 168.5, 145.0, 134.6, 131.5, 130.0, 128.1, 123.8, 71.4, 70.6, 67.6, 53.0, 33.6, 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 25.9, 22.9, 21.9, 14.3. **ESI-HMRS** [M+23] calcd for $C_{33}H_{47}NO_7SNa^+$: 624.2971, found: 624.3002.

(2S,3*S*,4*S*)-4-*N*-[(2-methylbenzoate)-carbamoyl]-2-tetradecyltetrahydofuran-3-ol (219)



219

Compound **162** (276 mg, 0.6 mmol) was dissolved in anhydrous dichloromethane and triethylamine (0.3 ml, 2.2 mmol). Then, DMAP and tosyl chloride were added and the mixture was stirred for 22 h at room temperature. The crude was acidified with HCl aqueous solution (10%) and then the organic layer was washed with aqueous solution of $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was remover under vacuum. Then, Na_2CO_3 (125 mg, 1.5 mmol) was added and the mixture was dissolved in anhydrous methanol and it was stirred for 20 h at room temperature. The solvent was removed under vacuum and the crude was directly purified by silica gel

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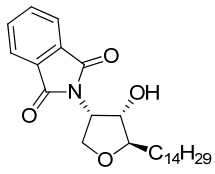
chromatography using 7:3 hexanes: ethyl acetate as an eluent to afford 165 mg of compound **219** as a white solid (61%).

$[\alpha]_D^{25}$ = - 8.3 (*c* 0.25, $CHCl_3$). **IR** (neat): 3453, 3279, 2970, 2922, 2852, 2361, 1727, 1633, 1547, 1464, 1292, 772 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.97 (d, 1H, *J* = 7.6 Hz), 7.58 (t, 1H, *J* = 7.6 Hz), 7.49 (t, 1H, *J* = 7.6 Hz), 7.44 (d, 1H, *J* = 7.6 Hz), 6.13 (d, 1H, *J* = 8.0 Hz), 4.72 (tdd, 1H, *J* = 8.4, 8.0, 4.0 Hz), 4.43 (dd, 1H, *J* = 4.0, 3.6 Hz), 4.13 (dd, 1H, *J* = 8.8. 8.4 Hz), 3.91 (s, 3H), 3.87 (td, 1H, *J* = 6.8, 3.6 Hz), 3.13 (brs, 1H), 1.70 (m, 2H), 1.45-1.25 (m, 23H), 0.88 (t, 3H, *J* = 6.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.2, 167.0, 138.7, 132.7, 130.4, 130.0. 129.7, 127.6. 82.6, 70.9, 69.2, 54.4, 52.9, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.0, 26.2, 22.7, 14.2. **ESI-HMRS** [M+23] calcd for $C_{27}H_{43}NO_5SNa$: 484.3039, found: 484.3048.

(2*R*, 3*S*, 4*S*)-4-*N*-phthalimido-2-tetradecyltetrahydrofuran-3-ol (220)



220

Sulphate **208** (0.09 mmol) was dissolved in anhydrous THF (1mL), then TFAF (117 ml, 0.117 mmol, 1M THF) were added dropwise. The solution was stirred 2 hours at room temperature and then the solution was dissolved in ethyl acetate, the organic layer was washed with NH_4Cl aqueous solution and brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using 7:3 hexanes:ethyl acetate as a solvent to afford 33 mg of product **220** as a white solid (86%).

$[\alpha]_D^{25}$ = + 8.3 (*c* 0.6, $CHCl_3$). **IR** (neat): 3300, 2958, 2920, 2895, 1392, 1280, 720 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ =7.85 (dd, 2H, *J* = 5.4, 3.2 Hz), 7.74 (dd, 2H, *J* = 5.4, 3.2 Hz), 4.95 (dd, 1H, *J* = 8.0, 5.6 Hz), 4.91 (dt, 1H, *J* = 8.4, 8.0 Hz), 4.59 (t, 1H, *J* = 8.4 Hz), 4.21 (dd, 1H, *J* = 8.4, 8.0 Hz), 4.15 (dt, 1H, *J* = 7.6,

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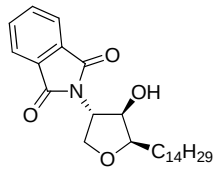
5.6 Hz), 1.68-1.62 (m, 2H), 1.57 (s, 1H), 1.34-1.25 (m, 20H), 0.86 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 168.2, 134.5, 131.6, 82.6, 75.7, 66.3, 50.7, 33.6, 32.1, 29.9, 29.8, 29.7, 25.8, 22.9, 20.7, 14.4. **ESI-HMRS** [M+23] calcd for $C_{16}H_{39}NO_4Na$: 452.2777, found: 452.2765.

(2*R*, 3*R*, 4*S*,)-4-*N*-phthalimido-2-tetradecyltetrahydrofuran-3-ol (222)



222

Alcohol **180** (200 mg, 0.44 mmol) and tosyl chloride (92 mg, 0.48 mmol) were dissolved in anhydrous dichloromethane (1 ml) and the solution was cooled at 0ºC. Pyridine (1 ml) was added and the mixture was stirred at 0ºC for 1h. Then, the mixture was warmed at room temperature for 10 hours, tosyl chloride (40 mg, 0.24 mmol) was added and the mixture was stirred 10 hours more. The mixture was treated with HCl aqueous solution (10%), the aqueous layer was washed with dichloromethane and the combined organic layers were washed with $NaHCO_3$ saturated aqueous solution and then they were washed with brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The mixture was purified by radial chromatography using hexanes:ethyl acetate (7:3) as a solvent to afford 190 mg of compound **222** as a white solid (60%).

$[\alpha]_D^{25}$ = + 11.5 (*c* 1.6, CH_2Cl_2). **IR** (neat): 3350, 2963, 2910, 2845, 1697, 1392, 720 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 (dd, 2H, *J* = 5.2, 3.0 Hz), 7.67 (dd, 2H, *J* = 5.2, 3.0 Hz), 4.67 (td, 1H, *J* = 7.6, 1.6 Hz), 4.53 (brs, 1H), 4.25-4.20 (m, 2H), 2.27 (d, 1H, *J* = 6.0 Hz), 1.70-1.60 (m, 2H), 1.41-1.25 (m, 24H), 0.792 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 126.2, 134.5, 131.9, 123.6, 82.9, 76.4, 67.6, 59.8. 32.1, 30.0, 29.9, 29.8, 26.6, 28.7, 26.4, 22.9, 14.3. **ESI-HMRS** [M+23] calcd for $C_{26}H_{39}NO_4Na$: 452.2777, found: 452.2779.

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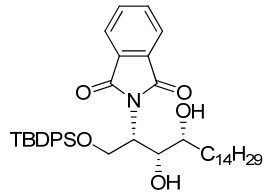
(2*S*,3*R*,4*R*)-(1-*tert*-buthyldiphenylsilyloxy)-2-*N*-phthalimido-octadecan-3,4-diol (223)



223

Alcohol **180** (107 mg, 0.24 mmol) was dissolved in dichloromethane (2mL) and DMF (0.5 mL). DMAP (1.5 mg, 0.012 mmol) and triethylamine (0.1 mL, 0.6 mmol) were added, then the solution was cooled at 0ºC and TBDPSCl (0.07 mL, 0.3 mmol) was added dropwise and after 1h, the mixture was warmed at room temperature and it was stirred for 18 h when TLC shows complete conversion. The crude was quenched with a NH_4Cl aqueous saturated solution, the aqueous layer was washed with dichloromethane and the combined organic layers were washed with brine and they were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the crude was purified by radial chromatography using 6:4 hexanes:ethyl acetate as a solvent to afford 163 mg of product **223** as a colorless oil (77%).

$[\alpha]_D^{25}$ = - 20.2 (*c* 0.9, CH_3Cl). **IR** (neat): 3424, 2924, 2853, 2361, 1706, 1465, 1430, 1389, 1213, 1111, 751 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.85 (dd, 2H, *J* = 5.4, 3.2 Hz), 7.75 (dd, 2H, *J* = 5.4, 3.2 Hz), 7.61 (dd, 2H, *J* = 8.0, 1.4 Hz), 7.51 (dd, 2H, *J* = 8.0, 1.4 Hz), 7.41-7.32 (m, 4H), 7.27 (t, 2H, *J* = 8.0 Hz), 4.77 (ddd, 1H, *J* = 8.8, 5.8, 3.2 Hz), 4.17 (t, 1H, *J* = 10.8), 4.15 (dd, 1H, *J* = 10.8, 8.8), 4.08 (d, 1H, *J* = 2.0 Hz), 3.91-3.88 (m, 1H), 3.55 (brs, 1H), 1.93 (brs, 1H), 1.43-1.38 (m, 2H), 1.25-1.22 (m, 24H), 0.89 (t, 3H, *J* = 6.8 Hz), 0.89 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.5 135.9, 135.7, 134.4, 133.2, 133.1, 132.0, 130.0, 129.9, 127.9, 127.9, 123.7, 75.4, 72.7, 60.8, 54.6, 32.6, 32.1, 29.9, 29.8, 29.7, 29.6, 26.8, 25.8, 22.9, 19.1, 14.3. **ESI-HMRS** [M+1] calcd for $C_{42}H_{60}NO_2$: 686.4241, found: 686.4245.

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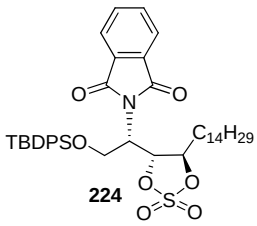
(2*S*,3*R*,4*R*)-1-(*tert*-butyldiphenlylsilyloxy)-2-N-phtalidimo-3,4-O-sulfuryloctadecane (224)



224

To a solution of diol **223** (0.16 g, 0.23 mmol) in dichloromethane (2 mL), triethylamine (90 μL, 0.68 mmol) and thionyl chloride (20 μl, 0.27 mmol) were added at 0ºC. After 40 minutes under stirring the reaction mixture was poured into brine and extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuum. The crude was dried in vaccuo for one night and then it was dissolved in $CCl_4/CH_3CN/H_2O$ (1mL:1mL:1mL). $RuCl_3 \cdot 3H_2O$ (6 mg, 0.011 mmol) and $NaIO_4$ (0.14 g, 0.68 mmol) were added. After 2.5 hours no starting material was observed by TLC. The reaction mixture was diluted with ethyl acetate, washed with a saturated solution of Na_2SO_3 and the organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford compound **224** as beige oil, which was not purified and was directly used in the next reaction.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.80 (dd, 2H, *J* = 5.6, 3.0 Hz), 7.50 (d, 2H, *J* = 6.6 Hz), 7.45 (d, 2H, *J* = 6.6 Hz), 7.41-1.36 (m, 4H), 7.30 (dd, 2H, *J* = 9.2, 8.0 Hz), 5.92 (dd, 1H, *J* = 11.4, 5.2 Hz), 5.86 (ddd, 1H, *J* = 11.4, 5.0, 2.8 Hz), 4.76 (ddd, 1H, *J* = 11.4, 8.6, 4.6 Hz), 4.16 (dd, 1H, *J* = 10.6, 8.6 Hz), 3.95 (dd, 1H, *J* = 10.6, 4.0 Hz), 1.52-1.39 (m, 2H), 1.28-1.15 (m, 20H), 0.88 (t, 3H, *J* = 6.8 Hz), 0.58 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 135.6, 134.9, 132.5, 131.6, 130.2, 130.1, 128.2, 128.0, 124.0, 85.6, 79.8, 61.4, 51.0, 32.1, 30.1, 29.9, 29.8, 29.7, 29.6, 29.3, 28.9, 27.9, 26.9, 26.7, 25.9, 25.0, 22.9, 19.1, 14.4. **ESI-HMRS** [M+23] calcd for $C_{42}H_{57}NO_7SNa$: 770.3523, found: 770.3551.

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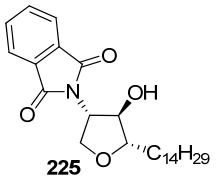
(2*S*, 3*R*, 4*S*)-4-*N*-phtalimido-2-tetradecyltetrahydrofuran-3-ol (3-*epi*-Jaspine B) (225)



225

Compound **224** (0.052 mmol) was dissolved in anhydrous dichloromethane (2mL) then a solution of TBAF in THF (57 ml, 0.057 mmol, 1M) was added. The solution was sirred for 2h at room temperature and then a drop of water and H_2SO_4 was added to the solution. The mixture was stirred at room temperature 2 hours more and then the crude was washed with a aqueous solution of $NaHCO_3$ and brine. The crude was purified by radial chromatography using 5:2 hexanes:ethyl acetate as a solvent to afford 20 mg as a white solid (92%).

$[\alpha]_D^{25}$ = +8.9 (*c* 1.4, $CHCl_3$). **IR** (neat): 3530, 3414, 2952, 2915, 2848, 2361, 2334, 1695, 1467, 1397, 720 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.71 (dd, 2H, *J* = 5.6, 3.2 Hz), 4.64 (ddd, 1H, *J* = 8.6, 8.0, 7.6 Hz), 4.53 (td, 1H, *J* = 7.6, 6.8 Hz), 4.24 (t, 1H, *J* = 8.8 Hz), 4.12 (dd, 1H, *J* = 8.8, 8.0 Hz), 3.75 (td, 1H, *J* = 7.6, 4.8 Hz), 2.74 (brs, 1H), 1.77-1.68 (m, 2H), 1.53-1.24 (m, 22H), 0.86 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 168.6, 134.5, 131.9, 123.6, 83.4, 77.8, 67.2, 59.3, 33.3, 32.1, 29.9, 29.8, 29.7, 29.6, 26.0, 22.9, 14.3. **ESI-HMRS** [M+23] calcd for $C_{26}H_{39}NO_4Na$: 452.2777, found: 452.2763.

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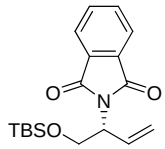
1-*tert*-butyldimethylsilyloxy-2-(*R*)-*N*-phthalimido-3-butene ((*R*)-270)



270

In a 25 mL dried flask 2- (*R*)-*N*-phthalimido-3-buten-1-ol (200 mg, 0.93 mmol) was dissolved in dichloromethane (5mL) and then imidazole (82 mg, 1.2 mmol), DMAP (11 mg, 0.09 mmol) and TBSCl (167 mg, 1.11 mmol) were added. The resulting solution was stirred for 7h at room temperature. The mixture was quenched with NH_4Cl aqueous and the organic layer was washed with water and brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude was purified by silica gel flash chromatography using 9:1 hexanes:ethyl acetate to afford 271 mg (90%) of compound **270** as a colorless solid.

$[\alpha]_D^{25}$ +16.3 (*c* 1, $CHCl_3$). **Mp** 34-36 °C. **IR** (neat): 3010, 2953, 2928, 2857, 1712, 1384, 1360, 1104, 837, 778, 718 cm^{-1}. **^{1}H NMR (**400 MHz, $CDCl_3$): δ 7.83 (dd, 2H, *J* = 5.2, 3.2 Hz), 7.70 (dd, 2H, *J* = 5.2, 2.8 Hz), 6.18 (ddd, 1H, *J* = 17.6, 10.4, 7.6 Hz), 5.30 (dt, 1H, *J* = 17.2, 1.4 Hz), 5.24 (dt, 1H, *J* = 10.4, 1.4 Hz), 4.91 (m, 1H), 4.15 (dd, 1H, *J* = 10.0, 9.6 Hz), 3.86 (dd, 1H, *J* = 10.0, 6.0 Hz), 0.75 (s, 9H), 0.00 (s, 3H), -0.07 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.2, 133.8, 132.2, 132.0, 123.1, 118.9, 62.2, 55.8, 25.6, 17.9, -5.5, -5.6. **ESI-HRMS** [M+1] calcd for $C_{18}H_{26}NO_3Si$: 332.1682, found: 332.1681.

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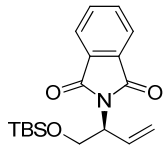
1-*tert*-butyldimethylsilyloxy-2-(*S*)-*N*-phthalimido-3-butene ((*S*)-270)



ent-270

In a dried flask of 5 mL 2-*N*-(*S*)-phthalimido-3-buten-1-ol (50 mg, 0.23 mmol) was dissolved in dichloromethane (2mL) and then imidazole (42 mg, 0.20 mmol), DMAP (3 mg, 0.023 mmol) and TBDSCl (42 mg, 0.28 mmol) were added. The resulting solution was stirred for 12 h at room temperature. The mixture was quenched with aqueous NH_4Cl, and the organic layer was washed with water and brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude was purified by silica gel flash chromatography using 9:1 hexanes:ethyl acetate to afford 70 mg of compound ***ent*-270** as a colorless solid (92 %).

$[\alpha]_D^{25}$ -15.8 (*c* 2, $CHCl_3$). **IR** (neat): 2953, 2928, 2857, 1712, 1384, 1360, 1104, 837, 778, 718 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 (dd, 2H, *J* = 5.2, 3.2 Hz), 7.70 (dd, 2H, *J* = 5.2, 2.8 Hz), 6.18 (ddd, 1H, *J* = 17.6, 10.4, 7.6 Hz), 5.30 (dt, 1H, *J* = 17.2, 1.4 Hz), 5.24 (dt, 1H, *J* = 10.4, 1.4 Hz), 4.91 (m, 1H), 4.15 (dd, 1H, *J* = 10.0, 9.6 Hz), 3.86 (dd, 1H, *J* = 10.0, 6.0 Hz), 0.75 (s, 9H), 0.00 (s, 3H), -0.07 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.2, 133.8, 132.2, 132.0, 123.1, 118.9, 62.2, 55.8, 25.6, 17.9, -5.5, -5.6. **ESI-HRMS** [M+1] calcd for $C_{18}H_{26}NO_3Si$: 332.1682, found: 332.1692.

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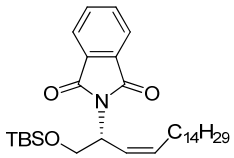
1-*tert*-Butyildimethylsilyloxy-2-(*R*)-N-phthalimido-3-octadecene ((*R*)-271)

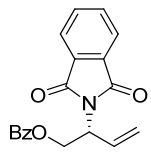


(*R*)-271

In an N_2-filled glovebox, an oven-dried 4mL vial with a magnetic stir bar was charged with compound **(*R*)-270** (100 mg, 0.3 mmol) and 1-hexadecene (677 mg, 3 mmol). Then benzene in situ-complex **261** solution (0.75 ml, 0.02 M) was added and the solution was stirred at 22ºC for 5h under vacuum. The crude was purified in a silica gel column chromatography using hexanes as a solvent to afford a 137 mg of compound **271** (90% yield) as a colorless oil *Z*:*E* >97:<3.

$[\alpha]_D^{25}$= +25.9 (*c* 1, $CHCl_3$). **IR** (neat): 2924, 2853, 1713, 1467, 1172, 873, 719 (cm^{-1}). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 (m, 2H), 7.69 (m, 2H), 5.82 (ddt, 1H, *J* = 10.8, 9.2, 1.2 Hz), 5.62 (dtd, 1H, *J* = 10.8, 7.4, 0.8 Hz), 5.19 (m, 1H), 4.12 (dd, 1H, *J* = 10.0, 10.0 Hz), 3.74 (dd, 1H, *J* = 10.0, 5.6 Hz), 2.15 (dtd, 2H, *J* = 7.4, 7.2, 1.6 Hz), 1.38-1.22 (m, 24H), 0.85 (t, 3H, *J* = 6.8 Hz), 0.73 (s, 9H), -0.01 (s, 3H), -0.08 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.4, 136.0, 134.0, 132.3, 123.5, 123.2, 62.7, 50.6, 32.2, 29.9, 29.9, 29.9, 29.8, 29.8, 29.7, 29.7, 29.6, 29.4, 28.0, 25.9, 22.9, 18.2, 14.3, -5.2, -5.4. **ESI-HRMS** [M+1] calcd for $C_{34}H_{48}N_4O_1$: 528.3851, found: 528.3851.

2-(*R*)-*N*-phthalimido-3-buten-1-yl benzoate (290)



290

Compound **139** (200 mg, 0.93 mmol) was dissolved in anhydrous dichloromethane (20 ml) and fresh distilled triethylamine (0.7 ml) was added. The solution was cooled at 0ºC and benzoyl chloride (0.25 ml, 1.92 mmol) was added

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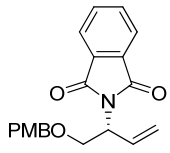
dropwise. The resulting mixture was warmed at room temperature for 12h. The mixture was quenched by saturated NH_4Cl aqueous solution, and then the organic layer was washed with water and brine. The solvent was removed under vacuum and the crude was purified by silica gel chromatography using 9:1 hexanes:ethyl acetate to afford 216 mg of compound **290** as a yellow solid (80%).

$[\alpha]_D^{25}$ = -7.8 (*c* 1, $CHCl_3$). **IR** (neat): 1707, 1381, 1267, 1109, 710 cm^{-1}. **Mp** 65-68 ºC **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92 (d, 2H, *J* = 7.2 Hz), 7.85 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.72 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.51 (t, 1H, *J* = 7.6 Hz), 7.37 (dd, 2H, *J* = 7.6, 7.6 Hz), 6.27 (ddd, 1H, *J* = 17.4, 10.4, 8.0 Hz), 5.41 (d, 1H, *J* = 17.4 Hz), 5.33 (d, 1H, *J* = 10.4 Hz), 5.21 (m, 1H), 4.83 (dd, 1H, *J* = 11.2, 9.2 Hz), 4.66 (dd, 1H, *J* = 11.2, 5.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.1, 166.2. 134.3, 133.3, 132.0, 131.6, 129.8, 128.6, 123.6, 63.8, 52.9. **ESI-HRMS [M+1]** calcd for $C_{19}H_{15}NO_4$: 322.1079, found: 332.1079.

1-*p*-Methoxybenzyloxy-2-(*R*)-N-phthalimido-3-butene (291)



291

Compound **139** (200 mg, 0.93 mmol) was dissolved in anhydrous THF (5 mL), the solution was cooled at 0°C and then NaH (56 mg, 1.4 mmol, 60%) and TBAI (34 mg, 0.093 mmol) were added. After stirring 30 minutes the suspension was warmed at room temperature and it was maintained at this temperature for 30 minutes more, and *p*-methoxybenzyl chloride (0.17 ml, 1.21 mmol) was added dropwise. The mixture was stirred at room temperature for 10 h. The crude was diluted with a NH_4Cl aqueous solution, and then the aqueous layer was washed with ethyl acetate. The combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was removed under vacuum and the crude was purified by silica gel chromatography using 7:3 hexanes:ethyl acetate as a solvent to afford a 250 mg of compound **292** as a colorless oil (80%).

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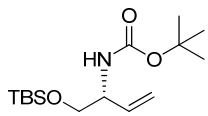
$[\alpha]_D^{25}$ = +2.4 (*c* 1, $CHCl_3$). **IR** (neat): 1706, 1512, 1383, 1247, 1090, 1033, 718 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.82 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.70 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.15 (d, 2H, *J* = 8.8 Hz), 6.78 (d, 2H, *J* = 9.2 Hz), 6.15 (ddd, 1H, *J* = 17.6, 10.2, 7.2 Hz), 5.28 (ddd, 1H, *J* = 17.2, 0.8, 0.2 Hz), 5.25 (dt, 1H, *J* = 10.2, 0.8 Hz), 5.06 (m, 1H), 4.09 (d, 1H, *J* = 11.6 Hz), 4.41 (d, 1H, *J* = 11.6 Hz), 4.08 (dd, 1H, *J* = 10.0, 10.0 Hz), 3.76 (s, 3H), 4.72 (dd, 1H, *J* = 10.0, 5.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.3, 159.4, 134.1, 132.5, 132.2, 130.1, 129.6, 123.4, 119.1, 113.9, 72.7, 68.8, 55.4, 53.4. **ESI-HRMS** [M+Na] calcd for $C_{20}H_{19}NO_4Na$: 360.1212, found: 360.1200.

1-*t*-Butyldimethylsilyloxi-3-buten-2-(*R*)-ylcarbamate (292)



292

Alcohol **142** (50 mg, 0.25 mmol) was dissolved in dry dichloromethane (2 ml), and then imidazole (22 mg, 0.33 mmol), DMAP (3 mg, 0.025 mmol) and TBSCl (45 mg, 0.3 mmol) were added. The mixture was stirred at room temperature for 10 hours. The reaction was diluted with NH_4Cl saturated aqueous solution and it was extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and then the solvent was removed under vacuum. The crude was purified by silica gel chromotography using 95:5 hexanes:ethyl acetate as a solvent to afford 55 mg of compound **292** as a colorless oil (73%).

$[\alpha]_D^{25}$ = +26.9 (*c* 1, $CHCl_3$). **IR** (neat): 2929, 1706, 1492, 1365, 1253, 1170, 1111, 836, 776. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.83 (ddd, 1H, *J* = 17.2, 10.4, 5.2 Hz), 5.19 (ddd, 1H, *J* = 17.2, 1.6, 1.6 Hz), 5.15 (dd, 1H, J = 10.4, 1.6 Hz), 4.82 (brs, 1H) 4.15 (m, 1H), 3.67 (dd, 1H, *J* = 10.0, 4.8 Hz), 3.61 (dd, 1H, *J* = 10.0, 4.0 Hz), 1.44 (s, 9H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.4, 136.6, 79.3, 65.3, 54.2, 28.4, 25.8, 18.3, -5.5, -5.5. **ESI-HRMS** [M+Na] calcd for $C_{15}H_{31}NO_3SiNa$: 324.1971, found: 324.1964.

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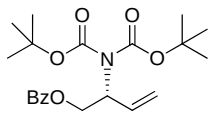
tert-Butyl-1-benzoyloxy-but-3-ene-2,2-(*R*)-di-ylcarbamate (293)



293

Compound **141** (150 mg, 0.5 mmol) was dissolved in freshly destilled triethylamine (5 mL), and then DMAP (127 mg, 1 mmol) was added. The mixture was cooled at 0 °C and di-*tert*-butyl dicarbonate (2.6 mmol, 563 mg) was added. After 10 minutes the mixture was warmed at room temperature and it was stirred for 10 h. The crude was dissolved in NH_4Cl aqueous and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water and brine and they were dried over $MgSO_4$. The solvent was removed under vacuum and the crude was purified by silica gel chromatography using 97:3 hexanes:ethyl acetate as a solvent to afford a 191 mg of product **293** as a colorless oil (98%).

$[\alpha]_D^{25}$= +25.9 (*c* 1, $CHCl_3$). **IR** (neat): 2980, 1701, 1347, 1266, 1111, 1027, 854, 710 cm^{-1}. **^{1}H NMR** (CDCl3, 400 MHz): δ 8.03 (dd, 2H, *J* = 8.4, 1.6 Hz), 7.55 (tt, 1H, *J* = 7.2, 1.6 Hz), 7.41 (dd, 2H, *J* = 8.4, 7.6 Hz), 6.02 (ddd, 1H, *J* = 17.6, 10.8, 6.4 Hz), 5.33 (ddd, 1H, *J* = 17.6, 1.6, 1.2), 5.27 (ddd, 1H, *J* = 10.4, 1.6, 1.2 Hz), 5.18 (m, 1H), 4.67 (dd, 1H, *J* = 11.0, 8.8 Hz), 3.60 (dd, 1H, *J* = 11.0, 6.4 Hz), 1.47 (s, 18H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.3, 152.9, 133.9, 133.2, 130.2, 130.0, 128.5, 118.5, 82.9, 64.9, 57.4, 28.2. **ESI-HRMS** [M+Na] calcd for $C_{21}H_{29}NO_6Na$: 414.1893, found: 414.1900.

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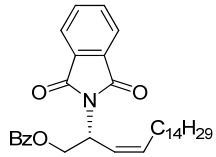
2-(*R*)-*N*-Phthalimido-3-octadecene-1-yl benzoate (296)



296

In an N_2-filled glovebox, an oven-dried 4mL vial with a magnetic stir bar was charged with compound **290** (19 mg, 0.06 mmol) and 1-hexadecene (134 mg, 0.6 mmol). Benzene *in situ*-complex **261** solution (0.75 μl, 0.02 M) was added the solution was stirred for 3 h under vacuum and then benzene *in situ*-complex solution was added and then a additional solution (0.75 μl, 0.02 M) and the mixture was stirred at 22ºC for 3 additional hours. The solvent was evaporated and the crude was purified by silica gel chromatography using 19:1 hexanes:ethyl acetate as a solvent to afford 31 mg of product **296** as a colorless oil (74%) Z:E = >98:<2**.**

$[\alpha]_D^{25}$ = +16.5 (*c* 1, $CHCl_3$). **IR** (neat): 2923, 2853, 1714, 1383, 1268, 1111, 711 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92 (dd, 2H, *J* = 8.4, 1.2 Hz), 7.84 (m, 2H), 7.71 (m, 2H), 7.51 (tt, 1H, *J* = 7.6, 1.6 Hz), 7.37 (dd, 2H, *J* = 8.0, 8.0 Hz), 5.96 (ddt, 1H, J = 10.8, 9.2, 1.6 Hz), 5.72 (dtd, 1H, *J* = 9.2, 5.6, 1.2 Hz), 4.21 (m, 1H), 4.81 (dd, 1H, *J* = 11.2, 9.6 Hz), 4.55 (dd, 1H, *J* = 11.2, 5.2 Hz), 2.18 (m, 2H), 1.39.1.19 (m, 24H), 0.87 (t, 3H, *J* = 6.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.1, 166.3, 137.0, 134.2, 133.2, 132.1, 129.9, 128.6, 123.5, 122.4, 64.2, 47.4, 32.1, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 28.0, 22.9, 14.3. **ESI-HRMS** [M+1] calcd for $C_{33}H_{44}NO_4$: 518.3270, found: 518.3270.

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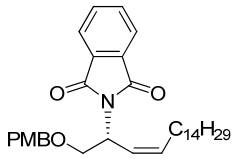
1-*p*-Methoxybenzyl-2-(*R*)-*N*-phthalimido-3-octadecyl ether (297)

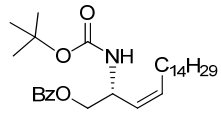


297

In an N_2-filled glovebox an oven dried 4 mL vial with a magnetic stir bar was charged with compound **291** (10 mg, 0.03 mmol) and 1-hexadecene (67 mg, 0.3 mmol). Benzene *in situ*-complex **261** solution (75 µl, 0.02M) was added and the mixture was stirred for 3.5 h at 22 ºC. Then the crude was purified by silica gel chromatography using 93:7 hexanes:ethyl acetate as a solvent to afford 9 mg of compound **297** as a colorless oil (56%).

$[\alpha]_D^{25}$ = +3.3 (*c* 1, $CHCl_3$). **IR** (neat): 2924, 2853, 1712, 1513, 1385, 1248, 719 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 (dd, 2H, *J* = 5.6, 2.8 Hz), 7.51 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.15 (d, 2H, *J* = 8.8 Hz), 6.77 (d, 2H, *J* = 8.8 Hz), 5.81 (dd, 1H, *J* = 10.8, 9.2 Hz), 5.62 (dtd, 1H, *J* = 10.8, 7.6, 1.2 Hz), 5.34 (dddd, 1H, *J* = 10.0, 9.2, 5.4, 0.8 Hz), 4.50 (d, 1H, *J* = 11.6 Hz), 4.39 (d, 1H, *J* = 11.6 Hz), 4.05 (dd, 1H, *J* = 10.2, 10.0 Hz), 3.76 (s, 3H), 3.58 (dd, 1H, *J* = 10.2, 5.4 Hz), 2.13 (m, 2H), 1.31-1.21 (m, 24H), 0.88 (t, 3H, *J* = 6.4 Hz).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.3, 159.3, 136.0, 134.0, 132.3, 130.3, 129.4, 123.5, 123.3, 113.9, 72.6, 69.2, 55.4, 47.9, 32.2, 29.9, 29.9, 29.9, 29.8, 29.7, 29.6, 29.5, 28.0, 22.9, 14.3. **ESI-HRMS** [M+23] calcd for $C_{34}H_{47}NO_4Na$: 556.3403, found: 556.3412.

(*R*)-*tert*-butyl-1-benzoyloxyoctadec-3-ene-2-yl-carbamate (299)



299

In an N_2-filled glovebox, an oven dried 4mL vial with a magnetic stir bar was charged with compound **141** (17 mg, 0.06 mmol) and 1-hexadecene (134 mg, 0.6 mmol). The benzene *in situ*-complex solution **261** (150 µl, 0.02M) was added

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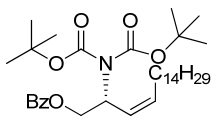
to the mixture and it was stirred for 5 h at 22ºC under vacuum. Then the crude was purified by silica gel chromatography using 95:5 hexanes:ethyl acatate as a solvent to afford 21 mg of product **299** as a colorless oil (72%) *E:Z* = >98:2.

$[\alpha]_D^{25}$ +5.3 (*c* 1, $CHCl_3$). **IR** (neat): 3384, 2924, 2854, 1723, 1603, 1517, 1457, 1367, 1712, 1116, 1070, 667 (cm^{-1}). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (dd, 2H, *J* = 7.6, 0.8 Hz), 7.56 (t, 1H, *J* = 7.6 Hz), 7.43 (d, 2H, *J* = 7.6 Hz), 5.62 (dt, 1H, *J* = 10.8, 7.6 Hz), 5.32 (dd, 1H, *J* = 10.8, 10.8 Hz), 4.83 (m, 1H), 4.64 (brs, 1H), 4.29 (d, 2H, *J* = 4.4 Hz), 2.17 (m, 2H), 1.43 (s, 9H), 1.29-1.25 (m, 24H), 0.88 (t, 3H, J = 6.4 Hz).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.7, 155.3, 135.3, 133.3, 130.2, 130.0, 129.6, 125.9, 79.8, 67.0, 47.5, 32.1, 29.9, 29.9, 29.8, 29.8, 29.7, 29.5, 28.5, 28.2, 22.9, 14.3. **ESI-HRMS** [M+Na] calcd for $C_{30}H_{49}NO_4Na$: 510.3559, found: 510.3574.

***tert*-Butyl-1-benxoyloxyoctadec-3-ene-2,2-(*R*)-di-yl-carbamate (300)**



300

In an N_2-filled glovebox, an oven dried 4mL vial with a magnetic stir bar was charged with compound **293** (117 mg, 0.3 mmol) and 1-hexadecene (667 mg, 3 mmol). The mixture was dissolved in benzene *in situ*-complex **261** solution (750 µl, 0.02 M) and it was stirred for 5 h at 22ºC under vacuum. Then the crude was purified by silica gel chromatography using 98:2 hexanes:ethyl acatate as a solvent to afford a 155 mg of compound **300** as a colorless oil (95%) *E:Z* = 98:2.

$[\alpha]_D^{25}$ = -4.4 (*c* 0.7, $CHCl_3$). **IR** (neat): 2924, 2854, 1726, 1702, 1454, 1367, 1347, 1268, 1113, 711 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (dd, 2H, *J* = 7.6, 1.6 Hz), 7.54 (tt, 1H, *J* = 7.6, 1.2 Hz), 7.41 (d, 2H, *J* = 7.6 Hz), 5.66 (dd, 1H, *J* = 10.8, 7.2 Hz), 5.62 (dt, 1H, *J* = 10.8, 5.6 Hz), 4.82 (ddd, 1H, *J* = 9.6, 7.2, 6.0 Hz), 4.63 (dd, 1H, *J* = 11.2, 9.6 Hz), 4.46 (dd, 1H, *J* = 11.2, 6.0 Hz), 2.16 (m, 2H), 1.46 (s, 18H), 1.38-1.25 (m, 24H), 0.88 (t, 3H, *J* = 6.8 Hz).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.1, 152.6, 136.3, 132.9, 130.1, 129.7, 128.2, 124.1, 82.4, 65.2, 52.0,

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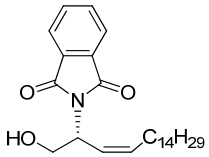
31.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 28.0, 22.7, 14.1. **ESI-HRMS** [M+23] calcd for $C_{35}H_{57}NO_6Na$: 610.4084, found: 610.4100.

2-(*R*)-*N*-Phthlimido-3-octadecen-1-ol (303)



303

Compound **(*R*)-271** (121 mg, 0.23 mmol) was dissolved in anhydrous dichloromoethane and a solution triethylaminotrihydrofluoride (139 ml, 0.35 mmol, ca 37%) was added dropwise. The mixture was stirred at rt for 9 h. Then the crude was directly supported in silica and it was purified by chromatographic column using a gradient from 7:3 to 6:4 (hexanes:ethyl actetate) as a solvent to afford 82 mg of compound **303** as white solid (86% yield)**.**

$[\alpha]_D^{25}$ + 54.8 (*c* 1, $CHCl_3$). **IR** (neat): 3465, 2923, 2853, 1710, 1387, 1357, 719 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.83 (dd, 2H, *J* = 5.6, 3.2 Hz), 7.71 (dd, 2H, *J* = 5.6, 3.2 Hz), 5.85 (ddt, 1H, *J* = 10.8, 9.2, 1.4 Hz), 5.67 (dt, 1H, *J* = 10.8, 7.4 Hz), 5.22 (ddd, 1H, *J* = 9.2, 9.2, 4.8 Hz), 4.08 (m, 1H), 3.88 (dd, 1H, *J* = 9.2, 4.8 Hz), 2.23 (brs, 1H), 2.17 (dtt, 2H, *J* = 7.6, 7.4, 1.4 Hz), 1.34-1.23 (m, 24H), 0.88 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.7, 136.4, 134.2, 132.2, 123.5, 123.0, 63.5, 50.6, 32.1, 29.9, 20.9, 29.9, 29.8, 29.8, 29.7, 29.6, 29.6, 29.5, 28.0, 14.3. **ESI-HRMS** [M+1] calcd for $C_{26}H_{40}NO_3$: 414.3008, found: 414.3010.

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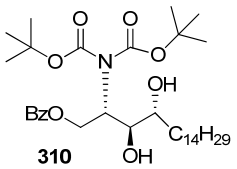
(3*R*, 4*R*)-*tert*-Butyl-1-benxoyloxyoctadeca-3,4-diol-2,2-(*R*)-di-yl carbamate (310)



310

NMO (21 mg, 0.18 mmol) was dissolved in dichloromethane (3 mL) under argon at room temperature. The solution was cooled at 0ºC and a water solution of OsO_4 (29 μl, 0.0045 mmol, 4%) was added. The solution was stirred at this temperature for 15 minutes. Then a solution of compound **300** (50 mg, 0.09 mmol) in dichloromethane (2 ml) was added and it was maintained for additional 15 minutes at 0ºC. Then the temperature was raised until room temperature and the solution was warmed at room temperature and it was stirred for 25 h. Then the mixture was dissolved in $Na_2S_2O_3$ aquous and it was extracted with ethyl acetate 3 times. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtrated and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using 9:1 hexanes:ethyl acetate as a solvent to afford a 28 mg of compound **310** as a colorless oil (89%).

$[\alpha]_D^{25}$ -13.6 (*c* 1, $CHCl_3$). **IR** (neat): 3468, 2979, 2922, 2853, 1725, 1703, 1584, 1454, 1392, 1270, 1155, 1120, 760 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.02 (d, 2H, *J* = 8.4 Hz), 7.54 (tt, 1H, *J* = 7.2, 1.6 Hz), 7.40 (dd, 2H, *J* = 7.6, 7.6 Hz), 5.93 (ddd, 1H, *J* = 7.2, 7.2, 2.8 Hz), 4.72 (d, 1H, *J* = 7.2 Hz), 4.29 (d, 1H, *J* = 7.2, Hz), 3.84 (m, 1H), 3.74 (m, 1H), 2.24 (d, 1H, *J* = 4.8 Hz), 1.64 (m, 1H), 1.54 (m, 1H), 1.44 (s, 18H), 1.32-1.25 (m, 24H), 0.89 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.5, 154.2, 133.1, 130.3, 130.0, 128.8, 128.5, 83.6, 76.5, 73.3, 62.3, 57.1, 32.7, 32.1, 29.9, 29.9, 29.8, 29.6, 29.6, 28.2, 28.1, 26.2, 22.9, 14.3 **ESI-HRMS** [M+23] calcd for $C_{35}H_{59}NO_8Na$: 644.4138, found: 644.4120.

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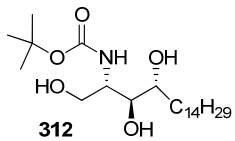
(2*R*,3*R*,4*R*)-*tert*-Butyl-1,3,4-octadecantriol-2-yl carbamate (312)



312

Compound **310** (40 mg, 0.07 mmol) was dissolved in THF (2.5 mL), then a water solution of LiOH (6 mg, 0.25 mmol, 1M) was added and the solution was stirred at room temperature for 20 h. The crude was dissolved in dichloromethane and it was extracted with aqueous $NaHCO_3$. The organic layer was washed with water, dried over $MgSO_4$ and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using a hexanes:ethy acetate 7:3 as a solvent to afford a 28 mg of compound **312** as a white solid (68%).

$[\alpha]_D^{25}$ = +6.2 (*c* 0.3, $CHCl_3$). **Mp** = 84-86 ºC. **IR** (neat): 3346, 2922, 2853, 1725, 1684, 1584, 1457, 1392, 1366, 1248, 1170, 1047, 1026, 912, 588, 720 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): 5.31 (m, 1H), 5.92-3.62 (m, 5H), 3.33 (m, 1H), 3.08 (brs, 1H), 2.52 (brs, 1H), 1.72 (brs, 1H), 1.58 (m, 1H), 1.49 (m, 1H), 1.25 (s, 9H), 1.35-1.25 (m, 24H), 0.8 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.5, 154.2, 133.1, 130.3, 130.0, 128.8, 128.5, 83.6, 76.5, 73.3, 62.3, 57.1, 32.7, 32.1, 29.9, 29.9, 29.8, 29.6, 29.6, 28.2, 28.1, 26.2, 22.9, 14.3 **ESI-HRMS** [M+Na] calcd for $C_{23}H_{47}NO_5Na$: 440.3352, found: 440.3345.

General procedure for aziridination of 2,4-dien-1-ols. A 10 mL Shchlenk containing a magnetic stirring bar was charged with catalyst (0.0025 mmol, 1%) and the alcohol (0.25 mmol), the flask was flushed three times with argon, then anhydrous dichloromethane (5 mL) was added. A freshly prepared PhINTs (0.27 mmol) was added in 3-4 portions over 2h and the mixture was stirred for an additional hour after the last addition. Finally the solvent was removed under vacuum and the resulting crude was characterized without purification because vinyl aziridines are unstable by silica gel or neutral alumina.[265]

PhINTs (322). KOH (2.80 g, 50 mmol) was dissolved in methanol (100 mL) at room temperature for 30 minutes before *p*-toluenesulfonamide (3.42 g, 20 mmol) was added. Then, the solution was cooled in a saturated NaCl water-ice bath and diacetoxyiodobenzene (6.40 g, 19.9 mmol) was added at that temperature. After

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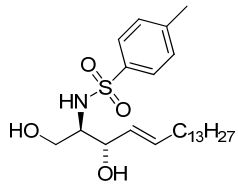
stirring the mixture for 2 h the crude was warmed at room temperature and it was stirred 2 h more. The crude was concentrated under vacuum for 20 minutes and then it was kept on the fridge overnight. The precipitated solid was filtered via cannula and dried under vacuum.

$Tp^{Br3}Cu(NCCH_3)$: $Tp^{Br3}Tl$ (1.19 g, 1 mmol) and CuI (190 mg, 1 mmol) were added to a flamed-dried Schlenck being both solids purged under vacuum/argon. The solids were dissolved in anhydrous acetonitrile (25 mL) and the solution was stirred at room temperature for 12h before the solvent was evaporated under vacuum. The residue was dissolved in anhydrous dichloromethane and the solution was stirred by 30 minutes. The liquid phase was filtered via cannula and the solvent was evaporated under vacuum to afford a white solid.

(*E*)- 2-*N*-tosyl-octadec-4-en-2-amino-1,3-diol (313)



313

Aziridine **314** (0.10 mmol) was dissolved in DMSO (0.75 mL) and an aqueous solution of KOH (10 %, 0.75 mL) was added. The solution was stirred for 1h at 40 ºC. The crude was neutralized with saturated NH_4Cl aqueous solution. The aqueous layer was extracted with diethyl ether (3 x 25 mL) and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and purified by radial chromatography using 7:3 hexanes:ethyl acetate to afford 31 mg of product **313** as a white solid (72%).

IR (neat): 3481, 3281, 2922, 2853, 1540, 1461, 1157, 1094 cm^{-1}. **^{1}H NMR** (400 MHz $CDCl_3$): δ = 7.70 (d, 2H, *J* = 8.4 Hz), 7.31 (d, 2H, *J* = 8.4 Hz), 5.71 (dt, 1H, *J* = 15.0, 7.2 Hz), 5.33 (dd, 1H, *J* = 15.0, 6.4 Hz), 5.30 (d, 1H, *J* = 8.0 Hz), 4.18 (m, 1H), 3.84 (d, 1H, *J* = 12.0 Hz), 3.48 (m, 1H), 3.19 (m, 1H), 2.43 (s, 3H), 2.29 (d, 1H, *J* = 5.2 Hz), 2.25 (brs, 1H), 1.99 (dt, 2H, *J* = 7.2, 6.4 Hz), 1.32-1.25 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 143.9, 135.0,

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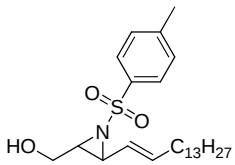
130.0, 128.2, 127.3, 74.9, 62.2, 57.9, 32.5, 32.1, 29.9, 29.7, 29.6, 29.4, 29.2, 22.9, 21.8, 14.4. **ESI-HMRS** (M+23) calculated for $C_{25}H_{43}SO_4NNa$: 476.2810, found 476.2789.

trans-(3-((*E*)-pentadec-1-enyl)-1-tosylaziridin-2-yl)methanol (314)

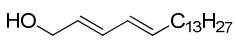


314

Aziridine **314** was synthetised following the general procedure for aziridination of 2,4-dien-1-ol using alcohol **315**.

IR (neat): 3516, 2935, 2924, 2854, 1463, 1377, 1338, 1161, 813 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.83 (d, 2H, *J* = 8.4 Hz), 7.32 (d, 2H, *J* = 8.4 Hz), 5.86 (dt, 1H, *J* = 15.0, 6.8 Hz), 5.50 (dd, 1H, *J* = 15.0, 9.0 Hz), 4.01 (dd, 1H, *J* = 13.0, 3.0 Hz), 3.73 (dd, 1H, *J* = 13.0, 6.8 Hz), 3.35 (dd, 1H, *J* = 9.0, 4.4 Hz), 3.18 (ddd, 1H, J = 6.8, 4.4, 3.0 Hz), 2.44 (s, 3H), 2.17 (2H, m), 1.43-1.30 (22H, m), 0.87 (t, 3H, J = 6.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): 144.4, 139.9, 129.9, 127.5, 126.7, 123.0, 61.0, 49.9, 48.6, 32.6, 32.1, 29.9, 29.8, 29.7, 29.6, 29.3, 29.0, 22.9, 21.9, 14.4. **ESI-HMRS** [M+23] calc for $C_{25}H_{41}NO_3SNa$: 458.2705, found: 458.2681.

(2*E*, 4*E*)-octadeca-2,4-dien-1-ol (315)



315

Ester **379** (0.2 g, 0.65 mmol) was dissolved in dichloromethane and the solution was cooled at -40ºC. DIBAL (0.33 mL, 1.6 mmol) was added dropwise over 1h and the mixture was stirred at -40ºC for 2 hours. The crude was quenched with methanol, the organic layer was washed with a saturated sodium potassium tartrate solution and the aqueous layer was washed with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvent was removed

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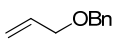
under vacuum. The crude was purified by silica gel chromatography using 7:3 hexanes:ethyl acetate to afford 91 mg of **315** as a white solid (53%).

Mp = 88-90 ºC. **IR** (neat): 3425, 2825, 2750, 1690, 1330, 1230, 1000, 720 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ= 6.19 (dd, 1H, *J* = 15.2, 10.8 Hz), 6.01 (dd, 1H, *J* = 15.2, 10.8 Hz), 5.68 (dt, 1H, *J* = 15.2, 7.0 Hz), 5.67 (dt, 1H, *J* = 15.2, 6.0 Hz), 4.13 (t, 2H, *J* = 6.0 Hz), 2.03 (dt, 2H, *J* = 7.2, 7.0 Hz), 1.51 (s, 1H), 1.36-1.22 (m, 22H), 0.85 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ= 136.0, 132.3, 129.5, 129.5, 63.7, 32.8, 32.1, 29.9, 29.8, 29.7, 29.6, 29.4, 22.9, 14.3. Collected data are in agreement with reported data.[265]

Allylbenzylether (317)



317

Allylic alcohol (2.3 mL, 33.8 mmol) was added dropwise to a suspension of NaH (1.5 g, 37.2 mmol) in THF (170 mL) at 0ºC over 0.5 h before the reaction was warmed at room temperature. Then, BnBr (4.4 mL, 37.2 mmol) was added dropwise over 1 h at room temperature and the raction mixture was stirred at that temperature for 12 h. The crude was quenched at 0ºC by saturated aqueous NH_4Cl solution until the gase evolution ceased. The crude was extracted with ethyl acetate and the aqueous solution was extracted with ethyl acetate (3 times). The combined organic layers were combined and they were washed with brine, dried over $MgSO_4$ and evaporated. The mixture was purified by flash chromatography 5:1 (hexanes:ethyl acetate) to afford 3.6 g of product **317** as a colorless oil (76%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.34-7.24 (m, 5H), 5.94 (dd, 1H, *J* = 14.0, 10.0 Hz), 5.28 (dq, 1H, *J* = 10.0, 2.4 Hz), 5.21 (dq, 1H, *J* = 14.0, 2.4 Hz), 4.51 (s, 2H), 4.02 (t, 2H, *J* = 8.0 Hz). **^{13}C NMR** (100 MHz,$CDCl_3$): δ= 138.5, 134.9, 128.5, 127.9, 127.7, 117.2, 72.3, 71.3.

[265] a) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514-2517.

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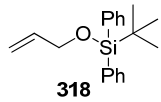
tert-butyl-diphenylsilyloxy-2-propene (318)

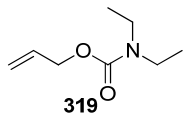


318

Allylic alcohol (1.15 mL, 16.9 mmol) was added to a solution of imidazole (1.3 g, 18.6 mmol) and DMAP (0.4 g, 3.38 mmol) in dichloromethane (125 mL). Then TBDPSCl (4.8 mL, 18.6 mmol) was added and the reaction was stirred 8 h at room temperature. After this time aqueous NH_4Cl solution was added to the mixture. The aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The crude was purified by flash chromatography using 8:2 (hexanes:ethyl acetate) to give 2.2 g of product **318** as colorless oil (86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72-7.39 (m, 4H), 7.36-7.34 (m, 6H), 5.91 (ddt, 1H, *J* = 17.2, 11.2, 4.0 Hz), 5.39 (dd, 1H, *J* = 17.2, 2.0 Hz), 5.12 (ds, 1H, *J* = 11.2, 2.0 Hz), 4.21 (ddd, 2H, *J* = 4.0, 2.0, 2.0 Hz), 1.07 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ ppm): δ= 137.2, 135.7, 129.8, 127.9, 114.1, 64.8, 27.0, 19.4.

Allyldiethylcarbamate (319)



319

Allylic alcohol (3.4 mL, 50 mmol) was added to a suspension of NaH (21.4 g, 75 mmol) in THF (200 mL) at 0ºC for 30 min. Then DMAP (0.61 g, 5 mmol) and carbomoyl chloride (9.5 mL, 75 mmol) were added and the mixture was stirred at room temperature for 6 h before. After that, a saturated aqueous saturated NH_4Cl solution was added at 0ºC. The crude was extracted with ethyl acetate and the aqueous solution was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were combined and they were washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The mixture was purified by flash chromatography 5:1 (hexanes:ethyl acetate) to afford 5g of product **319** as a yellow oil (86%).

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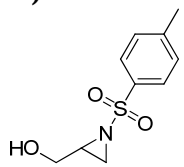
IR (neat) = 2975, 2935, 1695, 1478, 1417, 1269, 1169, 1066, 996, 928, 770 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.93 (ddt, 1H, *J* = 17.6, 10.8, 5.0 Hz), 5.29 (ddt, 1H, *J* = 17.6, 2.0, 2.0 Hz), 5.18 (ddt, 1H, *J* = 10.8, 2.0, 2.0 Hz), 4.58 (dt, 2H, *J* = 5.0, 2.0 Hz), 3.29 (m, 4H), 1.12 (t, 6H, *J* = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ= 154.0, 132.1, 118.2, 66.2, 45.0, 12.7.

(1-tosylazirin-2-yl)-methanol (323)



323

Compound **323** was synthesized following the general aziridination procedure starting from allylic alcohol. The crude was purified by flash chromatography using hexanes:ethyl acetate (6:1) obtaining the product **323** as a yellow oil.

IR (neat): 3505, 2925, 1730, 1321, 1155, 1097, 815 cm-1. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.83 (d, 2H, *J* = 8.2 Hz), 7.36 (d, 2H, *J* = 8.2 Hz), 3.87 (ddd, 1H, *J* = 12.6, 6.6, 3.0 Hz), 3.54 (ddd, 1H, *J* = 12.6, 6.6, 4.6 Hz), 3.04 (dtd, 1H, *J* = 7.6, 4.6, 3.0 Hz), 2.64 (d, 1H, *J* = 7.6 Hz), 2.46 (s, 3H), 2.33 (d, 1H, *J* = 4.6 Hz), 1.72 (t, 1H, *J* = 6.6 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ= 142.7, 134.3, 130.0, 128.2, 61.0, 40.6, 31.1, 21.9. Experimental data are in agreement with the reported data.[266]

[266] Young Choi, J.; Borch, R. F. Org. Lett. **2007**, *9*, 215.

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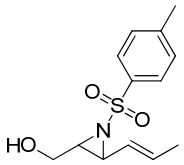
trans-(3-((_E_)-propen-1-enyl)-1-tosylaziridin-2-yl)methanol (336)

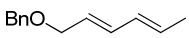


336

Aziridine **336** was synthesized following the general aziridination procedure using alcohol **335**.

IR (neat): 3517, 2923, 2856, 1598, 1455, 1377, 1091, 710 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 (d, 2H, *J* = 8.4 Hz), 7.31 (d, 2H, *J* = 8.4 Hz), 5.91 (dq, 1H, *J* = 15.4, 6.6 Hz), 5.55 (dd, 1H, *J* = 15.4, 8.8 Hz), 3.97 (dd, 1H, *J* = 12.8, 2.8 Hz), 3.72 (dd, 1H, *J* = 12.8, 6.4 Hz), 3.36 (dd, 1H, *J* = 8.8, 4.4 Hz), 3.18 (m, 1H), 2.44 (s, 3H), 2.42 (brs, 1H), 1.73 (dd, 3H, *J* = 6.6, 0.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ= 144.6, 134.7, 129.9, 127.7, 126.8, 124.6, 61.0, 49.9, 48.4, 21.7, 18.3. **ESI-HMRS** [M+1] calc for $C_{13}H_{17}NO_3S$: 268.1007, found: 267.9767.

(2_E_, 4_E_)-1-benzyloxy-hexa-2,4-diene (346)



346

Alcohol **335** (0.5 g, 5 mmols) was added to a suspension of NaH (0.3 g, 7.6 mmol, 60%) in THF at 0ºC. After 30 minutes, benzyl bromide (0.77 ml, 6.5 mmol) was added dropwise, the suspension was warmed at room temperature and the mixture was stirred for 10 hours. The crude was treated with ethyl acetate and it was washed with water, NH_4Cl aqueous solution and brine. The organic layer was dried over anhydrous $MgSO_4$ and it was purified by silica gel chromatography using 95:5 petroleum ether:ethyl acetate to afforded 0.9 g of product **346** as a colorless oil (96%).

IR (neat): 3028, 2926, 2855, 1454, 1074, 736 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.34-7.32 (m, 5H), 6.27 (dd, 1H, *J* = 15.0, 10.4 Hz), 6.11 (dd, 1H, *J* = 15.0, 10.4 Hz), 5.78-5.69 (m, 2H), 4.54 (s, 2H), 4.08 (d, 2H, *J* = 6.4 Hz), 1.8 (d, 3H, *J* =

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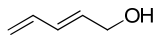
4.0 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ= 138.5, 133.4, 130.9, 130.1, 128.4, 127.8, 127.7, 126.7, 71.9, 70.6, 18.2. Collected experimental data are in agreement with the reported data.[267]

(2*E*, 4*E*)-penta-2,4-dien-1-ol (358)[268]



358

Lithium aluminum hydride (3.75 g, 11.6 mmol) was suspended in diethylether (80 mL) and cooled down at 0 °C. A solution of acid **366** (1g, 10.6 mmol) in diethyl ether was added dropwise over 1 h. The mixture was stirred over 1 h more and then it was stirred for 1h at reflux. Then, the mixture was warmed at room temperature, it was hydrolyzed with water and it was washed with NaOH aqueous solution (1M). The crude was poured through a short pad of Celite and diluted with diethylether (25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under vacuum to give 0.6 g of product **358** as a colourless liquid (75%) which was used without any further purification for the next step. The collected experimental date are in agrrement with the reported data.

^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): δ= 6.22 (2H, m), 5.73 (1H, dt, *J* =15.2, 5.7 Hz), 5.17 (1H, d, *J* = 16.4 Hz), 5.11 (1H, d, *J* = 9.2 Hz), 4.07 (2H, m). **^{13}C NMR** ($CDCl_3$, 100 MHz, δ ppm): δ= 135.0, 131.2, 130.7, 116.5, 61.9. NMR data are in agreement with reported data.[268]

267 Lindström, U. M.; Somfai, P. *Synthesis* **1998**, *1*, 109-117.

268 Linder, J.; Blake, A. J.; Moody, C. J. *Org. Biomol. Chem,* **2008**, *6,* 3908-3916.

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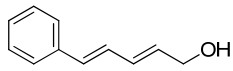
(2*E*, 4*E*)-5-phenylpenta-2,4-dien-1-ol (360)[269]

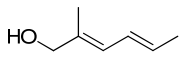


360

Ester **369** (10 mmol) was dissolved in dry dichloromethane (100 mL) and the solution was cooled at -40ºC. Then, a solution of DIBAL in dichloromethane (25 mL, 25 mmol, 1M) was added dropwise at -40ºC. The solution was stirred for 4h at 50ºC and the crude was treated with dichloromethane, methanol and water. The aqueous layer was washed with dichloromethane and the combined organic layers were washed with a sodium potassium tartrate aqueous solution, water and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The crude was purified by silica gel chromatography 7:3 hexanes:ethyl acetate as a solvent to afford 1.1 g of alcohol **360** as a white solid (68 %).

Mp = 76-77 ºC. **^{1}H NMR** (400 MHz,$CDCl_3$): δ= 7.40 (d, 2H, *J* = 7.6 Hz), 7.33 (dd, 2H, *J* = 7.6, 7.2 Hz), 7.24 (t, 1H, *J* = 7.2 Hz), 6.81 (dd, 1H, *J* = 15.6, 10.6 Hz), 6.57 (d, 1H, *J* = 15.6 Hz), 6.44 (dd, 1H, *J* = 15.4, 10.6 Hz), 5.98 (dt, 1H, *J* = 15.4, 6.0 Hz), 4.27 (dd, 2H, *J* = 6.0, 5.6 Hz), 1.40 (t, 1H, *J* = 5.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ= 137.3, 133.0, 132.7, 131.9, 128.8, 128.3, 127.8, 126.6, 63.7. Collected experimental data are in agreement with reported data.[269]

(2*E*, 4*E*)-2-methylhexa-2,4-dien-1-ol (361)



361

Ester **372** (8 mmol) was dissolved in dry dichloromethane (20 mL) and the solution was cooled at -40ºC, DIBAL solution (20 mL, 20 mmol, 1M) was added dropwise and the mixture was stirred at -40ºC for 4 h. Then the mixture was diluted with dichloromethane, methanol and water. The aqueous layer was

[269] a) Kim, D. D.; Lee, S. J.; Beak, P. *J. Org. Chem.* **2005**, *70*, 5376-5386. b) Drew, J.; Letellier, M.; Morand, P.; Szabo, A. G. *J. Org. Chem.* **1987**, *52*, 4047-4052.

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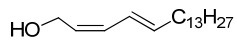
extracted with dichloromethane and the combined organic layers were washed with sodium potassium tartrate aqueous solutions, brine and water. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using 7:3 hexanes:ethyl acetate as a solvent to afford 681 mg of **361** colorless oil (76 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.24 (dd, 1H, *J* = 13.2, 11.2 Hz), 5.95 (d, 1H, *J* = 11.2 Hz), 5.67 (dq, 1H, *J* = 13.2, 6.6 Hz), 3.96 (s, 2H), 2.91 (brs, 1H), 1.75 (d, 3H, *J* = 6.6 Hz), 1.71 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 134.5, 129.2, 127.4, 125.0, 68.3, 18.4, 14.0. NMR data are in agreement with reported data.[270]

(2*Z*, 4*E*)-octadeca-2,4-dien-1-ol (362)[271]



362

Alkyne **375** (0.5g, 1.5 mmol) was dissolved in dichloromethane (40 mL) and methanol (10 mL), quinoline (0.35 mL) and Lindlar catalyst (0.3 g) were added. The mixture was stirred for 2 h at room temperature over H_2 atmosphere. The solvent was removed under vacuum and the crude was purified by silica gel chromatography using 10:1 (hexanes: ethyl acetate) as a solvent to afford 0.5 g of product **362** as a white solid (84% yield).

Mp= 62-64ºC. **IR** (neat): 3345, 3022, 2921, 2852, 1458, 1265, 742 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.29 (dd, 1H, *J* = 14.2, 11.0 Hz), 6.04 (dd, 1H, *J* = 11.0, 10.8 Hz), 5.73 (dt, 1H, *J* = 14.2, 7.2 Hz), 5.47 (dt, 1H, *J* = 10.8, 6.8 Hz), 4.27 (d, 2H, *J* = 7.2 Hz), 2.27 (brs, 1H), 2.09 (qt, 2H, J = 7.2, 7.2 Hz), 1.37 (m, 2H), 1.29-1.25 (m, 22H), 0.88 (t, 3H, *J* = 6.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 137.5, 131.2, 127.4, 125.0, 58.8, 33.0, 32.1, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 22.9, 14.3. **ESI-HRMS** (M+1) calculated for $C_{18}H_{35}O$: 267.2688, found 267.1996. Collected experimental data are in agreement with with reported data.[271]

[270] DeBoef, B.; Counts, W. R.; Gilbertson, S. R. *J. Org. Chem.* **2007**, *72*, 799-804.

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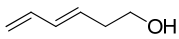
(3*E*, 5*E*)-hexa-3,5-diene-1-ol (363)

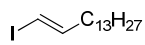


363

Ester **381** (40 mmol) was dissolved in anhydrous dichloromethane (80 mL) and the solution was coolded at -20ºC. DIBAL (100 mmol, 100 ml) was added dropwise at that temperature, and the mixture was stirred at -20 ºC for 2h. The crude was quenched at 0 ºC with ethyl acetate (5 ml) and then it was poured into a saturated aqueous Rochelle solution and it was vigourously stirred for 1h. Then, the phases were separated and the aqueous phase was washed with ethyl acetate. The combined organic layers were washed with brine and then they were dried over anhydrous $MgSO_4$. The solvent was removed and the crude was purified by flash chromatography using hexanes:ethyl acetate (8:2) to afford **363** as a beige oil (89%).

IR: 3384, 2933, 1650, 1419, 1266, 1044, 1004, 902, 734, 703 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.39 (ddd, 1H, *J* = 17.2, 10.0, 10.0 Hz), 6.16 (dd, 1H, *J* = 14.8, 10.0 Hz), 5.87 (dt, 1H, *J* = 14.8, 7.2 Hz), 5.15 (dd, 1H, *J* = 17.2, 1.2 Hz), 5.00 (dd, 1H, *J* = 10.0, 1.2 Hz), 3.68 (t, 2H, *J* = 6.0 Hz), 2.35 (dt, 2H, *J* = 7.2, 6.0 Hz), 1.47 (brs, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 136.8, 133.8, 130.5, 116.0, 61.9, 35.9. **ESI-HMRS** [M+1] calcd for $C_7H_{13}O$: 113.0966, found: 113.0989.

(*E*)-1-iodopentadec-1-ene (374)



374

Cp_2ZrCl_2 (2.5 g, 8.4 mmol) was dissolved in dry THF (20 mL). The solution was cooled at 0ºC and DIBAL solution (8.4 mL, 8.4 mmol, 1M) was added dropwise at 0ºC for 30 minutes. The mixture was stirred for 30 minutes at the same temperature. Then the corresponding alkyne **373** was added at 0ºC and the solution was stirred at room temperature for 45 minutes. The solution was cooled at -78ºC, iodine (2.3 g, 9 mmol) was added and the mixture was stirred for 2h. The solution was hydrolyzed with HCl (10%) and the organic layer was

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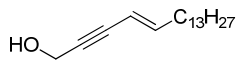
washed with $NaHCO_3$, $Na_2S_2O_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using hexanes as a solvent to afford 2 g of product **374** as a colorless oil (86%).

IR (neat): 2922, 2851, 1465, 942 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.52 (dt, 1H, *J* = 14.4, 7.2 Hz), 5.97 (dt, 1H, *J* = 14.4, 1.6 Hz), 2.05 (dtd, 2H, *J* = 7.2, 6.5, 1.6 Hz), 1.41-1.34 (m, 2H), 1.33-1.27 (m, 20H), 0.83 (t, 3H, J = 6.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 147.0, 74.5, 36.3, 32.2, 29.9, 29.8, 29.6, 29.2, 28.6, 22.9, 14.4. **ESI-HMRS** [M+1] calculated for $C_{15}H_{30}I$: 337.1392, found: 337.1354.

(*E*)-octadec-4-en-2-yn-1ol (375)



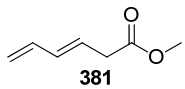
375

(*E*)-1-iodopentadec-1-ene **374** (1 g, 2.9 mmol) was dissolved in dry THF (20 ml) and tetrakis-(triphenylphosphine)palladium (90 mg, 0.08 mmol) was added. Then, CuI (5 mg, 0.03 mmol), freshly distilled diisopropilamine (4 mL) and propargyl alcohol (0.11 ml, 1.9 mmol) were added dropwise to the orange solution. The mixture was stirred at room temperature for 10 h. The solvent was removed under vacuum and the crude was purified by silica gel chromatography using 9:1 (hexanes:ethyl acetate) as a solvent to afford 0.5 g of product **375** as a colorless oil (98%).

IR (neat): 3615, 2962, 2841, 1462, 1384, 1155, 1007, 961 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.17 (dt, 1H, *J* = 15.8, 7.2 Hz), 5.50 (dt, 1H, *J* = 15.8, 1.8 Hz), 4.38 (dd, 2H, *J* = 6.2 Hz), 2.10 (tdd, 2H, *J* = 7.6, 7.2, 1.8 Hz), 1.52 (t, 1H, *J* = 6.2 Hz), 1.40-1.35 (m, 2H), 1.31-1.26 (m, 20H), 0.89 (t, 3H, *J* = 7.2 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 145.9, 109.0, 85.8, 84.9, 51.9, 33.3, 32.1, 29.9, 29.4, 29.1,

28.5, 23.2, 15.0. **ESI-HRMS** [M+23] calcd for $C_{18}H_{32}ONa$: 287.2351, found: 287.2099. Experimental data are in agreement with reported data.[271]

(*E*)-methyl hexa-3,5-dienoate (381)

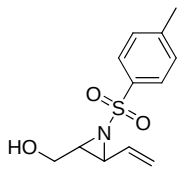


381

($^{i}Pr)_2NH$ (6.5 mL, 45 mmol) was dissolved in dry THF (63 mL), then the solution was cooled at -78ºC and BuLi (28 mL, 45 mmol, 1.6 M) was dropwise added for 30 minutes before HMPA (9 mL, 52 mmol) was added. Then, a solution of methyl sorbate (5g, 40 mmol) in THF (8mL) was slowly added at that temperature and the solution was stirred for 1h until complete disappearance of the starting material. The mixture was warmed at 0ºC and it was quenched with a solution of acetic acid (5 mL, 1M). The crude was extracted with ethyl acetate and the combined organic layers were washed with $NaHCO_3$ and brine, then the organic layer was dried over $MgSO_4$ and the solvent was removed. The crude was used in the next step without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.33 (ddd, 1H, *J* = 16.8, 10.0, 10.0 Hz), 6.13 (dd, 1H, *J* = 15.0, 10.0 Hz), 5.78 (dt, 1H, *J* = 15.0, 7.2 Hz), 5.15 (d, 1H, *J* = 16.8 Hz), 5.06 (d, 1H, *J* = 10.0 Hz), 3.42 (s, 3H), 3.03 (d, 2H, *J* = 7.2 Hz).

***trans*-(1-tosyl-3-vinylaziridin-2-yl)methanol (282)**



382

Aziridine **382** was synthetized following the general aziridination procedure using alcohol **358**.

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271 Garigipati, R. S.; Freyer, A. J.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 7861-7867.

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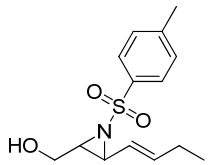
IR (neat): 3522, 2953, 2900, 1601, 1400, 718 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.78 (d, 2H, *J* = 8.3 Hz), 7.29 (d, 2H, *J* = 8.3 Hz), 5.91 (ddd, 1H, *J* = 17.2, 10.4, 8.8 Hz), 5.46 (d, 1H, *J* = 17.2 Hz), 5.41 (d, 1H, *J* = 10.4 Hz), 4.03 (dd, 1H, *J* = 12.6, 2.8 Hz), 3.79 (dd, 1H, *J* = 12.6, 6.4 Hz), 3.41 (dd, 1H, *J* = 8.8, 4.4 Hz), 3.21 (m, 1H), 2.78 (d, 1H, *J* = 6.8 Hz), 2.45 (s, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.1, 139.3, 137.6, 130.2, 129.3, 107.4, 60.8, 56.0, 52.7, 21.6. **ESI-HMRS** [M+1] calcd for $C_{12}H_{16}NO_3S$: 254.0851, found: 254.0794.

***trans*-(3-((*E*)-buten-1-enyl)-1-tosylaziridin-2-yl)methanol (383)**



383

Aziridine **383** was synthesized following the general aziridination procedure using compound **359**.

IR (neat): 3535, 2935, 2924, 2854, 1598, 1462, 1377, 1092, 736 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.76 (d, 2H, *J* = 8.2 Hz), 7.26 (d, 2H, *J* = 8.2 Hz), 5.84 (dt, 1H, *J* = 15.2, 6.4 Hz), 5.51 (dd, 1H, *J* = 15.2, 8.8 Hz), 3.99 (dd, 1H, *J* = 12.8, 3.2 Hz), 3.77 (dd, 1H, *J* = 12.8, 6.6 Hz), 3.33 (dd, 1H, *J* = 8.8, 4.4 Hz), 3.19 (ddd, 1H, *J* = 6.6, 4.4, 3.2 Hz), 2.42 (s, 4H), 2.09-2.95 (m, 2H), 0.98 (t, 3H, *J* = 7.0 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.6, 140.9, 129.9, 127.7, 127.5, 122.5, 61.0, 49.6, 48.5, 26.0, 22.0, 12.8. **ESI-HMRS** [M+1] calcd for $C_{14}H_{20}NO_3S$: 282.1163, found: 282.1142.

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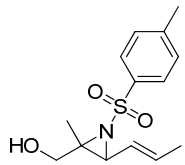
***trans*- (2-methyl-3-((*E*)-prop-1-enyl)-1-tosylaziridin-2-yl)methanol (384)**

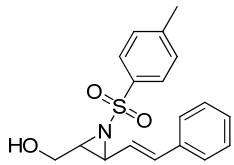


384

Aziridine **384** was synthesized following the genaral aziridination procedure using diene **361**.

IR (neat): 3384, 3002, 2920, 2891, 1460, 1321, 719. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.77 (d, 2H, *J* = 8.0 Hz), 7.38 (d, 2H, *J* = 8.0 Hz), 5.82 (dq, 1H, *J* = 15.0, 6.8 Hz), 5.22 (ddq, 1H, *J* = 15.0, 7.4, 1.6 Hz), 4.03 (d, 2H, *J* = 3.2 Hz), 3.56 (d, 1H, *J* = 7.4 Hz), 2.44 (s, 3H), 1.76 (brs, 1H), 1.69 (dd, 3H, *J* = 6.8, 1.6 Hz), 1.43 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.1, 137.5, 130.1, 129.3, 127.6. 127.0, 61.3, 56.2, 52.4, 21.7. **ESI-HMRS** [M+23] calc for $C_{14}H_{19}NO_3SNa$: 304.0983, found: 304.1201.

***trans*-((*E*)-3-styryl-1-tosylaziridin-2-yl)methanol (385)**



385

Aziridine **385** was synthesized following the general aziridination procedure using alcohol **360**.

IR (neat): 3511, 3279, 3059, 3029, 2924, 2361, 2336, 1725, 1671, 1448, 1325, 1156, 1092, 692 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.83 (d, 2H, *J* = 8.2 Hz), 7.37-7.26 (m, 6H), 7.19 (t, 1H, *J* = 7.6 Hz), 6.65 (d, 1H, *J* = 16.0 Hz), 6.25 (dd, 1H, *J* = 16.0, 8.8 Hz), 4.05 (dd, 1H, *J* = 12.8, 2.8 Hz), 3.84 (dd, 1H, *J* = 12.8, 6.8 Hz), 3.56 (dd, 1H, *J* = 8.8, 4.4 Hz), 3.33-3.30 (m, 1H), 2.42 (brs, 1H), 2.41 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.7, 137.7, 137.0, 130.4, 129.9, 128.9,

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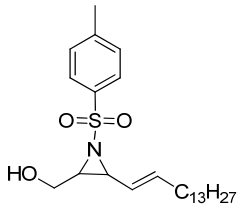
128.6, 127.7, 127.6, 126.8, 122.5, 60.9, 50.2, 48.4, 21.8. **ESI-HMRS** [M+23] calc for $C_{18}H_{19}NO_3SNa$: 329.1086, found: 329.1121.

cis-(3-((*E*)-pentadec-1-enyl)-1-tosylaziridin-2-yl)methanol (392)

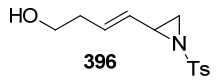


392

Aziridine **392** was synthesized following the general azirination procedures using compound **362**.

IR (neat): 3357, 2924, 2853, 1462, 1328, 1304, 1094, 815, 722 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.82 (d, 2H, *J* = 8.0 Hz), 7.33 (d, 2H, *J* = 8.0 Hz), 5.85 (dtd, 1H, *J* = 15.2, 6.2, 1.6 Hz), 5.23 (dd, 1H, *J* = 15.2, 7.8 Hz), 3.74 (dd, 1H, *J* = 12.0, 4.0 Hz), 3.59 (dd, 1H, *J* = 12.0, 6.8 Hz), 3.42 (ddd, 1H, *J* = 7.8, 7.2, 1.6 Hz), 3.11 (ddd, 1H, *J* = 7.2, 6.8, 4.0 Hz), 2.44 (s, 3H), 2.42 (brs, 1H), 1.99 (m, 2H), 1.32-1.23 (m, 22H), 0.88 (t, 3H, *J* = 6.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.9, 139.5, 129.9, 128.1, 126.6, 120.8, 59.7, 45.8, 45.6, 32.6, 29.9, 29.8, 29.6, 29.5, 29.3, 22.9, 21.9, 21.7, 14.3. **ESI-HMRS** [M+23] calc for $C_{25}H_{41}NO_3SNa$: 458.2705, found: 458.2802.

(*E*)-4-(1-tosylaziridin-2-yl)but-3-en-1-ol (396)



396

The vinyl aziridine **396** was synthesized from diene **363** following the general procedure for aziridination dienes and it was isolated by flash chromatography using hexanes:ethyl acetate (6:4 to 1:1) to afford **68** mg as a white solid (92%).

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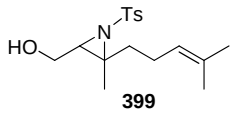
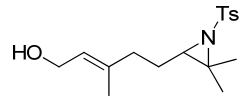
IR: 3507, 2941, 2924, 1321, 1156, 1090, 815, 663 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.82 (d, 2H, *J* = 8.4 Hz), 7.33 (d, 2H, *J* = 8.4 Hz), 5.88 (dt, 1H, *J* = 15.4, 7.6 Hz), 5.26 (ddt, 1H, *J* = 15.4, 8.2, 1.2 Hz), 3.64 (t, 2H, *J* = 6.6 Hz), 3.29 (ddd, 1H, *J* = 8.2, 6.8, 4.4 Hz), 2.73 (d, 1H, *J* = 6.8 Hz), 2.44 (s, 3H), 2.41 (brs, 1H), 2.30 (dt, 2H, *J* = 7.6, 6.6 Hz), 2.20 (d, 1H, *J* = 4.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.8, 135.3, 133.5, 129.9, 128.0, 127.9, 61.7, 40.8, 35.8, 34.6, 21.9. **ESI-HRMS** [M+23] calcd for $C_{13}H_{17}O_3NSNa$: 290.0827, found: 290.0824.

General aziridination of terpenes. $Tp^{*,Br}Ag$ (3.2 mg, 0.05 mmol) was dissolved in dichloromethane (10 mL), then therpene (1 mmol) and PhINTs (407 mg, 1.1 mmol) were added in four portions over 4h. The reaction mixture was stirred 3h more at room temperature and the solvent was removed under vacuum. The residue was purified by flah chromatography using hexanes:ethyl acetate (7:3 to 1:1) to afford the desired products.

***trans*-(3-methyl-3-(4-methylpent-3-en-1-yl)-tosylaziridin-2-yl)methanol (399) and (*E*)-5-(3,3-dimethyl-1-tosylaziridin-2-yl)-3-methylpentent-2-en-1-ol (400)**



399



400

Geraniol (**397**) was aziridinated following the general aziridination terpenes procedure to obtain compound **399** in 50% as a colorless oil and compound **400** in a 41% as a beige oil

Compound **399. IR** (neat): 3514, 2969, 2925, 1598, 1383, 1317, 1154, 1091, 1045, 941, 816, 709 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.85 (d, 2H, *J* = 8.2 Hz), 7.31 (d, 2H, *J* = 8.2 Hz), 5.12 (m, 1H), 3.68 (ddd, 1H, *J* = 12.0, 7.2, 4.8 Hz), 3.51 (ddd, 1H, *J* = 12.0, 7.2, 4.8 Hz), 3.12 (dd, 1H, *J* = 7.0, 4.8 Hz), 2.43 (s, 3H), 2.26-2.23 (m, 1H), 2.14-2.04 (m, 3H), 1.70 (s, 3H), 1.61 (s, 3H), 1.57 (brs, 1H), 1.32 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.1, 138.1, 132.8, 129.8, 127.5, 123.0, 60.5, 55.6, 52.5, 34.8, 25.9, 25.6, 21.8, 18.5, 17.9. **ESI-HRMS** [M+23] calcd for $C_{17}H_{25}O_3SNNa$: 356.4401, found: 346.1425.

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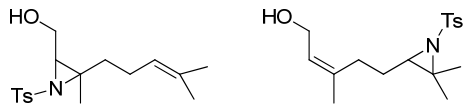
Compound **400. IR** (neat): 3514, 2969, 2925, 1598, 1383, 1317, 1154, 1091, 1045, 941, 816, 709 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81 (d, 2H, *J* = 8.2 Hz), 7.30 (d, 2H, *J* = 8.2 Hz), 5.31 (tq, 1H, *J* = 6.6, 1.2 Hz), 4.10 (t, 2H, *J* = 6.6 Hz), 2.81 (dd, 1H, *J* = 7.6, 5.2 Hz), 2.43 (s, 3H), 1.97-1.90 (m, 1H), 1.84-1.79 (m, 1H), 1.63 (s, 3H), 1.62-1.59 (m, 2H), 1.57 (s, 3H), 1.46-1.40 (m, 1H), 1.28 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 143.9, 138.5, 138.2, 129.6, 127.6, 124.3, 59.4, 52.4, 52.0, 37.1, 26.3, 21.8, 21.5, 21.4, 16.4. **ESI-HRMS** [M+23] calcd for $C_{17}H_{25}O_3SNNa$: 356.4401, found: 346.1430.

cis-(3-methyl-3-(4-methylpent-3-en-1-yl)-1-tosylaziridin-2-yl)methanol (401) and (*Z*)-5-(3,3-dimethyl-1-tosylaziridin-2-yl)-3-methylpent-2-en-1-ol (402)



401 **402**

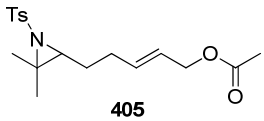
Nerol (**396**) was aziridinated following the general procedure for aziridination terpenes obtaining compound **401** in a 58% yield as a yiellow oild and compound **402** with 33% yield as a beige oil.

Compound **401. IR** (neat): 3511, 2967, 1452, 1318, 1152, 1091, 1041, 938, 814, 675 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.85 (d, 2H, *J* = 8.4 Hz), 7.30 (d, 2H, *J* = 8.4 Hz), 5.12 (m, 1H), 3.69 (ddd, 1H, *J* = 12.0, 7.2, 4.8 Hz), 3.51 (ddd, 1H, *J* = 12.0, 7.2, 4.8 Hz), 3.11 (dd, 1H, *J* = 7.2, 4.8 Hz), 2.43 (s, 3H), 2.26-2.16 (m, 1H), 2.14-2.04 (m, 3H), 1.70 (s, 3H), 1.62 (s, 3H), 1.32 (s, 3H), 1.26-1.17 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.0, 137.7, 132.6, 129.6, 127.4, 122.9, 60.1, 55.1, 53.0, 35.0, 25.6, 24.2, 21.6, 18.3, 17.6. **ESI-HRMS** [M+23] calcd for $C_{17}H_{25}O_3SNNa$: 356.4401, found: 346.1427.

Compound **402**. **IR** (neat): 3520, 2965, 1452, 1316, 1087, 930, 815, 732, 706, 667 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.83-7.81 (d, 2H, *J* = 8.0 Hz), 7.30 (d, 2H, *J* = 8.0 Hz), 5.36 (t, 1H, *J* = 7.4 Hz), 3.94 (d, 2H, *J* = 7.4 Hz), 2.79 (dd, 1H, *J* = 8.0, 4.8 Hz), 2.42 (s, 3H), 2.03-1.91 (m, 1H), 1.88-1.78 (m, 1H), 1.73 (brs, 1H), 1.63 (s, 3H), 1.61-1.59 (m, 1H), 1.44-1.33 (m, 1H), 1.28 (s, 3H), 1.19-1.22 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 143.9, 138.4, 138.2, 129.6, 127.6, 125.5,

58.9, 51.9, 29.7, 23.4, 21.9, 20.6. **ESI-HRMS** [M+23] calcd for $C_{17}H_{25}O_3SNNa$) calc.: 356.4401, found: 346.1427.

(*E*)-5-(3,3-dimethyl-1-tosylaziridin-2-yl)2-methylpent-2-en-1-yl acetate (405)

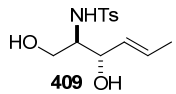


405

Compound **405** was obtained in a 83% yield as a beige oil following the general aziridination of terpenes procedure using geranyl acetate (**403**) as a substrate.

IR (neat): 2945, 2025, 1735, 1454, 1379, 1318, 1231, 1184, 1155, 1088, 1021, 931, 817, 708, 669 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.80 (d, 2H, *J* = 8.4 Hz), 7.29 (d, 2H, *J* = 8.4 Hz), 5.21 (td, 1H, *J* = 7.2, 1.2 Hz), 4.53 (d, 2H, *J* = 7.2 Hz), 2.79 (dd, 1H, *J* = 7.6, 6.0 Hz), 2.42 (s, 3H), 2.03 (s, 3H), 1.93 (m, 1H), 1.81 (m, 1H), 1.69 (s, 3H), 1.61-1.54 (m, 1H), 1.59 (s, 3H), 1.48-1.39 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 171.3, 143.8, 140.9, 138.4, 129.6, 127.6, 119.1, 61.3, 52.4, 52.0, 37.0, 26.2, 21.8, 21.5, 21.4, 21.2, 16.6. **ESI-HRMS** [M+23] calcd for $C_{18}H_{25}NO_4SNa$: 374.1402, found: 374, 1400.

(*E*)- 2-N-tosyl-hex-4-en-1,3-diol (409)

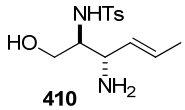


409

Aziridine **336** (0.25 mmol) was dissolved in DMSO (0.75 ml) and an aqueous solution of KOH (10%, 0.75 mL) was added. The solution was stirred for 1h at 40 ºC. The crude was neutralized with saturated NH_4Cl aqueous solution. The aqueous solution was extracted with diethyl ether (3 x 25 mL) and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and purified by radial chromatography using 4:6 hexanes:ethyl acetate to afford 56 mg of product **409** as a white solid (68%).

IR (neat): 3476, 3284, 2921, 2854, 1441, 1155, 1089, 1042, 967, 813, 662 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.77 (d, 2H, *J* = 8.2 Hz), 7.31 (d, 2H, *J* = 8.2 Hz), 5.71 (dqd, 1H, *J* = 15.4, 6.4, 1.2 Hz), 5.40 (d, 1H, *J* = 7.6 Hz), 5.35 (ddq, 1H, *J* = 15.4, 6.8, 1.6 Hz), 4.16 (t, 1H, *J* = 6.8, 5.2 Hz), 3.84 (dd, 1H, *J* = 11.6, 3.6 Hz), 3.50 (dd, 1H, *J* = 11.2, 3.6 Hz), 3.19 (ddt, 1H, *J* = 7.2, 7.2, 3.6 Hz), 2.43 (s, 3H), 2.41 (br, 1H), 1.67 (dd, 3H, *J* = 6.4, 1.6 Hz), 1.57 (brs, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 143.9, 137.5, 130.0, 129.7, 129.6, 127.4, 74.8, 62.3, 58.0, 21.8, 18.0. **ESI-HMRS** [M+23] calcd for $C_{13}H_{19}NO_4SNa$: 308.0932, found: 308.0592.

(*E*)-3-amino-2-*N*-tosyl-hex-4-en-1-ol (410)



410

Aziridine **336** (5 mmol) and yterbium triflate were dissolved in amonia solution (80 ml, 30%) and the mixture was stirred at 95 ºC for 8 hours. The crude was dissolved in ethyl acetate three times. The combined organic layers were washed with HCl aqueous solution (5%) and brine. The crude was purified by radial chromatography using 4:6 hexanes: ethyl acetate to afford 188 mg as colorless oil (64%).

IR (neat): 3489. 2921, 2880, 2361, 2336, 1449, 1326, 1277, 1158, 1091, 751 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.77 (d, 2H, *J* = 8.0), 7.30 (d, 2H, *J* = 8.0 Hz), 5.66 (dq, 1H, *J* = 15.2, 6.4 Hz), 5.34 (dd, 1H, *J* = 15.2, 6.4 Hz), 3.85 (d, 1H, *J* = 11.2), 3.71 (m, 1H), 3.26 (dd, 1H, *J* = 11.2, 3.2 Hz), 3.02 (m, 1H), 2.43 (s, 3H), 2.14 (brs, 4H), 1.67 (d, 3H, *J* = 6.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 143.6, 137.1, 130.3, 129.8, 128.6, 127.1, 62.4, 62.1, 57.3, 21.5, 17.9. **ESI-HMRS** (M+1) calcd for $C_{13}H_{21}N_2O_3S$: 285.1195, found 285.1259.

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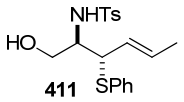
ISBN:/DL:T. 1036-2011

(*E*)-3-phenylthio-2-*N*-tosyl-hex-4-en-1-ol (411)



411

Aziridine **336** (0.25 mmol) was dissolved in dry THF (4 mL) and sodium thiophenolate (0.28 mmol, 36 mg) was added. The mixture was stirred for 12 h at room temperature. After 12 h, water was added to the mixture and the aqueous layer was washed with dichloromethane. The combined organic layers were washed with $NaHCO_3$ aqueous solution, and then they were washed with water and brine. The organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude was purified by radial chromatography using 7:3 to 6:4 hexanes:ethyl acetate to afford 74 mg of compound **411** as a yellow solid (46 %).

IR (neat): 3509, 3271, 3060, 2920, 2884, 2854, 2361, 1439, 1327, 1156, 1090, 1038, 966, 811, 736, 664 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.70 (d, 2H, *J* = 8.4 Hz), 7.14-7.24 (m, 7H), 5.36 (dqd, 1H, *J* = 15.4, 6.8, 0.8 Hz), 5.10 (d, 1H, *J* = 7.6 Hz), 5.08 (ddq, 1H, *J* = 15.4, 9.2, 1.6), 4.87 (brs, 1H), 3.83 (dd, 1H, *J* = 11.6, 5.2 Hz), 3.72 (dd, 1H, *J* = 11.6, 4.0 Hz), 3.57 (dd, 1H, *J* = 9.2, 6.4 Hz), 2.43 (s, 1H), 2.41 (s, 3H), 1.55 (dd, 3H, *J* = 6.0, 1.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 143.9, 137.1, 132.8, 130.5, 129.9, 129.0, 127.8, 127.5, 126.7, 63.0, 58.2, 53.9, 21.8, 17.9. **ESI-HMRS** [M+Na] calcd for $C_{19}H_{23}NO_3S_2Na$: 400.1017, found: 400.0997.

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