NOVEL STRATEGIES FOR THE SYNTHESES OF SPHINGOSINE KINASE INHIBITORS, B-FLUOROAMINES AND ENANTIOENRICHED ALLENES

Macarena Corro Morón

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Novel Strategies for the Syntheses of Sphingosine Kinase Inhibitors, β-Fluoroamines and Enantioenriched Allenes

Doctoral Thesis

Supervised by

Prof. Sergio Castillón Miranda and Dr. Yolanda Díaz Giménez

UNIVERSITAT ROVIRA i VIRGILI

Department of Analytical Chemistry and Organic Chemistry

Tarragona 2018

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Prof. Sergio Castillón Miranda and Dr. Yolanda Díaz Giménez from Department of Analytical Chemistry and Organic Chemistry from University Rovira i Virgili,

We STATE that the present study, entitled "Novel Strategies for the Syntheses of Sphingosine Kinase Inhibitors, β-Fluoroamines and Enantioenriched Allenes", presented by Macarena Corro Morón for the award of the degree of Doctor and European Mention, has been carried out under our supervision at the Department of Analytical Chemistry and Organic Chemistry of this university.

Tarragona, 2nd October 2018.

Prof. Sergio Castillón Miranda Dr. Yolanda Díaz Giménez

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The work performed in the present Doctoral Thesis has been possible thanks to the Formación de Profesorado Universitario grants program (reference: FPU14/02790), funded by the Ministerio de Educación, Cultura y Deporte.

This Thesis has been carried out thanks to the funding of the research projects:

- CTQ 2014-58664-R, funded by the Ministerio de Economía y Competitividad.

- CTQ 2017-89750-R, funded by the Ministerio de Economía y Competitividad.

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Agradecimientos

Por fin llega la parte más dulce de toda esta etapa, agradecer a los que han compartido conmigo esta aventura.

Primeramente me gustaría darte las gracias a ti Sergio, ya que sin conocerme siquiera me brindaste la oportunidad de venir a Tarragona a hacer el máster y posteriormente la tesis. Espero haber estado a la altura. Gracias por tu pasión, tu interés, por toda esa paciencia que tienes y por ayudarme a encauzar este trabajo. Por esto último también tengo que agradecerte a ti Yolanda, sin duda este trabajo no hubiera sido el mismo sin tu ayuda. Gracias por todo tu apoyo y tus consejos. Maribel y Omar, gracias también a vosotros. Todos vuestros comentarios y aportaciones siempre han sido valiosos y de gran ayuda.

Me gustaría también acordarme de los bioinformáticos. Gracias Santi y Raúl por vuestros consejos y ensayos biológicos. Y, por supuesto, a vosotros, Aleix y Maria José. Sin vuestra ayuda mis estudios sobre docking no hubieran sido posible.

For sure, I would like to thank to Prof. Fürstner to give me the opportunity of doing a stay in his research group. Thanks Karin, you were a special person to me in Mülheim. It was a pleasure to share with you and Felix the same project. I am very grateful with everyone in that lab, especially with Alex A., Lauren, Alberto (quién nos iba a decir que concidiríamos durante la estancia!!) and my amazing guys from box 2. Marc, Alex T., Luis, Bernard and Sebastian. I will always remember you. And now it is your turn, Alex. You know that you were my best support during these months there and although I left Mülheim one year ago, I miss you.

A ti Molina, que fuiste el que hizo que la química me apasionara desde edades bastantes tempranas.

Obviamente no habría llegado hasta aquí sin haber pasado antes por la Universidad de Huelva. Gracias a todos/as, de verdad.

Especialmente, me gustaría agradecer al grupo de Pedro por haberme acogido allí cuando aún era estudiante. Sobre todo, me gustaría darte las gracias a ti Manoli, porque pusiste tu confianza en mí y me enseñaste todo lo que sabía cuando llegué aquí. Ojalá hubiese coincidido contigo más tiempo, vales mucho la pena. Y, cómo no! Gracias a vosotr@s chi@s! No sólo habéis sido compañer@s de clase, habéis sido más que amig@s durante los 5 años que hemos estado junt@s y aún lo seguís siendo, que es lo mejor de todo. Maury y Gema, mis prefes; Jesús Ángel, Algaba, Cristina, Paqui y María, qué raro se me ha hecho hacer una tesis sin teneros cerca!! Cris, tú eres la excepción a esa regla ya que nos adentramos en esta aventura juntas a 1000 km de casa y vamos a acabarla casi al mismo tiempo… Cómo me alegro de haberla compartido contigo.

Tampoco me puedo olvidar de ti Sofi, mi otra compi de piso en Tarragona. Ha sido genial vivir contigo y sé que tengo una amiga en Benissa para lo que necesite.

Y ahora llega el turno de agradecer a la gente con la que he compartido estos últimos 5 años, porque sí, también cuenta el año del máster. Primeramente me gustaría empezar dando las gracias a las técnicas del Servei Irene, Sònia y Carme por todo su trabajo. Pero especialmente quiero y debo acordarme de ti, Ramón. Eres increíble de verdad. No sé cuántas horas habrás gastado conmigo y cuántas veces me habrás explicado las cosas y siempre se me han olvidado, pero tú siempre has tenido una sonrisa amable para mí. Mil gracias, de verdad.

Y a ti Raquel, que ya sabes que para mí no eres solo la técnica del grupo de Inor, sino que te has convertido en mi amiga, en una de las mejores de hecho, y no sabes qué suerte tengo de tenerte en mi vida. Gente como tú hay poca y yo me siento muy afortunada por contar con una amiga como tú.

A la gente del grupo de Inor: Carlota, Maria, Toni, Nùria, Jordi R., Jordi C.; Ricardo, Richi, Alberto, Fran, Myriam, Jorge, Marc, Marc Magre, Eli y Laia; a los poliméricos: Comí, Cristina, Daylin, Monti, Adrian, Lorena, Zeynep, Alev, Pere, Nabil, Aarón y Carmen. Ha sido un placer coincidir con vosotros.

Y ahora sí, os toca SINTCARB! Quisiera empezar por los que se fueron ya hace tiempo. Miriam D. e Isma, fue un placer compartir con vosotros vuestra etapa final en el lab. Guasch, tú eres uno de los mayores personajes que he conocido en mi vida, man. Creo que tienes el placer de ser la persona que más asco me ha dado comiendo una fruta... Emma, qué decir de ti? Qué pena que te fueras tan pronto, en serio. Esa sonrisa contagiosa, tu vitalidad y alegría nos hubieran venido bien durante más tiempo. Que seas muy, muy feliz. Seb, tú has sido el dandy por excelencia del lab. Espero que te vaya bien por allá donde estés. Colavida pisha, qué buenas risas que nos hemos echado!

Xochilt, Otty, Jenny, Kevin, Jesús, Adrián, Alex, Miguel, Carla, Isabel, Emma, Alex, Pedro!!!, Jordina, Jordi y Ester. Vosotros habéis pasado menos tiempo por el lab, pero sin duda habéis dejado huella en él. Gracias por toda vuestra simpatía y por el buen rollo que habéis desprendido siempre. Saltó, espero de verdad que te logres controlar y que puedas acabar la tesis como sé que tienes ganas. Está en ti. Puedes hacerlo. Arnau, sé de sobras que te va a ir genial por Inglaterra así que no pienso desearte suerte porque no la necesitas. Tienes talento y lo sabes. A por ello!

Ahora toca el turno del tito Collado. David eres otro grande, otro gran personajazo. El estar en la vitrina de atrás te ha hecho siempre enterarte de todo tarde, pero que gracia que nos hacías cuando llegabas dos días tarde a todo… Gracias por todos los momentos y risas compartidas illoh. Has visto? Tu frase está como frase célebre en mi tesis. Si es que ya me lo decías… Al final todo sale bien...

Jordi!! Mi Romeo Santos favorito. Qué buenos momentos también los que hemos compartido dentro y fuera del lab. De verdad te deseo que cumplas tu sueño de montar tu spin-off dentro de poco. Tienes una mente brillante. Por favor, no dejes que Omar te coma la cabeza con sus cosas, que coja a otro. Tú tienes un objetivo claro. Que nada te detenga.

Margarita, desde que llegaste al lab se respiraba diferente. Esa esencia latina ha dejado una huella muy, muy grande. Te convertiste de forma muy rápida en algo más que una amiga para mí. Supongo que los que vivimos más lejos de casa tendemos a formar una familia y no sabes qué contenta estoy porque tanto Alberto como tú forméis parte de la mía, porque sí, sois mi familia, mi familia mexicana. Por favor, volved ya!

Irene, mi pequeña y cuqui Irene. Y de ti? Qué puedo decir que no sepas?? Te he echado de menis estos meses, cari. Sentarme en la mesa y no verte en frente ha sido raro, pero ya queda menos para que vuelvas. No voy a decirte "ánimo que ya es el final" porque no te hace falta y lo sabes. Esto estará acabado antes de que te des cuenta. Solo te diré que, por favor, te cambies de zapatillas más a menudo y que vayas pensando en qué vestido vas a ponerte porque en unos meses tenemos una cita (carita con corazones por doquier).

Míriam, han sido muchos los momentos que hemos vivido juntas, seguramente hayamos compartido algunos de los más importantes de tu vida y no sabes lo afortunada que me siento por haberlos vivido contigo. Siempre has sido un apoyo muy importante para mí y no sabes cuánto me alegra el hecho de que a pesar de que ya no estés por el lab, que hayas vivido en China, que hayas sido mamá de una niña preciosa y que hayas vuelto a casa, sigamos siendo más amigas que antes.

Y ahora tú Cardona, THE SPECIAL ONE. Llegamos prácticamente juntos al lab y hemos convivido muchas, muchas horas codo con codo en vitrinas contiguas. Aunque lo mejor siempre fue el tiempo que pasamos fuera. No sabes lo duro que se me hizo volver de Alemania y no

encontrarte al lado mío para pincharme, reírnos o mirarnos sabiendo lo que el otro pensaba, gachón. Pero más duro fue el día que me dijiste que volvías a Castellón, porque eso no solo significaba que te ibas tú, sino que también lo hacía Paz y eso no me hizo mucha ilusión tampoco... Por suerte sé que siempre os tendré en mi vida como buenos amigos, de los mejores amigos.

Y ahora es el turno de mis amigos de toda la vida. Pri, Manu, Marín, Pepito, Caro, Noe, Pina N, David, Diego, Ana. Gracias por hacer que volver al pueblo sea algo fresco, por hacerme ver que aunque viva a 1000 km nada cambia cada vez que bajo, por todas vuestras tonterías, por todas las sierras, por todos los momentos que llevamos juntos compartiendo más de media vida y por todos los que nos quedan por vivir. Gracias, de verdad.

Flor y Cris, no sé que hubiera hecho sin vosotras en Huelva y después de eso. Sin duda, nada sería igual. Formáis una parte muy importante de mi vida y lo sabéis. Sois mis animalitas favoritas weys!

Gracia a mis ti@s y prim@s que siempre me han apoyado y han creído en mí desde el primer día. Y gracias a mis abuelos/as y a mi tita Antonia, que siempre apostaron por mí y pensaron que llegaría donde quería llegar. Especialmente tú abuela, no sabes cuánto te quiero y te voy a querer siempre. Este "libro" es para ti. Gracias también a la familia Márquez y a la familia Ruiz pero, sobre todo, a la familia Márquez-Ruiz por haberme acogido como a una más desde el primer día, por ponerme las cosas fáciles, por hacerme partícipe de todo en todo momento, por quererme como a una hija, hermana o nieta más. Manolo, Pilar, Clara, Pili y María, sois parte de mi familia, de verdad, y no sabéis lo feliz que me hace formar parte también de la vuestra. Os quiero mucho.

Y, por supuesto, gracias a mis padres. Si soy quien soy hoy día es gracias a vosotros. Nunca os agradeceré lo suficiente lo que habéis hecho, hacéis y sé que seguiréis haciendo tanto por mí como por mis

hermanas; además de esa fe ciega que tenéis en nosotras. Sois mi ejemplo a seguir, el motor de mi vida. Mi ejemplo de lucha, superación y valentía. Sois mis héroes. Ojalá y algún día alguien me quiera y me admire la mitad de lo que yo os quiero y admiro a vosotros. Y gracias a mis hermanas, Rosalía y Lidia. Sois parte de mí y os admiro tanto a las dos que creo que sinceramente no podéis imaginároslo. Rosalía, eres una persona bondadosa e inteligente. Lidia, tú eres la persona más luchadora y fuerte que conozco. Nunca abandonéis vuestros sueños, al final se cumplen, de verdad que sí. Luchad por ellos. No me puedo imaginar una vida de la que no forméis parte ninguno de vosotros cuatro, sinceramente no creo que pueda hacerlo nunca. Os quiero tanto…

Y por último, gracias a ti, Manuel. Gracias por aparecer en mi vida, por entenderme mejor que nadie, por quererme como lo haces, por apoyarme en todo incondicionalmente, por no dejarme caer nunca, por estar tanto en los buenos como en los malos momentos, por acompañarme en esta locura. Sinceramente, sin ti esto no habría sido posible ni habría valido la pena. No sabes lo afortunada que me siento al poder compartir la vida contigo y, solo deseo seguir caminando a tu lado. Gracias por ser como eres, infinitas gracias por todo. Te amo.

Gracias a todos/as. Gràcies a tots. Thank you.

Macarena

A mis padres, hermanas y
a la memoria de mi abuela Nati.

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A Manuel

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Al final todo sale bien.

David Collado

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CHAPTER 5

ABREVIATIONS AND ACRONYMS

A

Ac	Acetyl
app	apparent
Ar	aryl

B

bs	broad signal
Bz	benzoyl
Boc	*tert*-butyl carbamate

C

COSY	correlation spectroscopy
Cal.	Calculated

D

d (in NMR)	doublet
dt (in NMR)	doublet triplet
dd (in NMR)	doublet of doublets
ddd (in NMR)	doublet of doublet of doublet

E

equiv.	equivalents
Et	ethyl
ESI-TOF	electrospray ionization- time-of-flight resolution spectrometry
ED	electron-donating
EW	electron-withdrawing

G

g	gram(s)

H

h	hour(s)
HMBC	heteronuclear multiple bond correlation
HSQC	heteronuclear single quantum coherence
Hz	Hertz
HRMS	High-Resolution Mass Spectrometry

I

IR	infrared
i-Pr	isopropyl

J

J	coupling constant

L

LC-MS	liquid chromatography-mass spectrometry
L	ligand

M

m (in NMR)	multiplet
Mes	mesyl
Me	methyl
m/z	mass under charge
m.p.	melting point
MS	mass spectrometry
mL	mili Liter(s)

N

NMR	nuclear magnetic resonance
NOESY	nuclear overhauser effect spectroscopy
Nu	nucleophile

P

ppm	parts per million
Ph	phenyl
*p*d (in NMR)	pseudo doublet
Phth	phthalimide
Py	pyridine

Q

q (in NMR)	quadruplet

R

r.t.	room temperature

S

s (in NMR)	singlet

T

t (in NMR)	triplet
T	temperature
TLC	thin layer chromatography
Ts	tosyl

U

UV	ultra-violet

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Summary

Chapter 1. General introduction.

Sphingolipids are a family of natural products which play a central role in numerous physical and biological processes. Among all sphingolipids, ceramide (Cer), sphingosine (Sph) and sphingosine-1-phosphate (S1P) have attracted more attention since the dynamic metabolism that control their synthesis is involved in cancer processes. In this metabolism, Cer and Sph have been related to cell death whereas S1P is implicated in cell proliferation. These sphingolipids are converted into each other by the action of enzymes, being sphingosine kinase (SphK), which exists in two isoforms (SphK1 and SphK2), the enzyme involved in the transformation of Sph into S1P.

Because of their relevance in the regulation of important processes and illness, many reasearch groups have focused their efforts on investigating the inhibition of SphK to avoid the formation of S1P.

Chapter 2. Objectives.

The present PhD work can be divided in two main blocks according to the final goals. In this sense, the syntheses of sphingosine analogues as potential SphK inhibitors and β-fluoroamines are described in Chapters 3 and 4, respectively. Additionally, Chapter 5 is oriented towards the development of a new metodology for the preparation of enantioenriched allenes starting from hydroxysilanes.

Chapter 3. Syntheses of azo- and hydrazino- analogues of sphingosine.

Chapter 3 describes a novel strategy in the syntheses of sphingosine derivatives and their activity as sphingosine kinase inhibitors.

The syntheses of these compounds involve 8 or 9 steps each one where the required *anti* disposition of 2-amino-3-hydroxyl groups was introduced by alkene aziridination with I(III) reagents followed by ring-opening reaction. In comparison with sphingosine, these new compounds are characterized by incorporating a quaternary center at C2 and an additional nitrogen linked to amine through azo and hydrazino motives. Furthermore, changes in the lipophilic tail were also introduced by alkynyl, alkenyl or alkyl chains.

Docking studies were also performed to determine the plausible interactions between our designed compounds and SphK1. These virtual studies predicted interactions between our compounds and the residues Leu 268, Asp 81 and Asp 178 of the SphK1.

Finally, *in vitro* assays revealed that our compounds present inhibitory potencies comparable to those found for *N,N'*-dimethylsphingosine (DMS). Interestingly, some compounds only showed inhibitory activity against SphK2, being selective for this isoform.

Chapter 4. Synthesis of β-fluoroamines mediated by ring-opening of aziridines.

Following the strategy of aziridination and ring-opening reactions used in the previous Chapter, Chapter 4 deals with the syntheses of β-fluoroamines starting from cinnamyl carbamates and 4-MePhIF$_2$ as fluoride source and oxidant reagent. In turn, carbamates were previously prepared from the corresponding cinnamyl alcohols and 4-MePhIF$_2$ resulting from the oxidation of the corresponding 4-iodotoluene in the presence of Selectfluor and $Et_3N{\cdot}3HF$.

The reaction of the prepared carbamates with 4-MePhIF$_2$ gave access to a mixture of *syn/anti* fluoroamines where aziridines were detected as intermediates in all cases. Interestingly, the diastereselectivity strongly depended on the electronic properties of the

substituents of the aromatic ring. *Syn* derivatives were preferably formed, especially in the presence of electron-withdrawing groups. Thus, the use of *p*-NO_2 as substituent exclusively led to the formation of the *syn* product. These facts suggest that the reaction procceds through aziridinaditon/ring opening processes. The reaction between the carbamate and 4-Me$PhIF_2$ would give a imidoiodinane releasing HF. In turn, this imidoiodinane would undergo an intramolecular cyclization generating an aziridine, which would be opened to provide a carbocation in the reaction conditions, thus, explaining the formation of *syn/anti* mixtures. Nevertheless, the synthesis of only *syn* products when the formation of carbocation is less favorable might be explained by the formation of a pseudo-carbocation with a direct attack of the fluoride to aziridine through an interaction between a fluorine reagent, HF or 4-Me$PhIF_2$, with the nitrogen of the oxazolidinone. In this way, the aziridine would be activated and opened by a direct attack in a *syn* manner.

Chapter 5. Copper-mediated enantioselective synthesis of allenes.

This Chapter was developed during a PhD stay at Prof. Alois Fürstner Research Group at Max-Planck-Institute für Kohlenforschung in Mülheim an der Rurh, Germany.

Chapter 5 describes the enantioselective synthesis of allenes starting from enantiomerically pure *cis* hydroxysilanes which, in turn, were prepared from chiral propargilyc alcohols.

Allenylation reaction was mediated by mesityl copper leading to poor enantioselectivity. However, these results were improved by the presence of phosphines or phosphites, $P(OEt)_3$ providing the best result of enantioselectivity for *anti*-elimination. Surprinsingly, *syn* allenes were detected when the reaction was conducted in the presence of bulkier ligands but with similar electronic properties than $P(OEt)_3$.

This process demonstrated to be influenced by electronic and steric properties of the starting hydroxysilanes and showed moderate tolerance towards different functional groups. It was also proved that allenes racemized in the presence of copper at longer reactions time.

Finally, a mechanistic study by ^{1}H NMR was carried out to detect some reaction intermediate. Nonetheless, the complexity of the obtained spectra made imposible to visualize any important intermediates which would have helped us to elucidate the mechanism of the reaction.

Chapter 6. General conclusions.

In this Chapter the conclusions extracted from each Chapter are described.

CHAPTER 1

General introduction

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1.1. INTRODUCTION

Named in reference to mythological sphinx, sphingolipids play a central role in multiple biological and physiological processes including lymphocyte trafficking, cell growth, apoptosis, mitogenesis, radio and chemo-sensitization, angiogenesis, inflammation and cancer.[1] Among them, ceramide (Cer), sphingosine (Sph) and sphingosine-1-phosphate (S1P) are especially remarkable, being converted into each other through enzymes.

1.1.1. Sphingosine Kinase as mediator of several diseases including cancer.

One of the most relevant enzymes involved in sphingolipid metabolism is sphingosine kinase (SphK), which catalyzes the conversion of sphingosine into sphingosine-1-phosphate and exists in two isoforms, SphK1 and SphK2.[2] These two kinases are located in dissimilar sites in the cell and it seems that this difference induces different functions,[3] above all for SphK2 since existing data reveal contradictory action of this enzyme in cancer development.[4,5,6] SphK1 is found in cytoplasm from it is transported to the plasma membrane after stimulation of numerous growth factors, cytokines and oncogenes.[7] On the other hand, SphK2 is located in the mitochondria, endoplasmic reticulum and nucleus.[6,8]

In turn, S1P can be either, irreversibly cleaved through S1P lyase to form phosphoethanolamine and hexadecenal, or dephosphorylated by S1P phosphatases to regenerate Sph. By its part, Sph can be also acylated to Cer *via* Cer synthase (Figure 1.1).

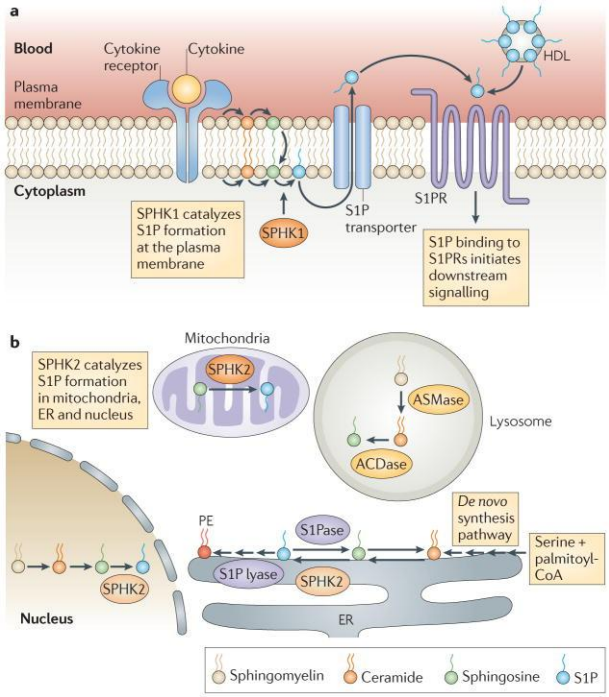
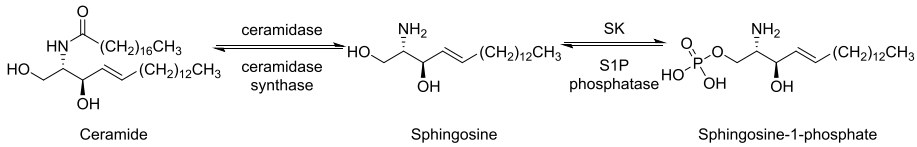


Figure 1.1. Synthesis of S1P promoted by SphK1 and SphK2. (a) Formation of S1P in plasma membrane. (b) Synthesis of S1P in mitochondria, endoplasmic reticulum and nucleus.[1d]

This dynamic balance produced in different places of the cell is commonly called *Ceramide-Sphingosine-1-Phosphate Rheostat* and determines the cell fate (Scheme 1.1). This equilibrium is related to apoptosis or survival processes depending on the position of this *rheostat.* In this regard, Cer and Sph are considered pro-apoptotic molecules whereas S1P favours the cell survival.[9]



Scheme 1.1. Ceramide-Sphingosine-1-phosphate rheostat.

Many diseases are derived from the position of this equilibrium where SphK has an important role on it. It has been demonstrated that overexpression of SphK1 is implicated in the death of cardiomyocytes

and dysfunctional hypertrophy related to pulmonary arterial hypertension.[10] Moreover, the activity of this kinase is also associated with sepsis,[11] rheumatoid arthritis[12] or asthma[13] and exerts a protective role on neuro-inflammation.[14] On the other hand, SphK2 is involved in thrombosis,[15] nociception[16] and ulcerative colitis processes.[17] Furthermore, it induces autophagy death of T-ALL cell lines,[18] has pro-inflammatory effect in multiple sclerosis[19] and it is related to inflammation and graft injury after liver transplantation.[20] Additionally, SphK2 plays an important role in Parkinson's disease, concretely in regulating the survival of the dopaminergic neurons.[21] There is also evidence that an overexpression of SphK2 generates a dysfunction of the endoplasmic reticulum. This dysfunction, in turn, induces an anomalous lipid biosynthesis, insulin resistance and may be implicated in diabetes.[19] Besides, both kinases seem to be involved in Alzheimer's disease.[21c,22]

Concerning other diseases, overexpression of SphK1 has pro-inflammatory effect in leukemia[23] and solid tumors[24] including breast, colon, lung, ovary, stomach, uteri, kidney, rectum and prostate. Furthermore, the increase of levels of SphK1 is also associated with drug resistance and reduced patient survival.[25] Despite the fact that SphK1 is apparently more related to cancer processes, some studies have indicated that anti-cancer effects derived from loss of SphK2 are stronger than derived from loss of SphK1.[26]

All these findings suggest that the modulation of the *rheostat* might produce changes in cell fate just shifting its position. It is therefore not surprising that the inhibition of SphK has become a target in several diseases including cancer therapies.

1.1.2. Crystal structure of human SphK1.

The elucidation of the structure of the SphK1 has not been accomplished until quite recently. In 2013, Wang and co-workers first reported the crystal structure of human SphK1 in the apo form and in complexes with sphingosine, acting as inhibitor, and with other inhibitors and adenosine diphosphate (ADP).[27] Similarly, the isolation of

the crystal structure of SphK1 with inhibitor PF-543 was published by Pyne one year later.[28]

The crystal of this kinase has been deeply analyzed and discussed by both authors and only the main features regarding the active site will be commented here:

- The structure has a two-domain architecture.
- The polar head of sphingosine is located between both domains and interacts with polar amino acids through hydrogen bonds.
- The long alkyl chain is buried in a hydrophobic pocket making interactions with non-polar residues.
- The lipid-binding cavity leaves little space; therefore bulky substituents in lipid skeleton might not fit well.

1.1.3. Sphingosine Kinase Inhibitors (SphKIs).

As discussed before, the cell fate depends on the position of the *ceramide-sphingosine-1-phosphate rheostat*. The inhibition of either of the two kinases, SphK1 or SphK2, would shift the equilibrium to the accumulation of Sph or biosynthesis of Cer favouring the cell apoptosis. Conversely, no inhibitory effect over this enzyme would promote the formation of S1P leading to cell proliferation. In this sense, several research groups and pharmaceutical companies have worked in the development of inhibitors of this kinase with the aim of shifting the equilibrium towards the formation of apoptosis cell signalling molecules.

The elucidation of crystal of SphK1 has brought about a great breakthrough in the inhibition of this enzyme. However, many SphKIs were described before its isolation. Taking into account these premises, here we will highlight some of the most relevant advancements in the development of SphKIs. These inhibitors will be classified according to their selectivity.

a) Dual SphK1/SphK2 inhibitors.

Some inhibitors are considered as non-selective ones since they do not demonstrate preference for any isomorf of SphK and work on both enzymes within the same range of concentration.

Safingol (DHS) and *N,N*-dimethylsphingosine (DMS) were reported as some of the first inhibitors of SphK. They were prepared by minor modifications of the own sphingosine structure consisting in removal of the *trans* double bond and methylation of amine group, respectively.[29] Enigmol is another sphingosine derivative prepared by formal transposition of a hydroxyl group from the position 1 to carbon 5, thus avoiding the phosphorylation by SphK to form S1P. *In vitro,* this compound has shown potent anticancer activity in cells present in multiple types of cancer as well as inhibition of ceramide synthase.[30] SKI-I and SKI-II were found in the same study[31] and although both decrease the cellular S1P, they also play different roles in several diseases. *In vitro*, SKI-I reduces cell growth of some kind of cancer cells and SKI-II intensifies the effects of other anti-cancer agents on cell lines. *In vivo*, SKI-I exerts anti-tumor activity in melanoma and breast cancer and SKI-II is effective at reducing growth of lung cancer xenografts, myeloid leukaemia, pulmonary fibrosis, inflammation and hyperalgesia as well as favoring the sensitivity of an inhibitor against breast cancer.[32] On the other hand, computational tools have also contributed to develop new SphKIs. In this regard, RB-042,[33] MP-A08,[34] and ABC294735[35] were screened after modeling studies revealing from moderate to good inhibition for both enzymes (Figure 1.2).

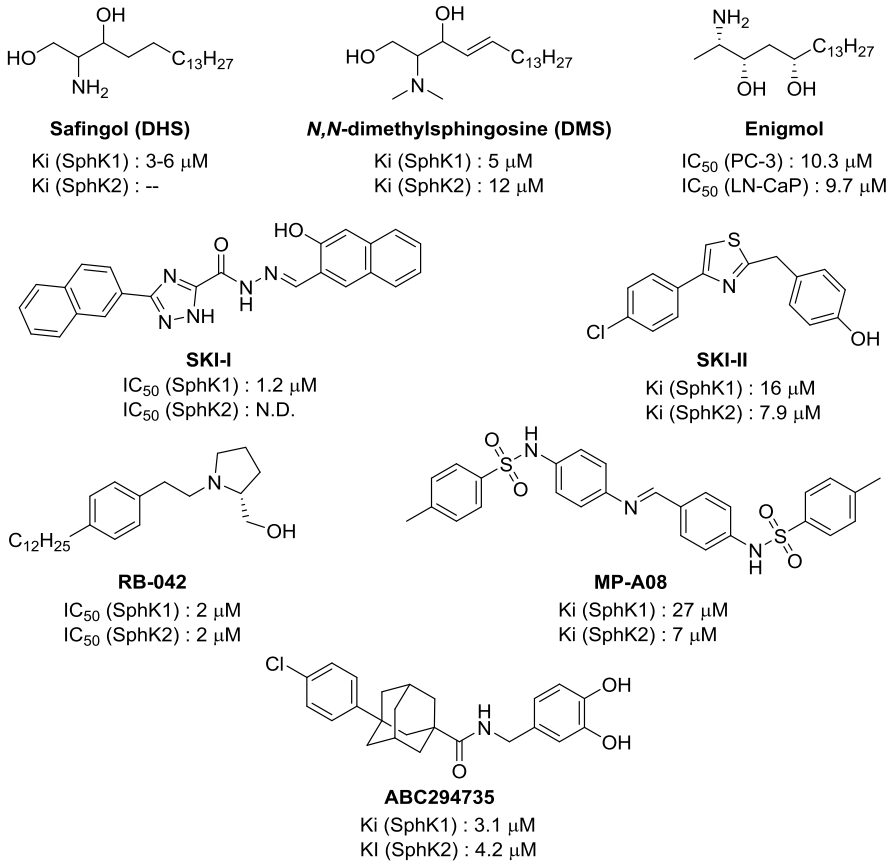


Figure 1.2. Non-selective inhibitors for SphK1 and SphK2.

b) Selective SphK1 Inhibitors.

Relative to the syntheses of SphKIs, SphK1 has been more deeply studied than SphK2. This is probably due to the availability of a crystal structure and to its greater association with cancer progress.

Modifications in sphingosine structure have led to the formation of promising inhibitors. FTY720 is a sphingosine derivative bearing an aryl group and a quaternary center in its structure, which has shown to act as agonist of S1P receptors after phosphorylation by SphK2.[36] Besides, it has demonstrated clinical utility in organ transplantation,[37] multiple sclerosis,[37] reduction of tumor growth and prevention of cancer progression in murine models of several types of cancer. It is also used in the treatment of several autoimmune diseases (Figure 1.3).[38]

A structurally related derivative of FTY720 is the (*S*)FTY720-vinylphosphonate in which one of the prochiral alcohols has been replaced by a vinylphosphonate group to block the phosphorylation by SphK2.[39] Other compounds including SKI-1, LCL 351 and SK1-5c can be also considered sphingosine derivatives. They are implicated in reducing tumor volumes in xenografts[40] and migration rate of some cells involved in prostate human cancer[41] and sensitizing chemotherapeutic agents in breast cancer,[42] respectively (Figure 1.3).

Guanidine moieties, as LCL 351 case, were introduced trying to increase binding interactions with SphK by hydrogen bonds besides to establish interaction with ATP responsible of phosphorylation.[43] In this sense, VPC96091,[44] compound **1.1**[45] and SLP7111228[46] were prepared showing inhibition in nanomolar scale in some cases. Other groups of compounds bearing carboxamide and aryl or heterocyclic moieties have also shown interesting results. CB5468139 acts reducing the proliferation of some kidney adenocarcinoma cells,[47] SK1-178 is effective against a multi-drug resistant AML line[32] and Genzyme 51 is associated with reducing some tumor growth (Figure 1.3).[48]

Computational tools have enormously contributed to develop of SphKIs. Some of aforementioned compounds were designed by using docking studies just like two of the most potent inhibitors of SphK1 known to date, PF543[46] and Amgen 82 (Figure 1.3).[25]

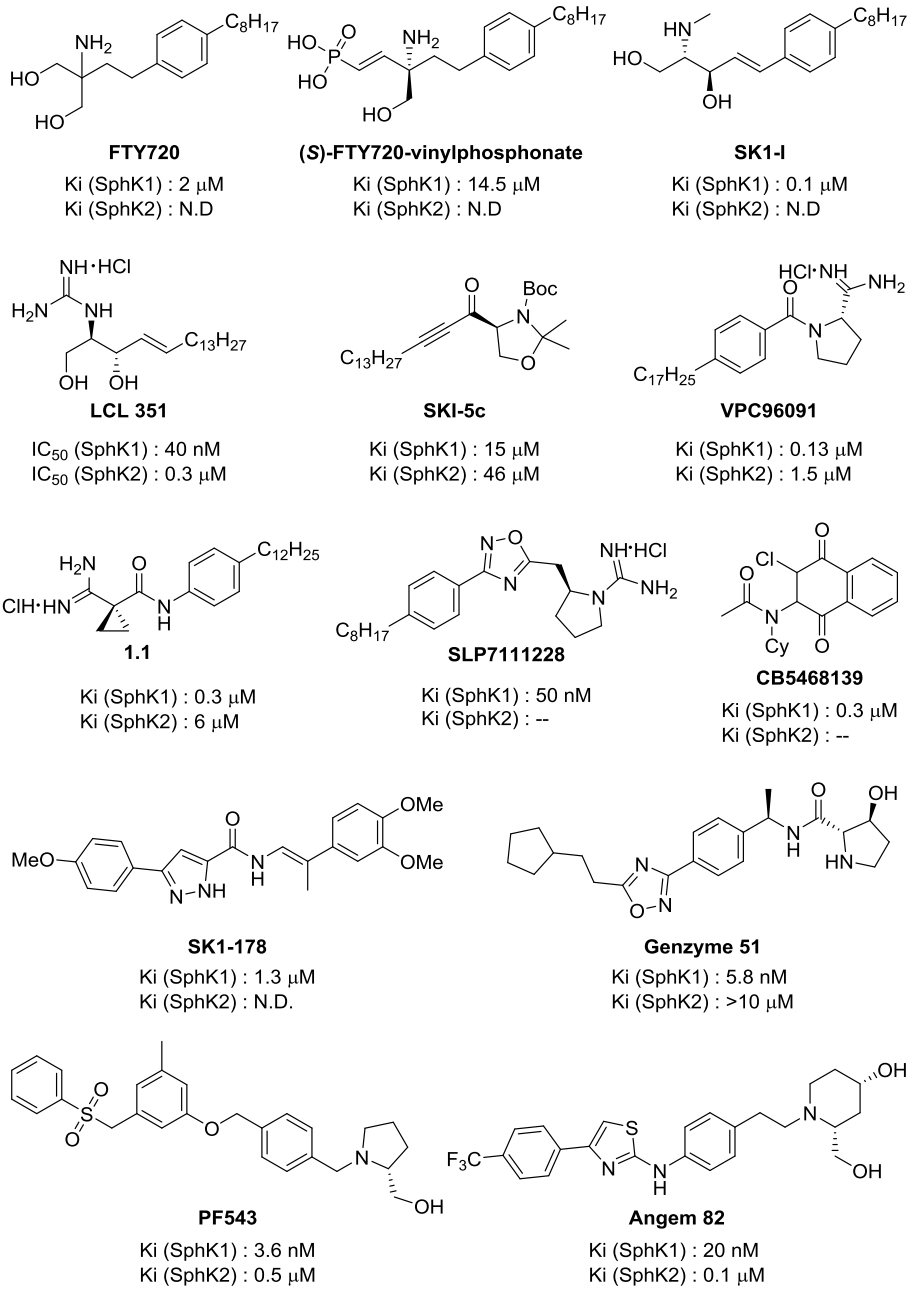


Figure 1.3. SphK1-specific inhibitors.

c) Selective SphK2 inhibitors.

To date, the absence of crystal structure of human SphK2 has slowed down the development of SphKIs for this isoform. Despite this

fact, some SphK2-specific inhibitors have emerged to be effective in numerous diseases acting in micromolar scale. As in the cases above, these inhibitors are sphingosine derivatives, carrying guanidine moieties or have been computationally designed before their syntheses.

(*R*)-FTY720-OMe and SG-12 are sphingosine analogues which induced apoptosis of cells involved in leukemia[18] as well as inhibiting DNA synthesis of breast cancer cells[49] and promote death cells of murine B-lymphoma after phosphorylation,[50] respectively. *In* vitro, SLR080811 decreases levels of S1P in leukemia and ovarian cancer cells although increases blood S1P levels *in vivo*.[4] On the other hand, K145 is implicated in dwindling S1P levels, hindering growth and suppressing ERK/AKT signaling in U937 cells and inhibiting tumor growth *in vivo*.[51] Docking studies have led to synthesis of aryladamantane ABC294640 which suppresses the cell proliferation *in vitro*[52] and has been used in the treatment of numerous diseases *in vivo* (Figure 1.4).[2,19]

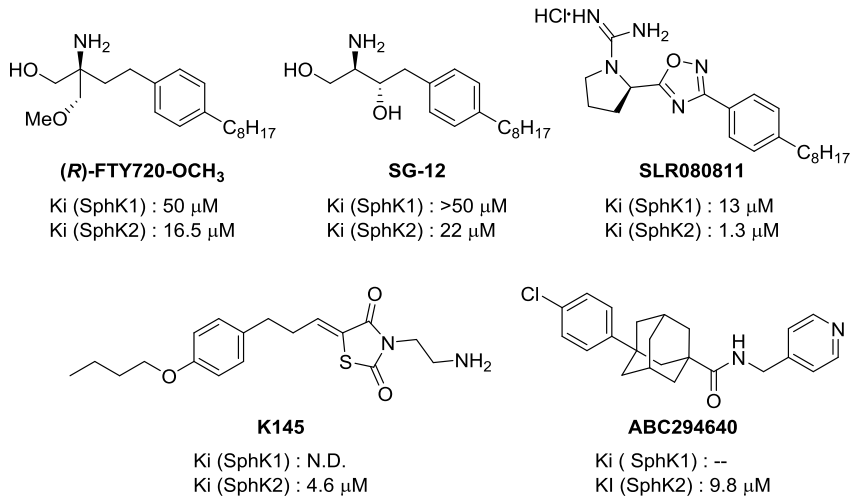


Figure 1.4. Selective SphK2 inhibitors.

In spite of that numerous SphKIs have been described to date, their selectivity and, above all, the inhibitory potency of many of them are not good enough to completely control or eradicate multiple diseases. As a consequence, many researches are focusing their efforts

on investigating different kind of compounds which are able to solve this problem.

1.2. REFERENCES

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UNIVERSITAT ROVIRA I VIRGILI
NOVEL STRATEGIES FOR THE SYNTHESES OF SPHINGOSINE KINASE INHIBITORS, B-FLUOROAMINES AND ENANTIOENRICHED ALLENES
Macarena Corro Morón

CHAPTER 2

Objectives

UNIVERSITAT ROVIRA I VIRGILI
NOVEL STRATEGIES FOR THE SYNTHESES OF SPHINGOSINE KINASE INHIBITORS, B-FLUOROAMINES AND ENANTIOENRICHED ALLENES
Macarena Corro Morón

As seen in the previous Chapter, sphingolipids play a central role in cancer processes and the inhibition of some of them constitute a big challenge for the researches nowadays. In this context, Chapter 3 is devoted to the synthesis and biological evaluation of a new family of sphingosine analogues bearing an azo or hydrazino groups and Chapter 4 is addressed to the synthesis of β-fluoroamines as potential precursors of sphingosine analogues. On the other hand, Chapter 5 has no connection with the formers and it is focused on the enantioselective synthesis of allenes derived from hydroxysilanes. The experimental part of this last chapter was carried out at Prof. Alois Fürstner Research group at Max-Planck-Institute für Kohlenforschung in Mülheim an der Rurh, Germany.

In particular, the research described in Chapter 3 aims to develop a novel methodology to synthesize sphingosine analogues and assess their inhibitory activity against sphingosine kinase 1 (SphK1), and sphingosine kinase 2 (Sphk2. More specifically the goals of this chapter are:

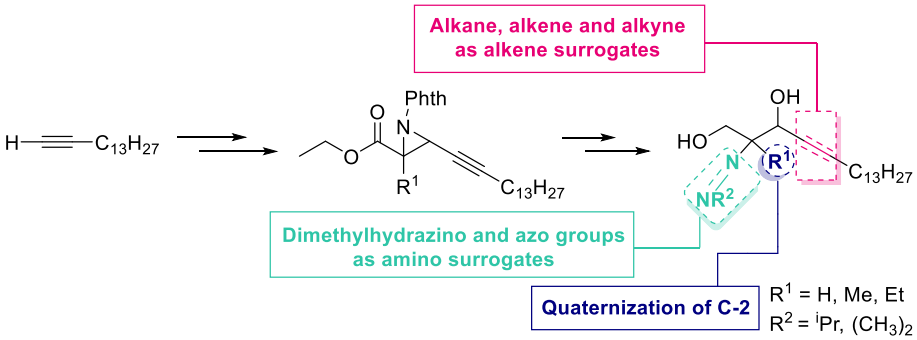
i) To synthesize a library of sphingosine derivatives bearing an azo or *N*,*N*-dimethylhydrazino groups at the quaternized center C2 containing a methyl or ethyl substituent.

ii) To introduce different degrees of insaturations in the lipidic tail incorporating alkynyl, akenyl or alkyl chains.

iii) To explore a general method of synthesis based on aziridination reaction.

iv) To perform docking studies to try to predict plausible interactions between our designed compounds and SphK1.

v) To test these compounds in *in vitro* assays measuring the IC_{50} value.

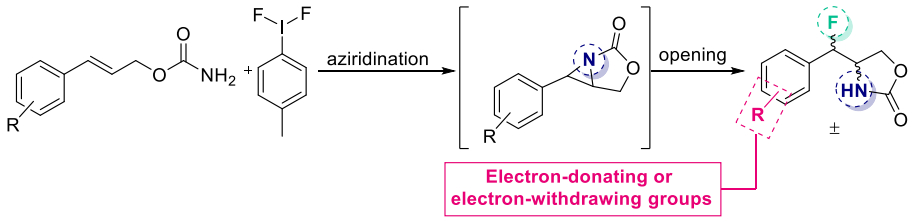


The research described in Chapter 4 aims to perform a novel route to prepare β-fluoroamines with defined stereochemistry through a metal-free aziridination reaction with $ArIF_2$ followed by a ring-opening reaction. More specifically, the main objectives of this chapter are:

i) To perform a carbamoylation reaction using cinnamyl alcohols as starting materials.

ii) To explore different fluoride sources in the preparation of the hypervalent 4-$MePhIF_2$ from 4-iodotoluene.

iii) To optimize an intramolecular and tandem metal-free aziridination/ring-opening reaction employing 4-$MePhIF_2$ as an oxidant and fluoride source.



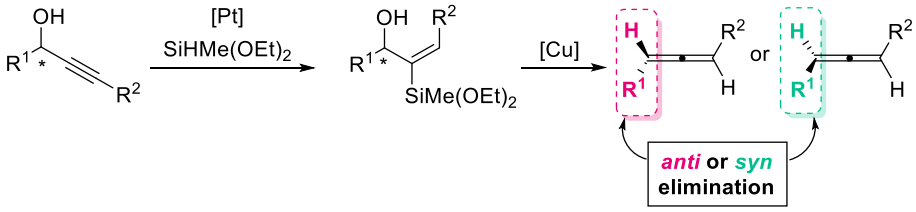
The research described in Chapter 5 aims to find a strategy to synthesize chiral allenes from hydroxysilanes employing copper sources. More specifically, the goals of this chapter are:

i) To prepare *cis* hydroxysilanes from chiral propargyl alcohols using platinum catalysis.

ii) To evaluate the enantioselective synthesis of allenes from *cis* hydroxysilanes in the presence of copper and different phosphites and phosphines as ligands.

iii) To test the racemization reaction of the corresponding allenes in the presence of copper at longer reaction times.

iv) To elucidate the plausible mechanism by isolation or detection of some intermediate.



UNIVERSITAT ROVIRA I VIRGILI
NOVEL STRATEGIES FOR THE SYNTHESES OF SPHINGOSINE KINASE INHIBITORS, B-FLUOROAMINES AND ENANTIOENRICHED ALLENES
Macarena Corro Morón

CHAPTER 3

Syntheses of azo- and hydrazino- analogues of sphingosine

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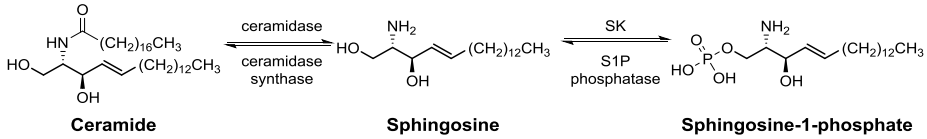
NOVEL STRATEGIES FOR THE SYNTHESES OF SPHINGOSINE KINASE INHIBITORS, B-FLUOROAMINES AND ENANTIOENRICHED ALLENES
Macarena Corro Morón

3.1. INTRODUCTION

Sphingolipids are bioactive lipids which possess key roles in biological and physiological processes.[1] Particularly, sphingosine (Sph), the first sphingolipid indentified, ceramide (Cer) and sphingosine-1-phosphate (S1P) are especially remarkable since the reversible balance that controls their formations determines the cell fate (Scheme 1).[2] Sph and Cer are considered pro-apoptotic molecules[3] whereas S1P is implicated in cell survival, proliferation and inflammation.[4] S1P is synthesized by phosphorilation of Sph. This action is carried out by the enzyme sphingosine kinase (SphK), which exits in two isoforms (SphK1 and SphK2). Therefore, the inhibition of this enzyme in either of its forms will shift the balance towards the formation of Cer favouring the cell apoptosis.



Scheme 3.1. Ceramide-Sphingosine-1-phosphate rheostat.

In the past years, the interest in inhibiting SphK has increased in both pharmaceutical and academic fields. In fact, numerous inhibitors of SphK (SphKIs) have been reported. As commented in Chapter 1, some of these compounds were designed containing a quaternary center and/or including guanidine- or amidine- moieties. The inclusion of these groups to the skeleton, especially those containing poli-nitrogenated motifs, seemed to improve the interaction with the binding pocket of the enzyme providing potent inhibitors.[5]

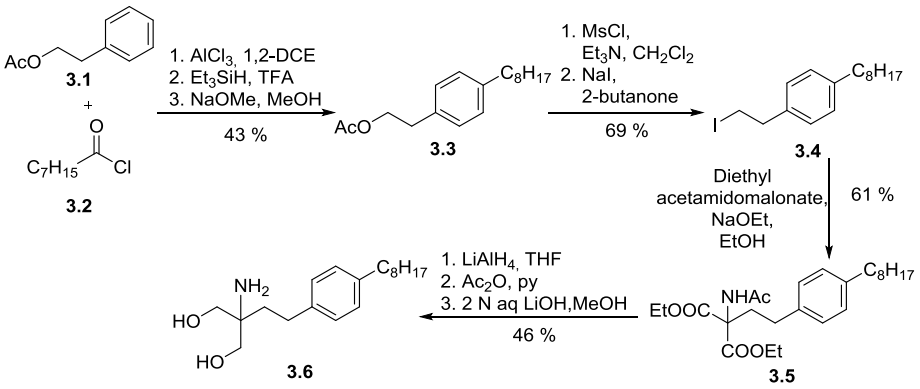
In regard with theses breakthroughs, we decided to investigate the role of poli-nitrogenated scaffolds in combination with the presence of quaternary centers. Hydrazine- and azo- moieties were chosen as poli-nitrogenated groups and methyl and ethyl as motifs incorporated in the quaternary center.

Therefore, part of this introduction will be focused on the synthesis of some quaternary and poli-nitrogenated inhibitors.

3.1.1. Synthetic strategies for developing quaternized- and guanidine- and amidine- based sphingosine kinase inhibitors (SphKIs).

Fingolimod (FTY720) was one of the first synthesized SphKIs incorporating a quaternary center in its skeleton. Despite being agonist of the receptors of S1P, it also has shown inhibitory effects against SphKs. Because of its key role in multiple diseases, many researchers have focused on FTY720 and numerous methods for its synthesis have been reported.[6] Here we highlight some of these strategies.

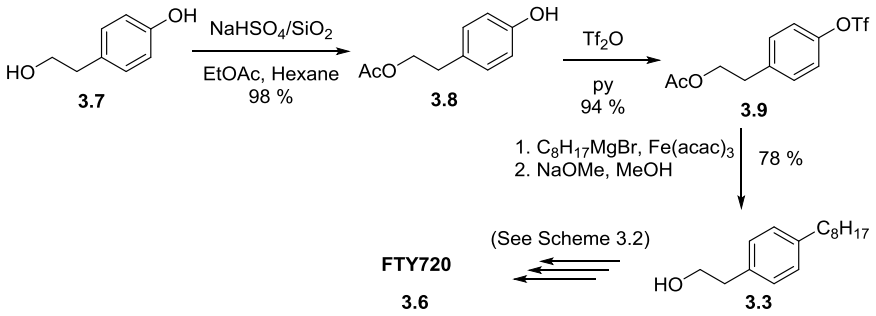
FTY720 was firstly prepared in 1992 by chemical modifications of natural product myriocin.[7] In 2000, Fujita and co-workers synthesized FTY720 starting by Friedel-Crafts acylation of phenylethyl acetate **3.1** with octanoyl chloride **3.2**.[8] Subsequent reactions including reductions, nucleophilic substitution, acetylation or hydrolysis provided the desired fingolimoid **3.6** (Scheme 3.2).



Scheme 3.2. FTY720 preparation following the methodology reported by Fujita**.**

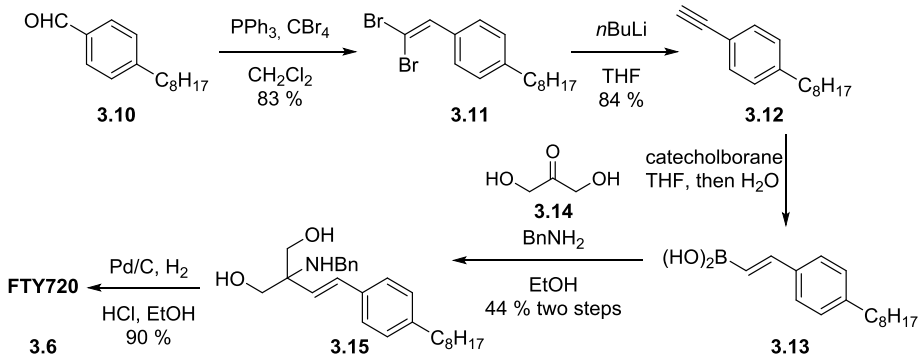
Alternatively, the selective acetylation of 2-(4-hydroxyphenyl) ethanol **3.7** to generate the corresponding ester **3.8** and its further modifications in the lipophilic tail provided the intermediate **3.3** in

72 % yield over four steps. Then, a sequence of reactions including iodination, alkylation or acetylation gave FTY720 (Scheme 3.3).[9]



Scheme 3.3. Synthesis of FTY720 starting from diol **3.7.**

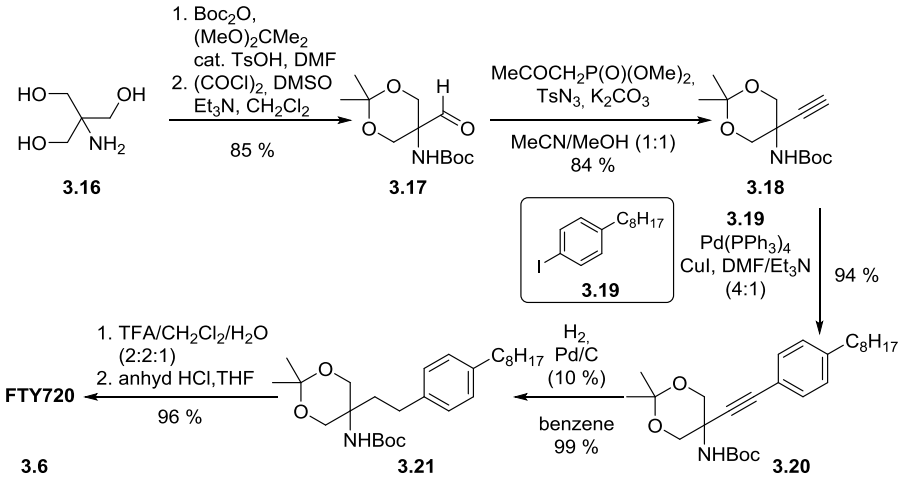
Compound **3.6** can be also prepared from 4-octylbenzaldehyde as starting material. Corey-Fuchs homologation afforded **3.12**, which reacted with catecholborane rendering **3.13**. Reaction with **3.14** in the presence of $BnNH_2$ accomplished **3.15** with the installation of a new quaternary center. Final reduction provided **3.6** in 28 % overall yield (Scheme 3.4).[10]



Scheme 3.4. Synthetic approach to afford FTY720 inhibitor reported by Keitaro.

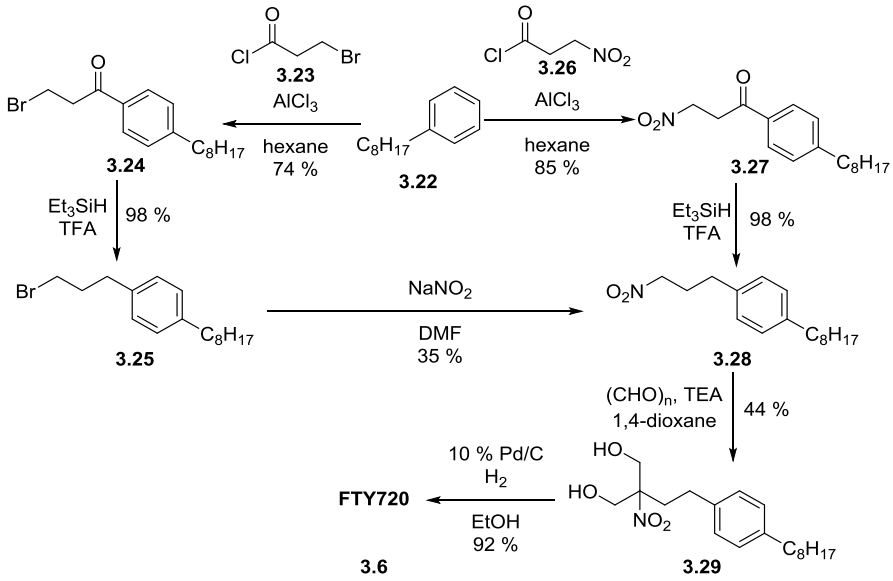
Another strategy was reported by Kim in 2006[11] whereby FTY720 was synthesized from aldehyde **3.17**, which had the quaternary center already incorporated. This compound was then converted into alkyne **3.18** mediated by Roth's protocol.[12] The Sonogashira coupling reaction between this partner and the aryl iodide **3.19**, followed by the

hydrogenation of the triple bond, the removal of protecting groups and the treatment with HCl, provided **3.6** as hydrochloride salt (Scheme 3.5).



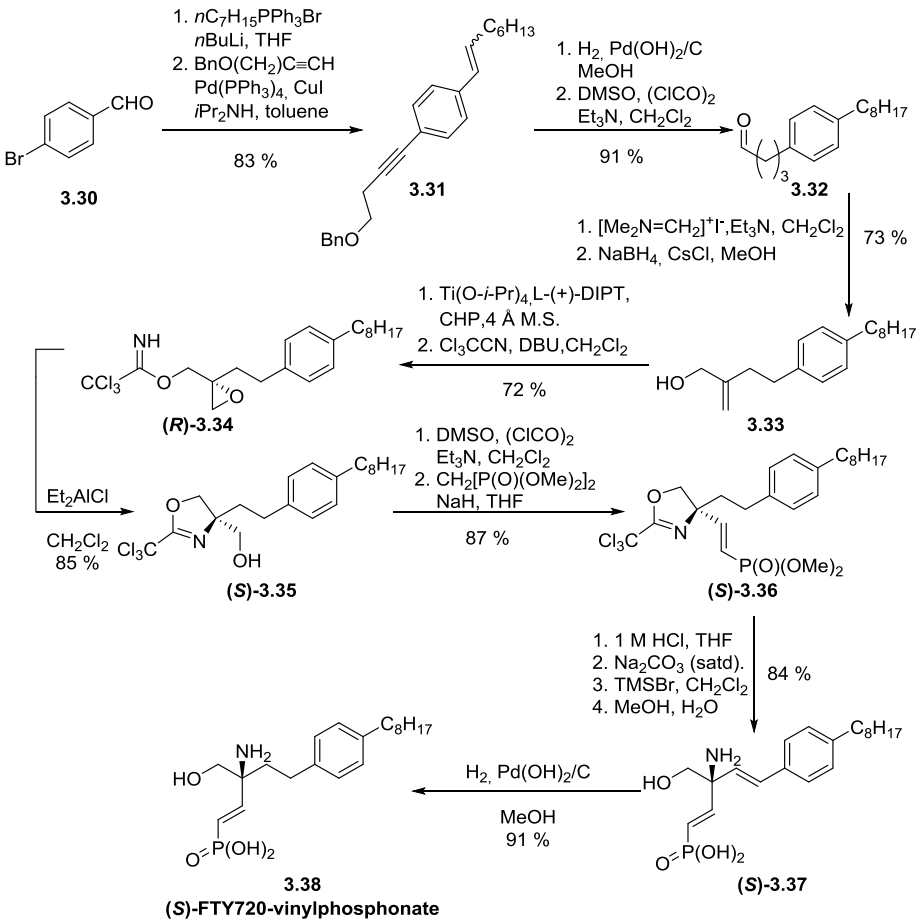
Scheme 3.5. Sonogashira coupling-mediated synthesis of FTY720.

Two similar routes based on Friedel-Craft reactions and converging in the same key intermediate **3.28** were described by Yao in 2015.[13] First, *N*-octylbenzene **3.22** was treated with 3-bromopropanyl chloride **3.23** in the presence of $AlCl_3$ affording **3.24** in high yield. Then, the ketone reduction and the subsequent introduction of the nitro group rendered the key intermediate **3.28** in moderate yield. Alternatively, the use of 3-nitropropanoyl chloride **3.26** led to the formation of compound **3.27** which was selectively reduced with triethylsilane and TFA accomplishing the key intermediate **3.28**. With the key intermediate in hand, a double Henry type reaction[14] with formaldehyde followed by reduction of nitro group provided **3.6** (Scheme 3.6).



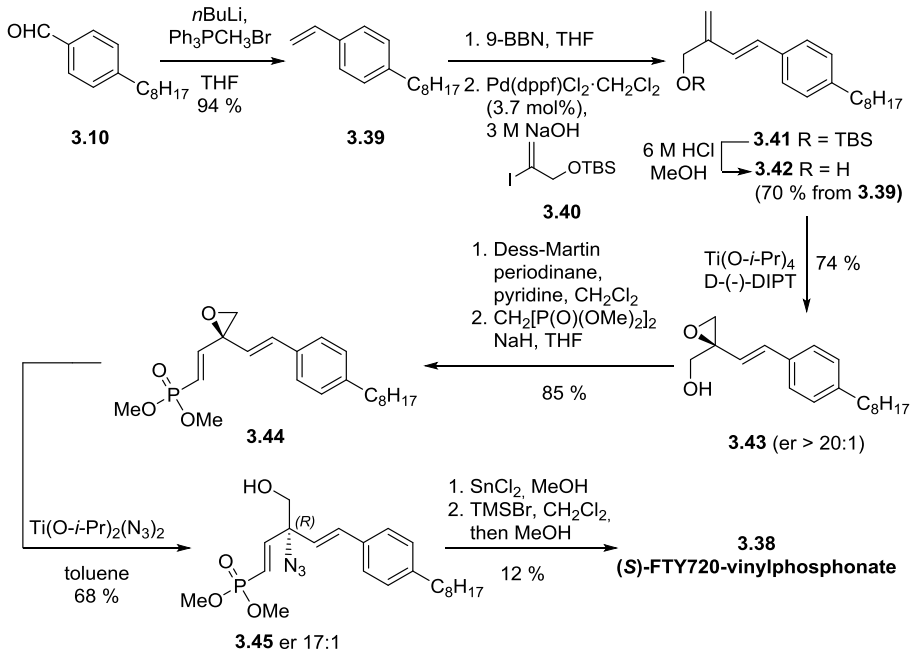
Scheme 3.6. Synthesis of FTY720 with a nitro compound **3.28** as key intermediate.

Fingolimod derivative (*S*)-FTY720-vinylphosphonate **3.38** was first synthesized in 13 steps and 25 % overall yield by Bittman in 2009.[15] This methodology started with a Wittig reaction of the compound **3.30** followed by a cross-coupling reaction to render **3.31** with a full carbon structure of the target compound. After reduction, oxidation and Mannich reactions to afford **3.33**, the introduction of the quaternary center was carried out by Sharpless epoxidation. Further amidation, ring-opening, phosphonate hydrolylisis, deprotection and selective double bond reduction provided **3.38** (Scheme 3.7).



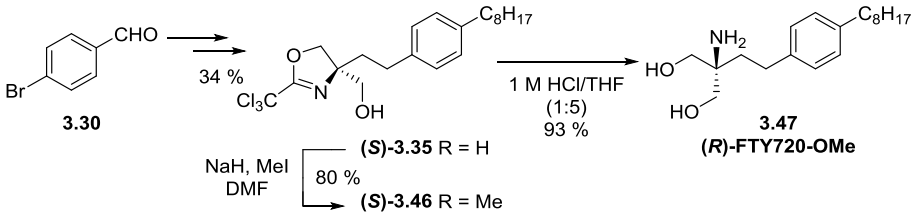
Scheme 3.7. First synthesis of (*S*)-FTY720-vinylphosphonate.

Some years later, the same author reported another protocol to synthesize this inhibitor where the quaternary stereocenter was also introduced by Sharpless epoxidation of **3.42**. The regioselective ring-opening with azide in acid media followed by reduction and hydrolysis, furnished the final compound **3.8** in 3 % overall yield (Scheme 3.8).[16]



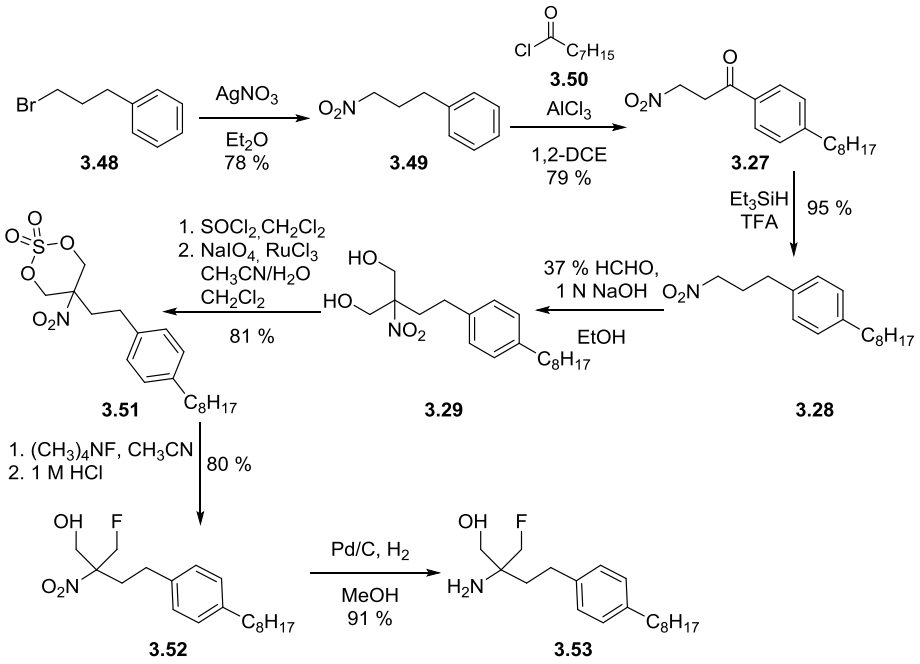
Scheme 3.8. Synthesis of (*S*)-FTY720-vinylphosphonate with formation of quaternary stereocenter mediated by Sharpless epoxidation.

The synthesis of (*R*)-FTY720-OCH_3 was based on the preparation of (*S*)-FTY720-vinylphosphonate and little modifications in the final steps led to the formation of this SphK2 inhibitor.[15] In fact, the replacement of a hydroxyl group by a methoxy one in the compound **(*S*)-3.37** with MeI and NaH and the further deprotection of amino and hydroxyl moieties, provided the desired compound in 29 % overall yield (Scheme 3.9).[17]



Scheme 3.9. Stereoselective synthesis of (*R*)-FTY720-OMe based on the preparation of (*S*)-FTY720-vinylphosphonate reported by Bitmann.

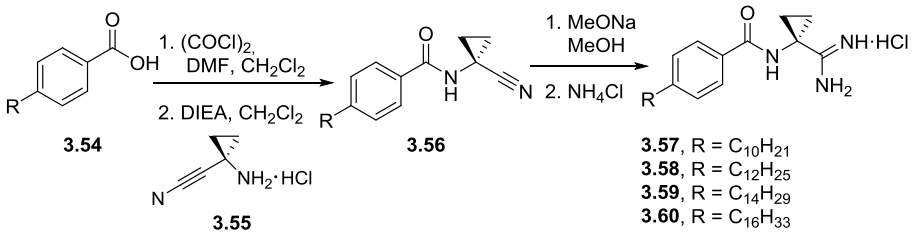
The corresponding fluorinated FTY720 derivative was prepared from **3.49** by nitro formation, Friedel-Craft reaction and carbonyl deoxygenation to give **3.51**. Subsequent reactions involving bisalkylation via nitro-aldol reaction of **3.51**, nucleophilic fluorination of cyclic sulphate **3.53** and nitro reduction, led to the formation of the inhibitor in 34 % over 10 steps (Scheme 3.10).[18]



Scheme 3.10. Preparation of the fluorinated FTY720 derivative **3.53**.

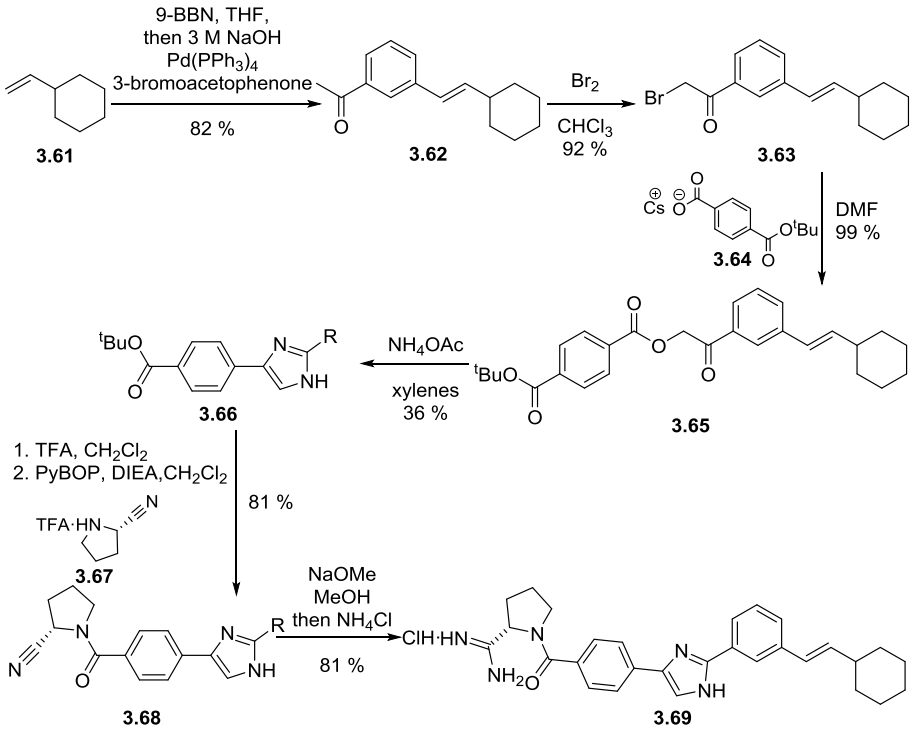
Inhibitors bearing poly-nitrogenated moieties in the polar head has also emerged as promising inhibitors. In fact, the combination of guadinidino- or amidino- motives with aryl and/or heterocyclic partners in the skeleton have given interesting results in inhibitory activity.

In 2010, Macdonald reported the first family of SphKIs containing a guanidine moiety. The synthesis of this class of compounds was initiated by coupling of the corresponding benzoic acid and the appropriate amino-carbonitrile compound. Then, the conversion of nitrile motif into guanidine provided a series of inhibitors analogues (Scheme 3.11).[19]



Scheme 3.11. Synthesis of the first SphKIs containing a guanidine moiety.

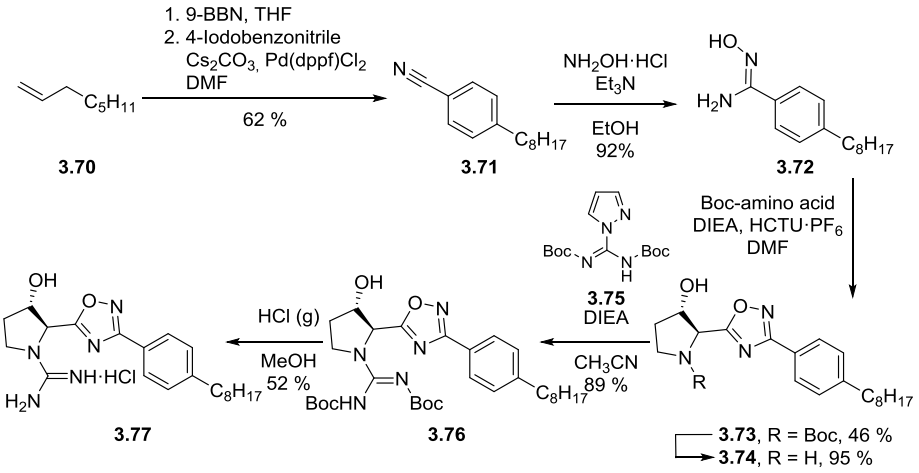
One year later, Kennedy *et al.* prepared the inhibitor **3.69** bearing a guanidinium and imidazole groups from **3.61**. The key step in this synthesis was the introduction of the imidazole moiety, afforded by the reaction of **3.65** with ammonium chloride. Furthermore, the guanidinium partner was synthesized from nitrile **3.68** (Scheme 3.12).



Scheme 3.12. Approach to synthesize compound **3.69**.

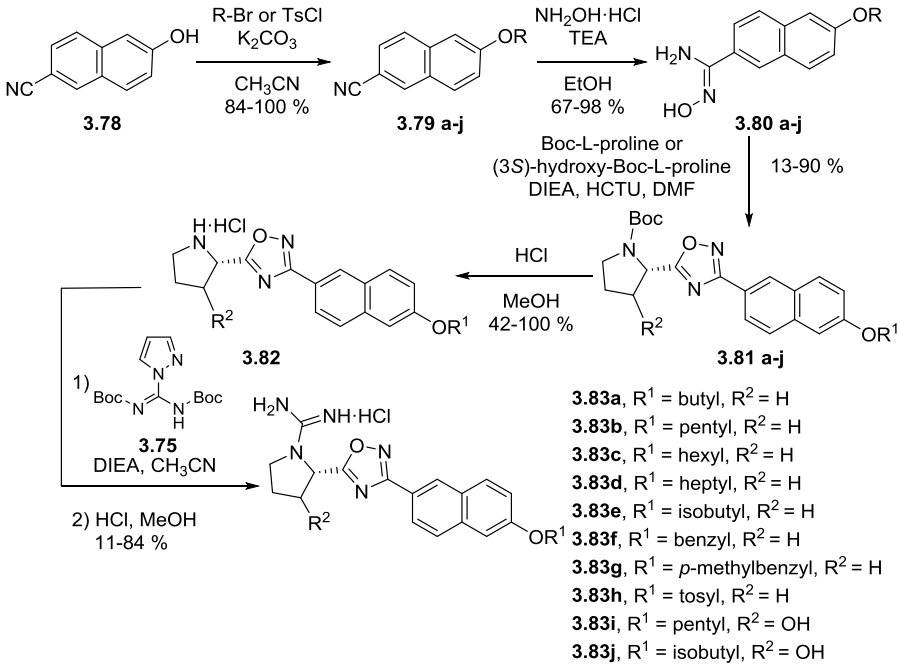
Similar compounds were prepared by Santos and co-workers using 1-octene as starting material. This kind of inhibitors were characterized by bearing a 1,2,4-oxadiazol and a pyrrolidine moieties.

The oxadiazol ring was introduced by coupling and dehydration of the corresponding amino acid with **3.72**, in turn prepared by cross-coupling and reaction with hydroxylamine. Then, compound **3.77** was furnished by removal of Boc motif, guanidylation of **3.74** with *N,N*-di-Boc-1H-pyrazole-1-carboxamidine and deprotection of **3.76** with chloridric acid (Scheme 3.13).[20]



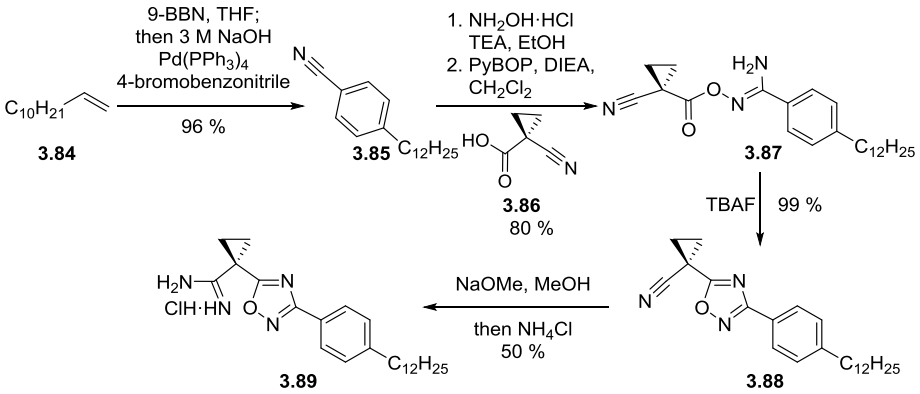
Scheme 3.13. Synthesis of **3.77**.

Napthalene-based analogues **3.83a-j** were also prepared taking into account the aforementioned strategy from intermediates **3.80a-j**. In turn, these latter compounds were synthesized from coupling reaction of **3.80** with different alkyl bromides or tosyl to render **3.79a-j** (Scheme 3.14).[21]



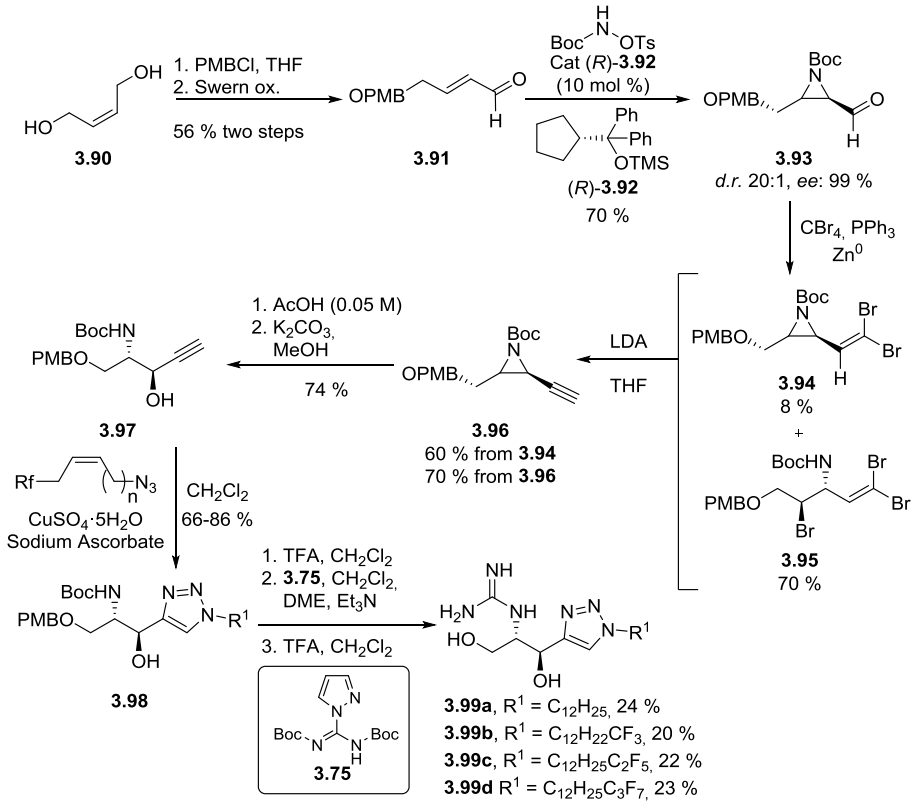
Scheme 3.14. Synthesis of **3.83a-j** bearing a naphthalene, oxadiazole and guanidine moieties.

Houck published the synthesis of new inhibitors sharing a very similar structure related to compounds reported by Santos.[21] The difference with these last compounds is based on the replacement of the pyrrolidinyl moiety by a cyclopropyl. The synthesis started with the reduction of **3.84** with 9-BBN followed by Suzuki coupling. Subsequent amidoximination followed by coupling and cyclization reactions yielded the 1,2,4-oxadiazol intermediate **3.88**. Finally, the guanidine motif was afforded by base-catalyzed Pinner conditions (Scheme 3.15).[22]



Scheme 3.15. Synthesis of compound **3.89** following the strategy described by Houck.

Very recently, our group reported a new series of SphKIs combining the sphingosine skeleton with guanidino mioety and a central triazole ring as a mimmetic unit of the alkene as well as a fluorinated chain in the lipophilic tail (Scheme 3.16).[23] The synthesis was initiated by an enantioselective organocatalytic aziridination of α,β-unsaturated aldehyde **3.91** followed by a Corey-Fuchs reaction involving metal-exchange and α-elimination reactions to render the alkyne **3.96**. The subsequent ring-opening with AcOH and further hydrolysis of the acetate intermediate led to alkyne **3.97**, which was treated with an azide chain to afford a triazole ring through a click-reaction. Final deprotections with TFA and guanidylation of **3.98** with **3.75** provided the guanidino sphingosine analogues **3.99a-d**.



Scheme 3.16. Syntheses of sphingosine analogues bearing a central triazole ring, a guanidino moiety and different fluorinated chains.

3.2. OBJECTIVES.

With this background, sphingosine derivatives bearing a quaternary centre and/or basic amino moieties seem to increase affinity for sphingosine kinase 1 or 2 (SphK1, SphK2). In this context, the specific aims of this work are:

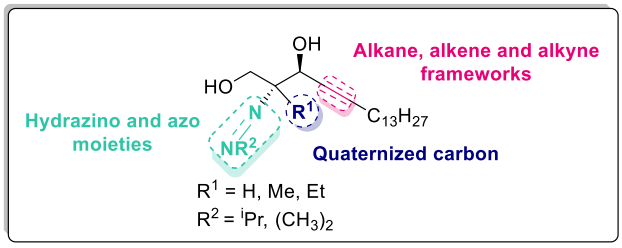
i) To synthesize a family of sphingosine analogues containing a containing a quaternary center α to the amino functionality in order to explore the role of this moiety in the inhibition of the SphK.

ii) To compare the importance of the restricted 4,5-*trans* double bond during the inhibition with analogues bearing triple, double and saturated bonds at the same position.

iii) To modify the polar head incorporating a hydrazino moiety as a novel basic group. This unit will be also modified as *N,N*-dimethyl hydrazine and azo groups.

iv) To carry out a series of computational studies in order to predict the plausible interactions between our compounds and the SphK1.

v) To determine the inhibition potency of these compounds over SphK1 and SphK2 measuring the IC_{50}.



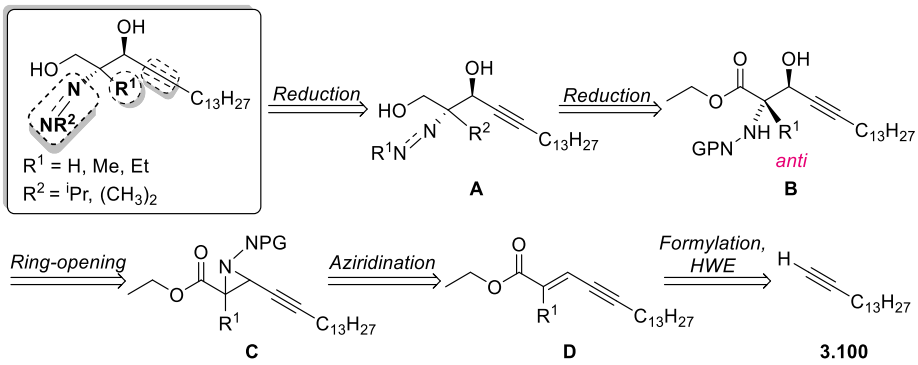
3.3. RESULTS AND DISCUSSION.

3.3.1. Retrosynthetic pathway.

The syntheses of azo- and hydrazine sphingosine analogues can be envisioned as shown in Scheme 3.17. As mentioned above, our goal is the syntheses of sphingosine derivatives containing triple and single bonds as mimics of the double bond, a quaternary centre at carbon 2 as well as modifications in the polar head including azo- and *N,N*-dimethylhydrazino moieties.

These compounds can be prepared from the key structure **3.100**, which possesses the carbon skeleton of the desired products. The final sphingolipid analogues can be accessed by total of partial reduction of

the alkynyl alcohol precursor **A**, which in turn will be obtained by reduction of the ester functionality in **B**. The anti relative configuration of the amino and alcohol moieties in **B** was envisioned to be obtained through the nucleophilic ring opening of a trans alkynylaziridine intermediate **C**, prepared from **B** by means of an alkene nitrene transfer reaction. Problems derived from the chemoselectivity of this reaction should not be discarded although an unfavourable transition state resulting from the reaction between the nitrene source and alkyne is expected. In turn, aziridination reaction would lead to *trans*-α,β-unsaturated ester **B**, generated by formylation and subsequent Horner-Wadwords-Emmons olefination from compound **3.100**. Conversion of the protected hydrazyno group into the azo- and *N,N*-dimethylhydrazine group is anticipated to be explored along the synthetic route.



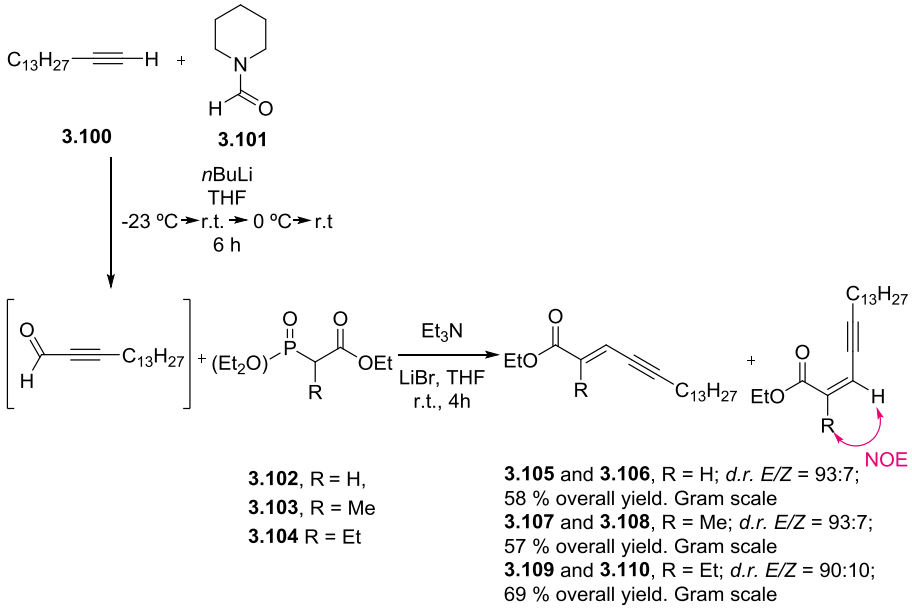
Scheme 3.17. Retrosynthetic pathway of sphingosine analogues.

3.3.2. Syntheses of sphingosine analogues.

3.3.2.1. α,β-unsaturated compounds.

The syntheses of sphingosine can be carried out using multiple methodologies reviewed by our group[24] and more recently by Gao and co-workers.[25] Among several options to prepare sphingosine, Bittman reported the synthesis of this sphingolipid starting from a formylation reaction followed by a Horner-Wadwords-Emmons olefination.[26]

Taking into account this approach, we envisioned the synthesis of the compounds **3.105**, **3.107** and **3.109** containing the skeleton of the target compounds by formylation of 1-pentadecyne **3.90** with 1-formylpiperidine **3.101**, and subsequent treatment of the resulting aldehyde with phosphonates **3.102-3.104** in basic medium. Then, the subsequent olefination of the freshly generated alkynal with the corresponding stabilised phosphonate provided a mixture of *E/Z* diasteroisomers in good yields and good *E* stereoselectivities (**3.105/3.106** = 93/7; **3.107/3.108** = 93:7; **3.109/3.110** = 90:10) (Scheme 3.18).



Scheme 3.18. Synthesis of esters.

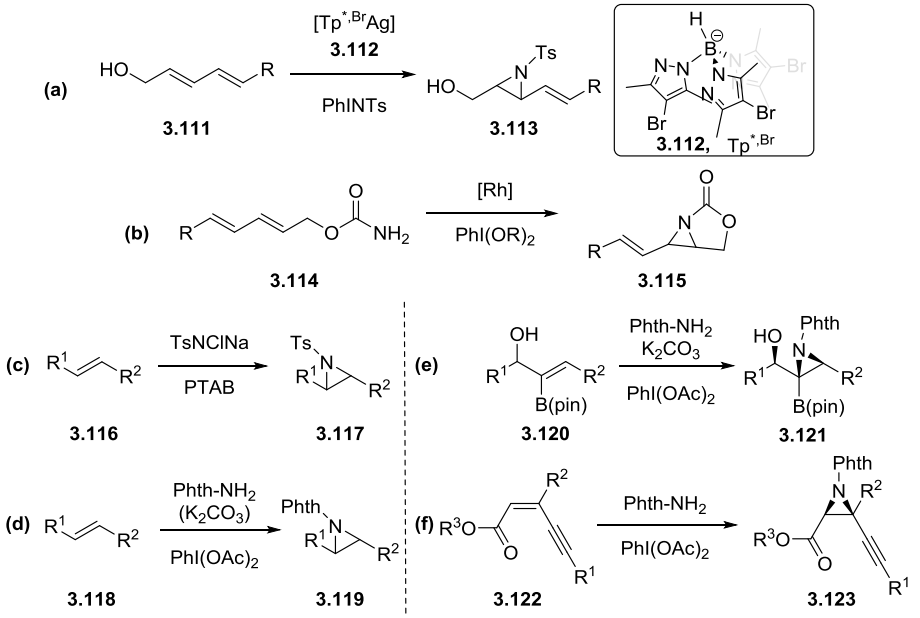
The *E* configuration of the major compound was assigned on the basis of a NOE experiment. The presence of NOE correlations between proton H-3 and the methyl group of the olefinic moiety in compounds **3.106, 3.108** and **3.110** contrasted with the absence of the corresponding NOE correlations in **3.105**, **3.107**, and **3.109**, thus confirming the *E* configuration of the latter.

3.3.2.2. Alkene aziridination.

As discussed in *section 3.2.1*, the *anti* vicinal amino alcohol fragment could be formed though ring-opening reaction of the corresponding aziridine intermediate.

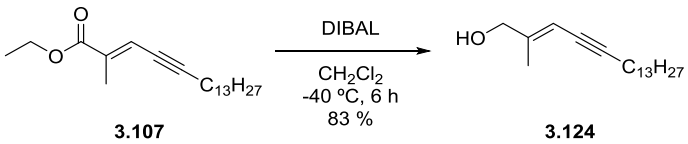
Alkene aziridination can be achieved by an intra- or intermolecular way *via* several strategies.[27] In 2010, our group reported the regio- and stereoselective alkene aziridination of conjugated dienols *via* a nitrene-transfer reaction. This work was carried out in collaboration with Prof. Pedro Pérez, who previously had studied the aziridination reaction in simple alkenes using different trispyrazolylborate copper complexes [Tp^xCu] as catalysts and PhINTs as nitrene transfer reagent.[28] Specifically, our group described the synthesis of vinylaziridines using PhINTs as nitrene source and mediated by [$Tp^{*,Br}Ag$] as a catalyst, characterized by bearing methyl group and bromine as substituent in the pyrazole ring (a, Scheme 3.19).[29] An intramolecular version was also developed starting from dienylcarbamates and using rhodium paddlewheel catalysts and (bis(acyloxy)iodobenzene (b, Scheme 3.19).[30] This reaction also proceeded through a metalonitrene complex where the catalyst played a second role as Lewis acid during the S_N2 opening process. Furthermore, alkene aziridination can also be performed using metal-free conditions. Indeed, Sharpless reported the aziridination of allylic alcohols using Chloroamine-T as nucleophilic nitrogen source and phenyltrimethylamonium tribromide (PTAB) as catalyst affording good to excellent yields (c, Scheme 3.19).[31] Some years later, Che and co-workers[32] and Yudin *et al.*[33] independently described an aziridination methodology mediated by the formation of the acetoxy nitrenium ion *N*-acetoxyaminophthalimide*.* In this case, aziridines were prepared by using *N*-aminophthalimide as nitrogen source, phenyliodine(III) diacetate (PIDA) as oxidant and styrene and chalcones as starting materials (d, Scheme 3.19). In comparison with Yudin, Che also included K_2CO_3 in his reaction mixtures to avoid the opening of the aziridines by AcOH generated as by-product during the formation of the nitrenium

ion. Based on this report, in 2011, Walsh described the aziridination of B(pin)-substituted allylic alcohols (e, Scheme 3.19).[34] Analogously, Liu also used the aforementioned strategy in the synthesis of *N*-phthalkynylaziridines starting from α,β-unsaturated compounds. Aziridines were afforded in high diastereoselectivity and only some products were obtained as a mixture of invertomers (f, Scheme 3.19).[35]



Scheme 3.19. Different approaches in the synthesis of aziridines.

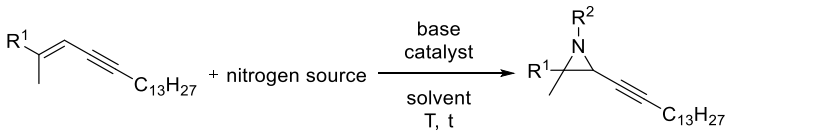
In this context, we sought to explore the intermolecular alkene aziridination protocols described above starting from α,β-unsaturated ester **3.107** and alcohol **3.124** as alkene substrates. Alcohol **3.124** was synthesized from **3.107** by reduction with DIBAL in an 83% yield (Scheme 3.20).



Scheme 3.20. Synthesis of the compound **3.124** by reduction of **3.107**.

When **3.124** was reacted in the presence of PhINTs and [Tp^{*,Br}Ag] in dichloromethane, no reaction was observed and only starting material was detected by thin-layer chromatography (Table 3.1, entry 1). Likewise, the reaction performed using the Sharpless protocol with Chloramine T in different solvents and conditions did not provide the expected aziridine (Table 3.1, entries 2-4). However, aziridine was chemo- and diastereoselectively formed when alcohol **3.124** was treated with *N*-aminophthalimide and PhI(OAc)$_2$ in the presence of K_2CO_3 and dichloromethane. The *N*-Pthth-alkynylaziridine **3.125** was obtained as a mixture of two invertomers (86:14) but isolated in poor yield (Table 3.1, entry 5). We then tested the aziridination reaction starting from the α,β-unsaturated ester **3.107** and using *N*-aminophthalimide and PhI(OAc), which furnished the aziridine **3.126** in quantitative yields[35] (Table 3.1, entry 6). In this case, the reaction also proceeded diastereoselectively and the expected complete chemoselectivity was confirmed since only one product was detected. As commented in *section 3.2.1.*, the chemoselectivity can be attributed to the unfavourable reaction path leading to the anti-aromatic 1H-azirine resulting from reaction of the nitrene source with the alkyne.[36] It is worth mentioning that this reaction was carried out in the absence of K_2CO_3, as previously Liu did. Fortunately, the employment of this base was not necessary because our aziridine did not open by AcOH. Hence, another experiment in its presence was not performed.

Table 3.1. Optimization of the aziridination process starting from **3.124** or **3.107**.



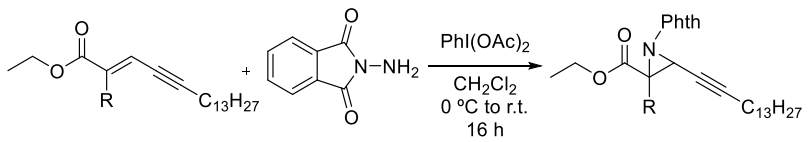
3.124, R^1 = CH_2OH
3.107, R^1 = C(O)OEt

3.125, R^1 = CH_2OH, R^2 = Ts, Phth
3.126, R^1 = C(O)OEt, R^2 = Phth

Entry	Subst.	Cat.	Nitrogen source	Solvent	T (°C)	t (h)	Yield (%)[e]
1[a]	**3.124**	$Tp^{*,Br}Ag$	PhINTs	CH_2Cl_2	r.t.	16	N.R.[f]
2[b]	**3.124**	PTAB	TsNClNa	MeCN	r.t. to 40	48	N.R.[f]
3[b]	**3.124**	PTAB	TsNClNa	CH_2Cl_2	r.t.	48	N.R.[f]
4[b]	**3.124**	PTAB	TsNClNa	MeCN	r.t.	24	N.R.[f]
5[c]	**3.124**	--	$PhthNH_2$	CH_2Cl_2	0 to r.t.	16	31[g]
6[d]	**3.107**	--	$PhthNH_2$	CH_2Cl_2	0 to r.t.	16	100

[a] Alcohol **3.124** (0.25 mmol), [$Tp^{*,Br}Ag$] (0.003 mol), PhINTs (0.25 mmol), CH_2Cl_2 (5 mL). [b] *General conditions of the aziridination using Chloramine T*: alcohol **3.124** (0.20 mmol), Chloroamine-T (0.22 mmol) , PTAB (0.02 mmol), solvent (1 mL). [c] Alcohol **3.124** (0.18 mmol), $PhthNH_2$ (0.25 mmol), $PhI(OAc)_2$ (0.27 mmol), K_2CO_3 (0.50 mmol), CH_2Cl_2 (2.4 mL) [d] Ester **3.107** (0.16 mmol), $PhthNH_2$ (0.32 mmol), $PhI(OAc)_2$ (0.23 mmol), CH_2Cl_2 (1.6 mL). [e] Isolated yield. [f] N.R. = No reaction. [g] Two invertomers were detected by ^1H NMR (86:14).

Similarly, compounds **3.105** and **3.109** were then reacted with *N*-aminophthalimide and phenyliodine(III) diacetate affording the corresponding aziridines **3.127** and **3.128** in 89 and 88 % yield, respectively (Scheme 3.21). It is worth to note that **3.127** was obtained as a mixture of invertomers (78:22).



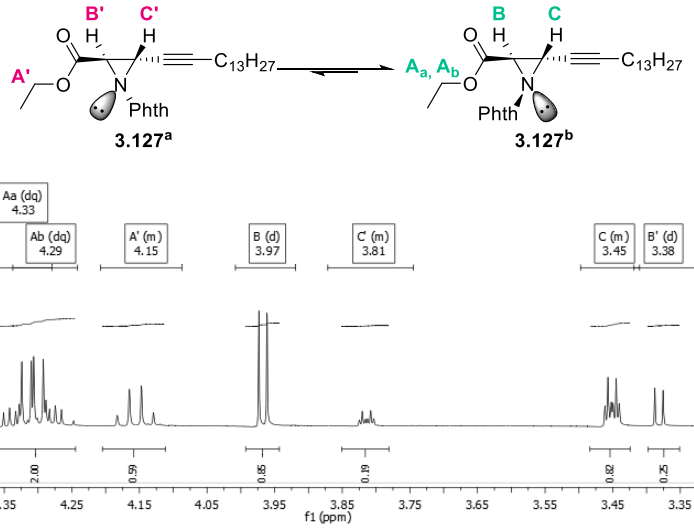
3.105, R = H
3.109, R = Et

3.127, R= H, 89 %, invertomers (78:22)
3.128, R = Et, 88 %

Scheme 3.21. Aziridination reaction for **3.95** and **3.99**.

Invertomers are produced by inversion of nitrogen from a tetrahedral configuration to another one through trigonal planar configuration. The presence of these species was confirmed by ^{1}H RNM. They showed similar coupling constants for protons of the aziridine **3.127** although the CH_2 of ester moiety exhibited interesting changes (Table 3.2).

Table 3.2. Invertomers of aziridine **3.127**. Shifts, multiplicity and coupling constants.

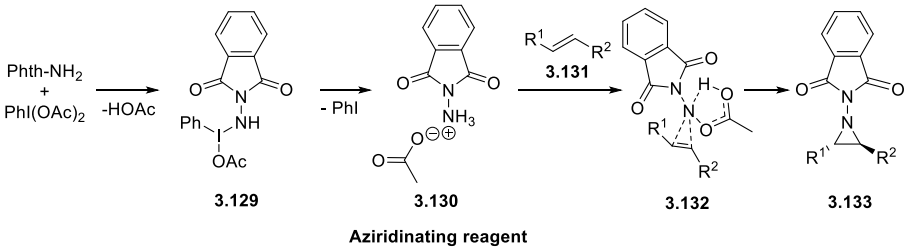


Inv.	Signal	δ (ppm)	Multiplicity	J (Hz)
3.127a	A’	4.16	q	7.1
	C’	3.81	dt	4.9, 1.8
	B’	3.38	d	4.9
3.127b	A_a	4.33	dq	10.8, 7.2
	A_b	4.29	dq	10.8, 7.1
	B	3.97	d	4.8
	C	3.43	dt	4.8, 1.9

[a] Shifts, multiplicity and coupling constants for compound **3.127a**. [b] Shifts, multiplicity and coupling constants for compound **3.127b**.

Whereas CH_2 signal was detected as two doublets of quartets (dq) in the major invertomer (signals $\mathbf{A_a}$ and $\mathbf{A_b}$), a quartet was observed in the minor one (**A'**). This fact can be explained by the place of the lone pair and the phthalimido group. When the electron pair is *syn* to the ester moiety, CH_2 is able to rotate freely and, as consequence, both protons are equivalents appearing as a quartet (**3.127a**). Nevertheless, the presence of phthalimido group prevents free rotation, so that the methylenic protons become anisochronous as the ^1H NMR spectrum reveals appearing as two complex signals in an AB system (**3.127b**).[37]

It is well-known that conventional alkene aziridination involving sources of nitrogen and aryliodinanes procceds *via* nitrene. However, a different mechanism[33] has been proposed in this case based on the mechanism previously reported by Atkinson.[38] Thus, the process would start with the reaction between $PhI(OAc)_2$ and Phth-NH_2 to form **3.129** releasing acetic acid. Then, the reduction of iodine (III) to iodine (I) would favour the formation of the acetoxy nitrenium ion **3.130** as an aziridinating agent. Finally, the aziridine **3.133** would be intermolecularly generated through transition state **3.132** which resembles that accepted for oxygen-atom transfer of peracids to alkenes (Scheme 3.22).



Scheme 3.22. Proposed mechanism for aziridination in the presence of Phth-NH_2 and $PhI(OAc)_2$.

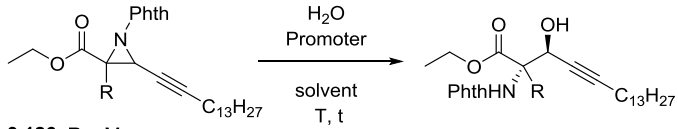
3.3.2.3. Ring-opening aziridine.

With aziridines **3.126**, **3.127** and **3.128** in hand, we focused our efforts on investigating the ring-opening step (Table 3.3).

Initially, aziridine **3.126** was treated with KOH in refluxing dichloromethane in the presence of 18-crown-6. However, the ring-opened product **3.134** was not detected but only hydrolysis of ester moiety (Table 3.3, entry 1). This result is consistent with the fact that the aziridine **3.126** is not activated at the N. In this sense, we then tested the ring-opening process in the presence of a series of promoters.

When the aziridine **3.126** was reacted with $HClO_4$ as a promoter in a mixture THF/H_2O (1:1), the reaction led to the formation of **3.134** in poor yield (Table 3.3, entry 2). The replacement of $HClO_4$ by PTSA as a promoter improved the yields despite the fact that longer reaction time was required to complete the reaction (Table 3.3, entry 3). Gratifyingly, the use of dioxane/water 1:1 drastically decreased the reaction time and rendered better yield for **3.134** although a minor by-product was also detected (Table 3.3, entry 4). Analogously, when these conditions were applied to aziridines **3.127** and **3.128**, the reactions led to the formation of the ring-opened products in moderate yields (Table 3.3, entries 5-6).

Table 3.3. Optimization for ring-opening aziridines.



3.126, R = Me
3.127, R = H
3.128, R = Et

3.134, R = Me
3.135, R = H
3.136, R = Et

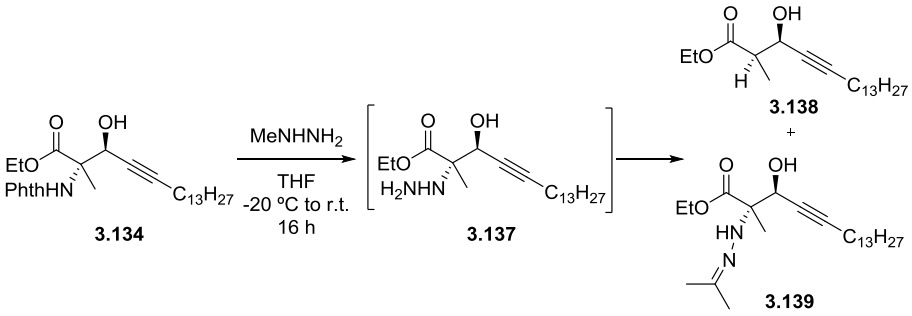
Entry[a]	Subst.	Promoter (equiv.)	Solvent/water (x:y)	T (°C)	t (h)	Yield (%)[b]
1[c]	**3.126**	--	CH_2Cl_2 (1:0)	Reflux	24	--
2	**3.126**	$HClO_4$ (1.0)	THF (1:1)	50 to reflux	24	32
3	**3.126**	PTSA (1.1)	THF (1:1)	Reflux	72	49
4	**3.126**	PTSA (1.1)	Dioxane (1:1)	Reflux	24	82
5	**3.127**	PTSA (1.1)	Dioxane (1:1)	Reflux	12	45
6	**3.128**	PTSA (1.1)	Dioxane (1:1)	Reflux	48	37

[a] *General conditions*: aziridine (0.02 mmol), promoter (x equiv.), solvent/H_2O in proportion 1:1. [b] Isolated yield. [c] Aziridine **3.126** (0.02 mmol), KOH (0.15 mmol), 18-crown-6 (0.02 mmol), CH_2Cl_2 (3 mL).

3.3.2.4. Dephthaloylation and synthesis of the first azo-sphingosine derivatives.

Several reports have been published to deprotect hydrazines when phthalamido or similar groups are used as protecting groups.[39] Most of them use hydrazine or methylhydrazine as reagent since the reaction proceeds under mild conditions. Nevertheless, methylhydrazine is commonly more employed because the reaction is cleaner than using hydrazine or phenylhydrazine. This fact is because of the by-product generated, *N*-methylphthalhydrazide, is less acid than the by-products generated with other hydrazine derivatives what avoids the formation of a complex with the free amine.[39b,40]

Taking all these issues into account, compound **3.134** was treated with methylhydrazine in THF (Scheme 3.23).



Scheme 3.23. Dephthaloylation of **3.134**.

As TLC plate revealed, total deprotection of hydrazine moiety was confirmed by ^{1}H NMR from the crude (a, Figure 3.1). However, two different products were isolated after flash chromatography. The ^{1}H NMR spectrum of one of them displayed a quintuplet at 2.60 ppm and the peaks located at 4.40 and 1.20 ppm appeared as a doublet of triplets and a doublet, respectively rather than a triplet and a singlet as expected, respectively (b, Figure 3.1). Besides, HMBC experiment revealed that the peak at 2.60 ppm correlated with carbonyl carbon and triple bond at long distances. These facts suggested that hydrazine had been removed from the compound and that one proton was present in its place. This

may be explained by oxidation of hydrazine into unstable diazo moiety followed by its decomposition to nitrogen and hydrocarbon **3.138**.[41]

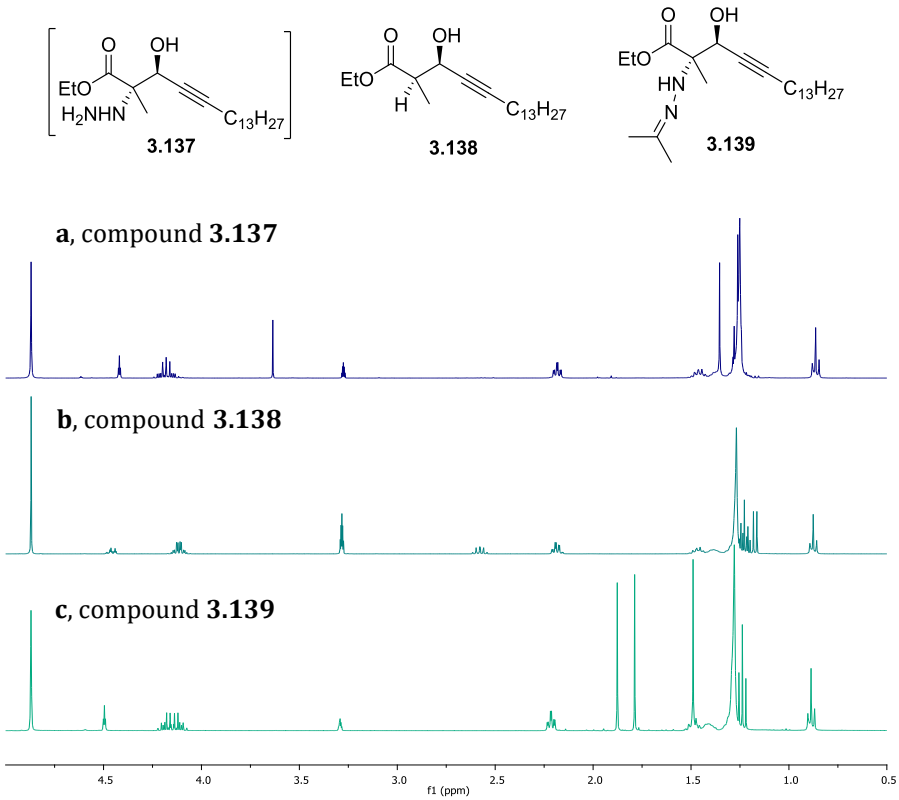
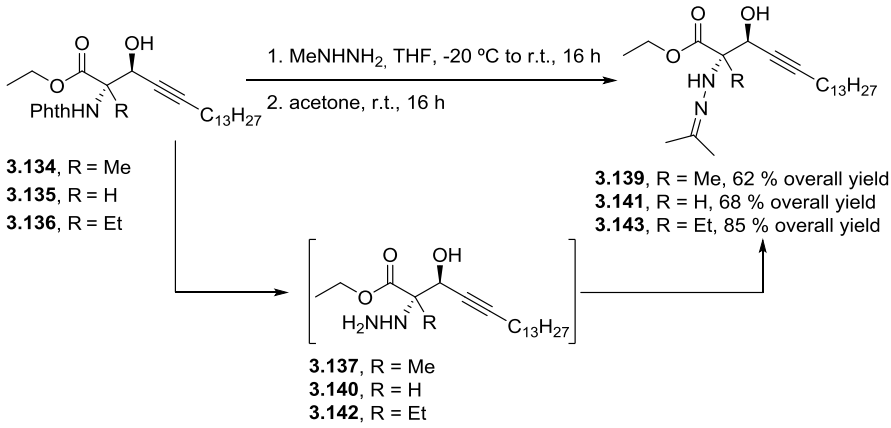


Figure 3.1. ^{1}H NMR spectra of compounds **3.137**, **3.138** and **3.139**.

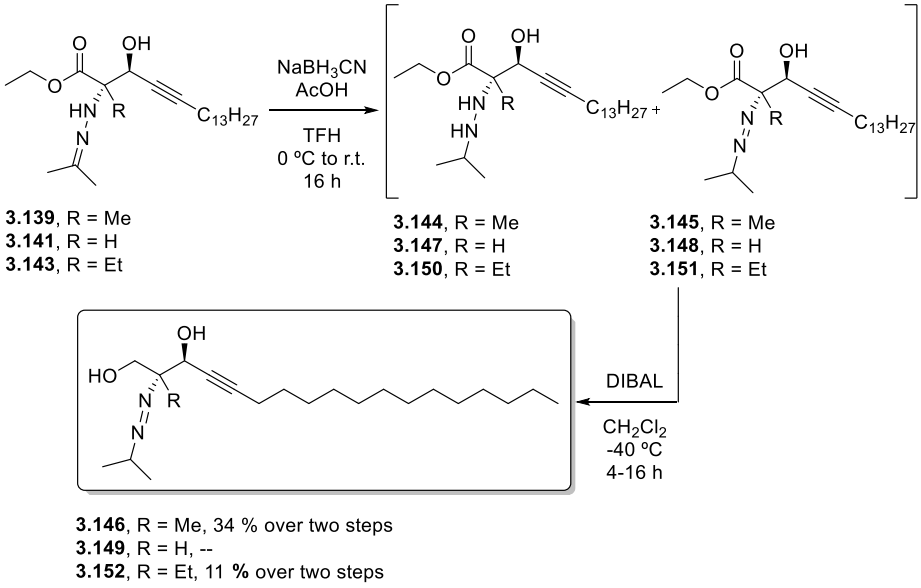
On the other hand, the second compound showed two singlets at 1.80 and 1.90 ppm and each signal integrated 3 protons. Moreover, the ^{13}C NMR exhibited a peak at 149.6 ppm related to a sp^2 carbon and mass spectrometry showed an M^+ 40 units higher than the expected (c, Figure 3.1). Our first hypothesis was that the formation of a hydrazone derived from acetone had taken place. In 2015, Llebaria and co-workers reported a similar result.[42] They explained that any trace of acetone inside the material used favoured the formation of the corresponding hydrazone. Thus, we assume that the hydrazone **3.139** arose from traces of acetone of no totally dry material.

Thus, faced with the impossibility of isolating the free hydrazine we decided to immediately protect it again with acetone to form the hydrazones. In this context, compounds **3.134**, **3.135** and **3.136** were treated with methylhydrazine to give the unprotected hydrazines **3.137**, **3.140** and **3.142**, which were reacted *in situ* with acetone to afford hydrazones **3.139**, **3.141** and **3.143** in 62%, 68% and 85% yield, respectively (Scheme 3.24).



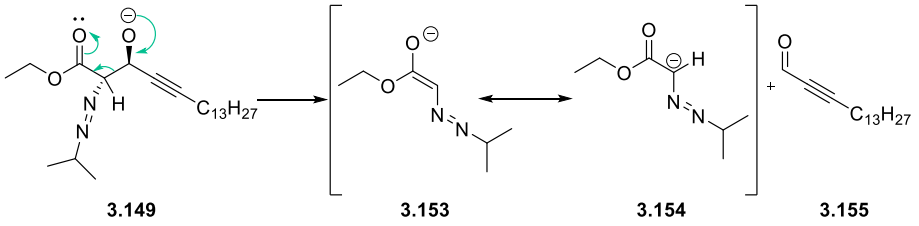
Scheme 3.24. Deprotection of compounds **3.134**, **3.135** and **3.136** with methylhydrazine followed by capture with acetone.

We tried next the reduction in one step of the hydrazine and ester motives in the presence of $LiBH_4$ but the reaction proved unsuccessful. For that reason, we decided to explore each reaction independently. In this sense, when hydrazones **3.139**, **3.141** and **3.143** were reacted with $NaBH_3CN$, a mixture of hydrazino and azo compounds was afforded, which was used in the next step without previous purification. According to Wang and co-workers[43] and as commented above,[41] azo- derivatives can result from oxidation of hydrazine in the presence of air (Scheme 3.25). Finally, the mixtures of hydrazine/azo compounds **3.144**/**3.145**, **3.147**/**3.148** and **3.150**/**3.151** were directly treated with DIBAL in dichloromethane at low temperature to furnish compounds **3.146** and **3.152** in 34% and 11% yield, respectively over the two steps (Scheme 3.25).



Scheme 3.25. Synthesis of azo-sphingosine derivatives bearing a triple bond.

Final compounds **3.146** and **3.152** were obtained as mixtures of *Z*/*E* azo derivatives which isomerized to the *E* isomer when the mixtures were stirred in the presence of air and light.[44] Furthermore, compound **3.149** could not be obtained as it decomposed readily presumably through a retro-aldol reaction. Likely, this reaction was enhanced by acidic proton located at α-position of ester framework rendering an alkynylaldehyde and releasing the hydrazino moiety (see Figure 3.2 in *Section 3.3.2.7. a*) (Scheme 3.26).

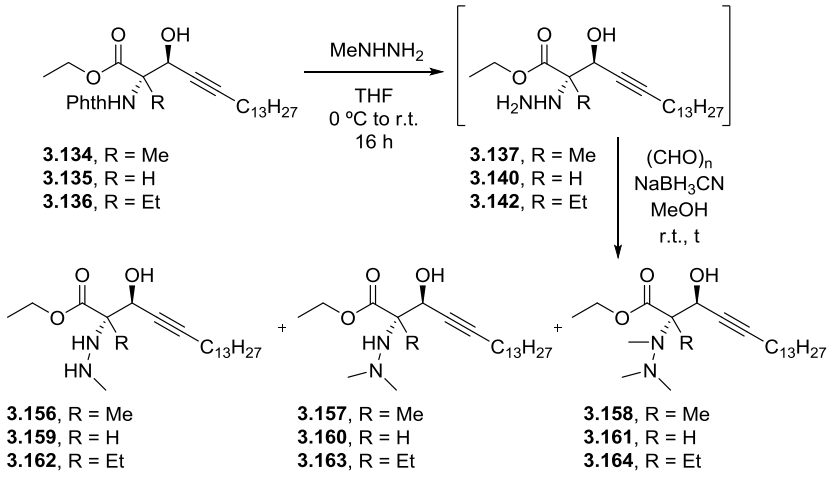


Scheme 3.26. Retro-aldol reaction for compound **3.149**.

3.3.2.5. Synthesis of N,N-dimethylhydrazino sphingosine analogues bearing triple bond in the aliphatic chain.

As explained in *Section 3.2*, one of our goals was to install a *N,N*-dimethylhydrazino motif in a library of sphingosine analogs. For that purpose and following the strategy described above, the protected product **3.134** was submitted to dephthaloylation to achieve the free hydrazine. This intermediate was then methylated in the presence of paraformaldehyde and $NaBH_3CN$ affording polyalkylated products resulting from the mono-, di- or trimethylation of the hydrazine moiety (Table 3.4).

Table 3.4. Syntheses of *N,N*-dimethylated compounds **3.157**, **3.160** and **3.163**.

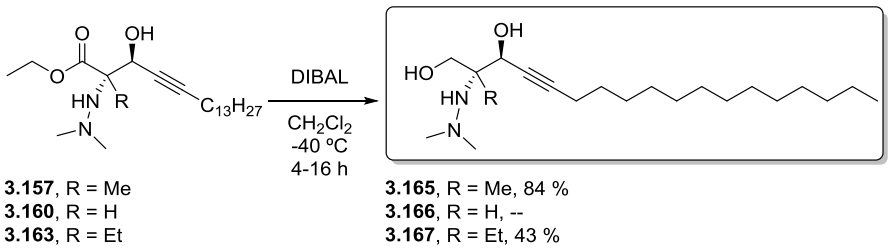


Entry[a]	Subst.	$(CHO)_n$ (equiv.)	$NaBH_3CN$ (equiv.)	time (h)	Mono- (%)[b]	Di- (%)[b]	Tri- (%)[b]
1	**3.134**	10	5	24	10	49	10
2	**3.134**	5	2	24	3	62	5
3	**3.135**	5	2	24	4	20	13
4	**3.136**	5	2	48	N.D.[c]	35	N.D.[c]

[a] *General conditions*: i) Protected hydrazine (0.20 mmol), methylhydrazine (0.3 mmol), THF (2.3 mL); ii) $(CHO)_n$ (x equiv.) , $NaBH_3CN$ (y equiv.), MeOH (5.6 mL). [b] Overall yield. [c] N.D. = Not determined.

The reaction was first explored starting from compound **3.134** and using high amount of paraformaldehyde and cyanoborohydride, yielding the desired compound **3.157** in 49 % as well as other by-products (entry 1). A decrease in the amount of reagents increased the percentage of *N,N*-dimethylated product over the other two secondary ones (entry 2). On the other hand, when compounds **3.135** and **3.136** were screened under the optimized conditions, *N,N*-dimethylated hydrazines **3.160** and **3.163** were afforded in moderate yields (entries 3-4).

With the desired compounds **3.157**, **3.160** and **3.163** in hand, the final reduction of ester moiety provided the *N,N*-dimethylhydrazino sphingosine derivatives **3.165** and **3.167** in moderate to good yield. Compound **3.166** could not be isolated despite its formation had been observed from the crude since it decomposed during column chromatography, presumably by another retro-aldol reaction (Scheme 3.27).



3.157, R = Me
3.160, R = H
3.163, R = Et

3.165, R = Me, 84 %
3.166, R = H, --
3.167, R = Et, 43 %

Scheme 3.27 *N,N*-dimethylhydrazino sphingosine derivatives bearing a triple bond.

3.3.2.6. Over-reduction and selective trans reduction of triple bond.

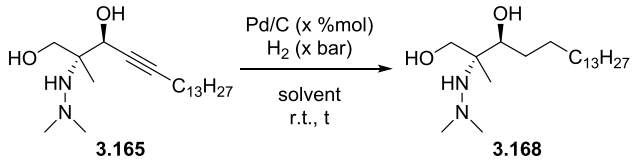
As commented in *section 3.2*, another of our goals was to compare the influence in the inhibitory activity of the sphingosine analogues synthesized with the presence of a 4,5-*trans* double in comparison with a triple bond and the full unsaturated chain. For that purpose, we decided to reduce the triple bond to *trans*-double bond and to a fully saturated alkyl chain.

In this context, compounds **3.157** and **3.165** were submitted to reduction under different conditions to afford the corresponding sphingosine analogues.

a) Over-reduction of triple bond.

The reaction between an alkyne in the presence of palladium on carbon and in hydrogen atmosphere are conditions widely used in the over-reduction of this kind of bonds. In this sense, the first exploratory tests were designed to apply the standard conditions in the compound **3.165** (Table 3.5).

Table 3.5. Over-reduction of compound **3.165**.



3.165 3.168

Entry[a]	Pd/C (wt%)	H_2 (bar)	Solvent	t (h)	Observations[b]
1	40	1	CH_2Cl_2	16	N.R.[c]
2	15	1	MeOH	16	N.R.[c]
3	30	1	MeOH	48	--[d]
4	75	5	MeOH	48	--[d]

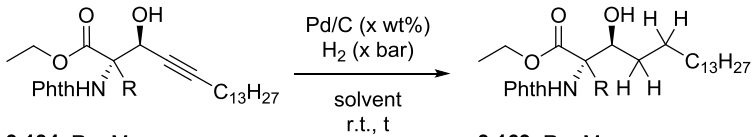
[a] *General conditions*: **3.165** (0.05 mmol), Pd/C (x wt%), H_2 (x bar), solvent (5 mL). [b] Determined by ^{1}H NMR. [c] N.R. = No reaction. [d] Partial hydrogenation.

When the reaction was performed in the presence of **3.165**, 40 mol% of Pd/C, 1 bar of hydrogen pressure and in dichloromethane, no product was formed and unaltered starting material was recovered (entry 1). Unfortunately, the replacement of an aprotic solvent by a protic one (methanol) did not work either and only starting material was recovered after treating the compound **3.165** with Pd/C (15 wt%) (entry 2). The use of high amount of Pd/C (75 wt%) and 1 or 5 bar of hydrogen rendered the partial reduction of the triple bond despite stirring the reaction at room temperature for 48 h (entries 3 and 4).

Thus, in view of these results and having in mind the problems observed in the case of non-quaternized compounds, we decided to investigate the over-reduction in compounds **3.134** and **3.136**.

We then tested the over-reduction of **3.134** in the presence of Pd/C (20 wt%) and hydrogen (5 bar) in methanol in a Fisher-Porter reactor (Table 3.6, entry 1). Gratifying, the reaction proceeded in 57 % yield. Yield improved up to 95% by replacing methanol by AcOEt and increasing the amount of palladium (Table 3.6, entry 2). Unluckily, when these conditions were used in compound **3.136**, no reaction or partial reduction of the triple bond was observed even increasing the reaction time (Table 3.6, entries 3-4). However, when the reaction was carried out under 2 bar of hydrogen pressure and 40 °C for 40 h, the saturated product **3.170** was obtained in 69 % yield (Table 3.6, entry 5). Another attempt to improve this result by increasing the temperature up to 70°C led to the formation of the compound **3.170** as well as other by-products (Table 3.6, entry 6).

Table 3.6. Over-reduction of compounds **3.134** and **3.136**.



3.134, R = Me
3.136, R = Et

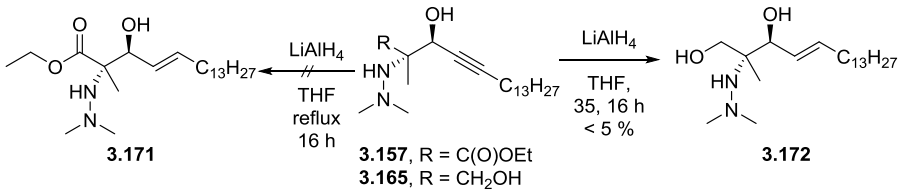
3.169, R = Me
3.170, R = Et

Entry[a]	Subst.	Pd/C (wt%)	H_2 (bar)	Solvent	T (°C)	t (h)	Yield (%)[b]
1	**3.134**	20	5	MeOH	r.t.	16	57
2	**3.134**	30	5	AcOEt	r.t.	16	95
3	**3.136**	30	5	AcOEt	r.t.	48	N.R.[c]
4	**3.136**	30	4	AcOEt	r.t.	96	--[d]
5	**3.136**	40	2	AcOEt	40	16	69
6	**3.136**	40	2	AcOEt	70	22	44[e]

[a] *General conditions :* ester (0.1 mmol), Pd/C (x wt%), H_2 (x bar), solvent (9.5 mL). [b] Isolated yield. [c] N.R = No reaction. [d] Partial hydrogenation. [e] Formation of other two by-products.

b) Selective and partial hydrogenation of triple bond.

A well-known method to selectively reduce triple bonds bearing propargyl alcohols to double C-C bonds is with $LiAlH_4$. However, allenes are also usually obtained depending on the conditions used. Indeed, a complex mixture was obtained when the reduction reaction was explored by mixing **3.155** and $LiAlH_4$ in refluxing THF. This result is consistent with the fact that ester moiety is also susceptible to be reduced, as well as other by-products such as allenes might also have been formed. On the other hand, the decrease of the temperature did not work either and only traces of the product **3.172** were achieved when the reaction was performed at 35°C (Scheme 3.28).



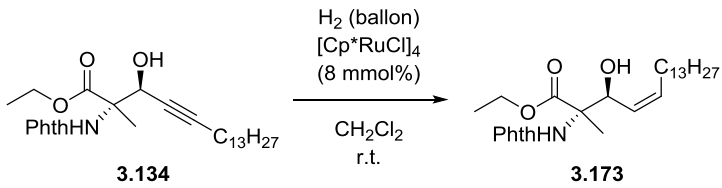
Scheme 3.28. Direct reduction of compounds **3.157** and **3.165** with $LiAlH_4$.

Due to these inconveniences and considering the problems which were found to over-reduce the triple bond (see section *3.3.2.6 a*), we decided to reduce earlier intermediates **3.134** and **3.136**.

In 2013, Fürstner and co-workers developed a novel *trans* hydrogenation of alkynes in the presence of ruthenium catalyst.[45] This methodology was described to be highly *trans* selective as well as to have a great functional group tolerance. Later, the same group extended the use of this kind of catalyst in the selective *trans* reduction of alkynes *via* hydroboration,[46] hydrostannation,[47] hydrogermylation[47b] and hydrosilylation.[47b]

In this context, and during a predoctoral stay at Institut Max-Planck für Kohlenforschung, compounds **3.134** and **3.136** were reacted with Chloro(pentamethylcyclopentadienyl)ruthenium(II) tetramer ($[Cp^*RuCl]_4$) to afford their partial hydrogenations.[48]

When we explored the direct hydrogenation of compound **3.134** at 1 atm of hydrogen pressure, ruthenium catalyst and in dichloromethane, *cis* alkene product **3.173** in a very low conversion was obtained (Scheme 3.29).

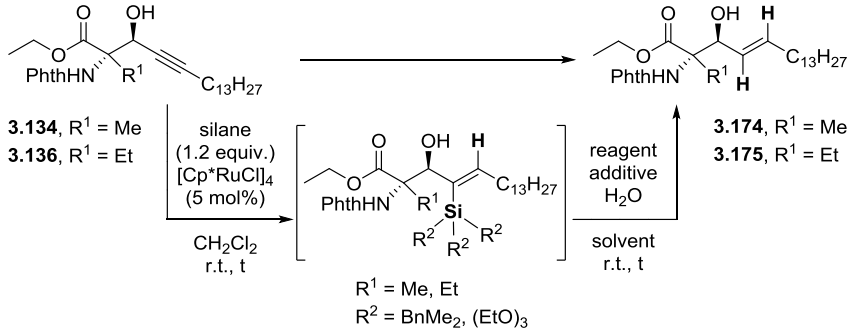


Scheme 3.29. Direct hydrogenation of compound **3.136** in the presence of $[Cp^*RuCl]_4$.

On the other hand, the treatment of **3.134** with silanes $BnMe_2SiH$ and $(EtO)_3SiH$ in the presence of $[Cp^*RuCl]_4$ and dichloromethane provided different results (Table 3.7, entries 1-2). While the reaction with $BnMe_2SiH$ rendered only 50 % of conversion after one hour of reaction, complete conversion was obtained after 15 min when $(EtO)_3SiH$ was used instead.

We then screened the conditions for the protodesilylation of the resulting alkenylsilane intermediate. When the reaction took place in the presence of TBAF, decomposition of the product was observed by ^1H NMR (Table 3.7, entry 3). Similarly, the addition of CuI also led to decomposition of the product (Table 3.7, entry 4). In contrast, the replacement of TBAF by AgF afforded **3.174** in 45 % overall yield when the reaction was performed in darkness, in the presence of AgF, small amount of water and in dioxane (Table 3.7, entry 5). Gratifyingly, the change of solvent from dioxane to THF and the addition of MeOH in the protodesilylation step increased the overall yield up to 53 % (Table 3.7, entry 6). Likewise, the use of these conditions in compound **3.136** yielded the product **3.175** in 63% (Table 3.7, entry 7).

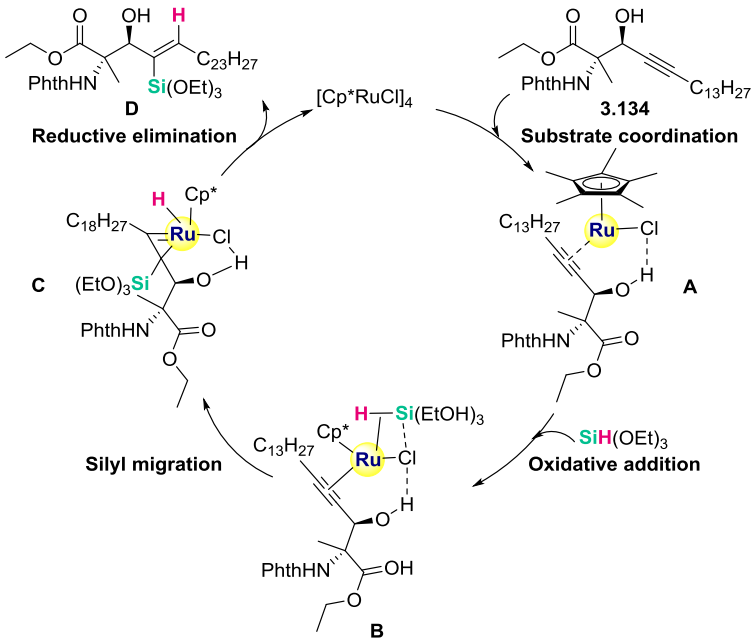
Table 3.7. Formation of *trans* double bond by hydrosilylation/ protodesilylation reactions.



Entry[a]	Subst.	Silane	Reagent (equiv.)	Solvent	time (h)	Product	Yield (%)[b]
1	**3.134**	$BnMe_2SiH$	--	--	1	**--**	--[c]
2	**3.134**	$(EtO)_3SiH$	--	--	0.25	**--**	--[d]
3[b]	**3.134**	$(EtO)_3SiH$	TBAF (2.0)	THF	0.25+20	**3.174**	--[e]
4[b,f]	**3.134**	$(EtO)_3SiH$	TBAF (2.0)	THF	0.25+20	**3.174**	-[e]
5[c]	**3.134**	$(EtO)_3SiH$	AgF (0.015)	Dioxane	0.25+3	**3.174**	45
6[c,g]	**3.134**	$(EtO)_3SiH$	AgF (0.015)	THF	0.25+1.5	**3.174**	53
7[c,g]	**3.136**	$(EtO)_3SiH$	AgF (0.015)	THF	0.15+1.5	**3.175**	63

[a] *General conditions for hydrosilylation*: **3.134** (0.02 mmol), silane (1.2 equiv.), $[Cp^*RuCl]_4$ (5 mol%), CH_2Cl_2 (0.1 mL). [b] *Conditions for hydrosilylation followed by protodesilylation in the presence of TBAF*: **3.134** (0.04 mmol), $(EtO)_3SiH$ (1.2 equiv.), $[Cp^*RuCl]_4$ (5 mol%), TBAF (2 equiv.), CH_2Cl_2 (0.2 mL), THF (0.2 mL); [c] *General conditions for hydrosilylation followed by protodesilylation in the presence of AgF*: alcohol (0.04 mmol), $(EtO)_3SiH$ (1.2 equiv.), $[Cp^*RuCl]_4$ (5 mol%), AgF (0.015 mmol), H_2O (27 μL), CH_2Cl_2 (0.27 mL), dioxane or THF (0.27 mL). [b] Isolated yield. [c] Hydrosilylation complete at 50 % after 1 h of reaction. [d] Complete conversion for hydrosilylation reaction after 15 min. [e] Decomposition. [f] The protodesilylation was performed in the presence of CuI (2 equiv.) as a additive. [g] The protodesilylation reaction was performed in the presence of MeOH (0.1 mL).

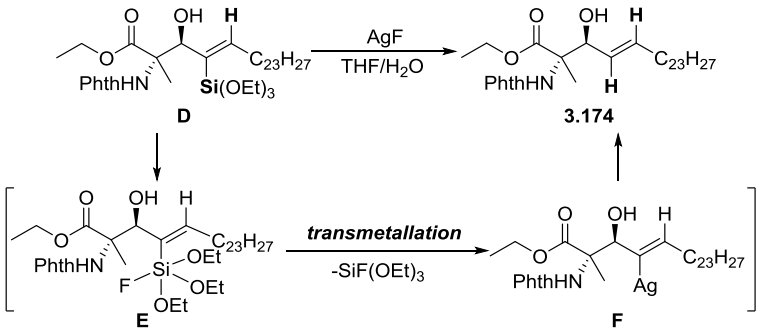
According to recent studies carried out by Fürstner group[49] in combination with other computational data reported by Wu,[50] after coordination of substrate, the triple bond would act as a four-electron donor. Furthermore, an interligand hydrogen bond would be formed between the polarized [Ru-Cl] bond and a proton of the propargylic alcohol providing **A**. This chloride would also interact with silicon upon the silane entering to the coordination sphere leading to **B** and directing the migration of the silyl via inner-sphere towards the acetylene carbon with a hydroxyl at the vicinity position. As a consequence, a ruthenacyclopropene complex **C** would be afforded. Finally, this complex would evolve through a reductive elimination to give *trans* intermediate **D** (Scheme 3.30).



Scheme 3.30. Plausible mechanism for silylation of **3.134** with $[Cp^*RuCl]_4$.

Additionally, protodesilylation might work through a synergic mode of action of fluoride anion and silver cation.[51] The fluoride affinity for silicon would lead to a pentacoordinate silicate specie[52] which would favour the transmetallation with silver providing a vinyl silver

intermediate. Then, this species would be immediately trapped to render the final alkene **3.174** (Scheme 3.31).

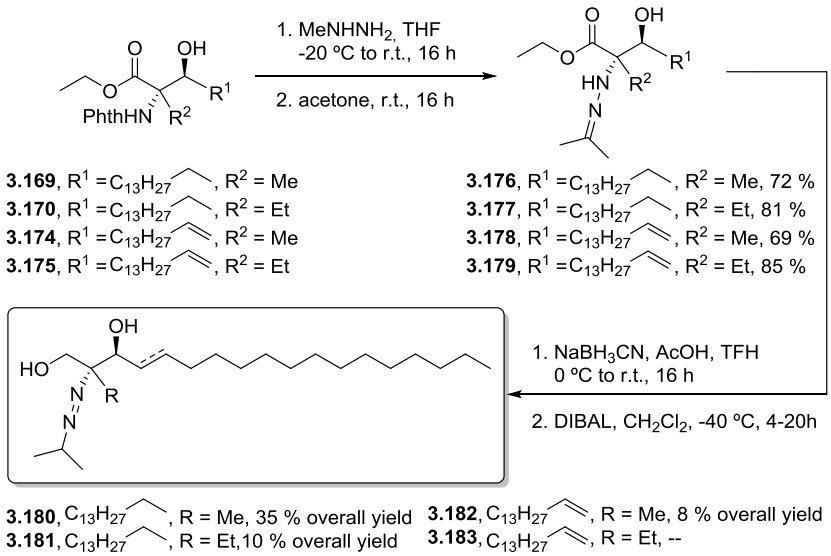


Scheme 3.31. Plausible mechanism for protodesilylation of **D** with AgF.

3.3.2.7. Synthesis of azo- and N,N-dimethylhydrazino sphingosine analogues containing single and double bond in the aliphatic chain.

a) Azo-sphingosine derivatives.

According to the procedure described in *section 3.3.2.4*, compounds **3.169**, **3.170**, **3.174** and **3.175** were first deprotected and then treated with acetone to afford the corresponding hydrazone derivatives **3.176-3.179**. Subsequently, these hydrazones were reduced in the presence of $NaBH_3CN$ and acetic acid and then with DIBAL in dichloromethane to reduce the ester moiety. Both reductions rendered the final sphingosine analogues **3.180-3.183** in moderate yields (Scheme 3.32).



3.169, R^1 = $C_{13}H_{27}$, R^2 = Me
3.170, R^1 = $C_{13}H_{27}$, R^2 = Et
3.174, R^1 = $C_{13}H_{27}$, R^2 = Me
3.175, R^1 = $C_{13}H_{27}$, R^2 = Et

3.176, R^1 = $C_{13}H_{27}$, R^2 = Me, 72 %
3.177, R^1 = $C_{13}H_{27}$, R^2 = Et, 81 %
3.178, R^1 = $C_{13}H_{27}$, R^2 = Me, 69 %
3.179, R^1 = $C_{13}H_{27}$, R^2 = Et, 85 %

3.180, $C_{13}H_{27}$, R = Me, 35 % overall yield
3.181, $C_{13}H_{27}$, R = Et,10 % overall yield
3.182, $C_{13}H_{27}$, R = Me, 8 % overall yield
3.183, $C_{13}H_{27}$, R = Et, --

Scheme 3.32. Last steps in the synthesis of azo-sphingosine derivatives.

As it happened to compounds **3.149** and **3.166**, compound **3.183** suffered a retro-aldol reaction in solution once the product was isolated. Figure 3.2 shows the product after purification and the evolution of the decomposition reaction with the time. It can be observed that the characteristic peak of the aldehyde at 9.5 ppm started to appear after the isolation of the product and its intensity increased after some hours in solution. At the same time, new peaks emerged at the double bond region while the signal of olefinic protons corresponding with **3.183** decreased. The rest of the region of the spectrum also changed resulting in the final aldehyde, whose structure was confirmed by comparison with bibliographic data.[53] The other fragment could not be determined due to the complexity of the aliphatic region although further rearrangement of the fragment cannot be discarded.

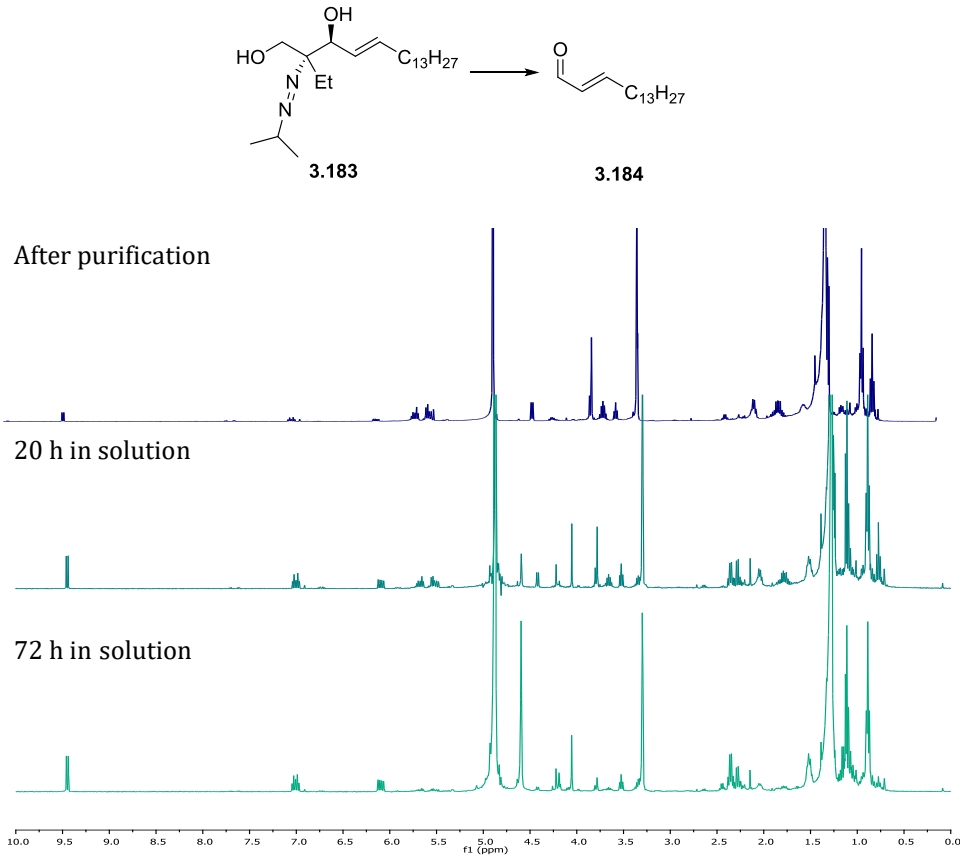
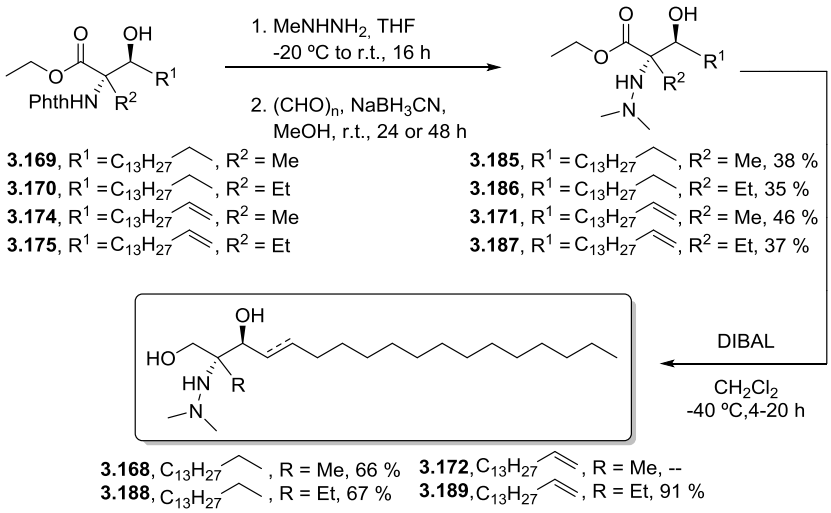


Figure 3.2. ^{1}H NMR spectra showing the evolution of fragmentation of compound **3.183** *via* retro-aldol reaction.

b) N,N-dimethylhydrazino sphingosine analogues.

Dephthaloylation and further *N,N*-dimethylation of compounds **3.169**, **3.170**, **3.174** and **3.175** took place by reaction, first, in the presence of methylhydrazine and then, with paraformaldehyde and $NaBH_3CN$. Finally, ester moiety was reduced with DIBAL providing the sphingosine derivatives **3.1658**, **3.172**, **3.188** and **3.189** in moderate to excellent yield (Scheme 3.33).



Scheme 3.33. Last steps in the syntheses of *N,N*-dimethylsphingosine derivatives.

It should be mentioned that the compound **3.172** was not obtained because the reduction failed. The amount of recovered starting material was not enough to perform the reduction again and its further biological assay.

3.3.3. Computational prediction of the interactions between our designed compounds and SphK1.

Advancements in structural determination techniques such as X-ray crystallography have contributed to increase the number of three-dimensional structures of proteins. Many of these proteins have demonstrated to have therapeutic potential;[54] hence, understanding how small ligands bind to them is crucial for pharmaceutical applications.

Computational methodologies have emerged as a key tool in the development of new drugs. In fact, this can be done by, for example, virtual high-throughput screening (VHTS).[55] This technique uses software programs in the prediction of plausible ligand-protein complexes by doing *protein-ligand docking*. In turn, a docking program is characterized by predicting the coordinates of a complex formed by the

ligand with the protein assuming that the protein is rigid, what reduces the number degrees of freedom. To do so, first it uses an algorithm which determines the best initial location for the conformations of each ligand. Then, the conformation with the lowest energy, known as the best pose, is estimated by a minimization of the ligand in the protein. Afterwards, this predicted pose and the rest of them are ranked depending on the interaction energy with the protein estimated by an optimized scoring function. This function is based on hydrogen bonds, hydrophobic interactions, formation of salt bridges and restriction of dihedral angle freedom in the ligand by the protein.[56]

Because of docking programs are able to predict interactions between ligands and proteins in static way, we decided to perform docking studies to establish which kind of interactions might take place between the compounds prepared in this chapter and SphK1.

3.3.3.1. Self-docking and cross-docking.

The ability of a docking program to reproduce the ligand pose found in a known protein-ligand complex is commonly checked by obtaining the root mean square deviation (RMSD) between the position of the ligand, taken as reference and obtained from the co-crystallized protein, and the best pose of the ligand predicted by the docking program. Docking a ligand into the protein structure from which they were extracted is known as self-docking. Using the protein structure co-crystallized with a different ligand is known as cross-docking. An outcome RMSD value below 2 Å guarantees that the protein structure and the docking program can be used to predict the binding of new compounds.[57]

The cross-docking analysis is also used to determine which protein structure is the most suitable to perform the rest of the study. In this way, the best prediction will be done using the protein structure which provides the lowest RMSD during the cross-docking.[58]

Having this on mind and considering all available protein structures of SphK1 at the PDB (3VZB, 3VZC, 3VZD, 4L02 and 4V24) and their corresponding ligands (SQS, UUL, UUL', 1V2 and GYR respectively), self-docking and cross-docking studies were performed (Figure 3.3). These analyses were carried out following the standard protocols which consist in protein preparation, grid generation, ligand preparation and ligand docking (for more information, see experimental part).

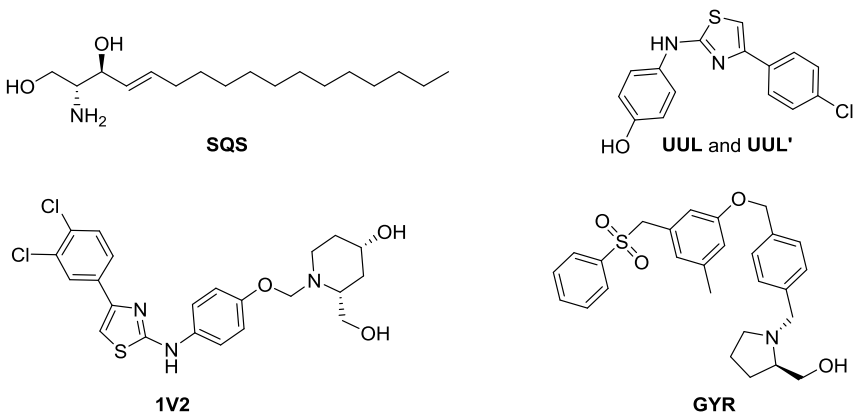


Figure 3.3. Structures of co-crystallized ligands with SphK1.

Once dockings were completed for each SphK1 structure and each ligand, a RMSD value was calculated (Table 3.8). Specifically, these both ligands were superimposed in the case of the self-ligand. By contrast, RMDS related to cross-docking were computed by comparing the ligand crystallized of the studied protein with the crystallized ligand of another protein. For instance, GYR ligand (4V24 protein) with UUL one (3VZC protein).

Table 3.8. RMSD values (in Å) between the best-scoring docked ligand pose and the crystal ligand pose for several inhibitors of SphK1 obtained from the Protein Data Bank (PDB). Self-docking and cross-docking results are shown in blue and black, respectively.

		SphK1 Crystal Structure				
		3VZB	**3VZC**	**3VZD**	**4L02**	**4V24**
Ligand	**SQS**	**1.13**	0.23	0.15	0.43	0.77
	UUL	1.16	**0.10**	0.12	0.52	1.52
	UUL'	1.11	0.11	**0.06**	0.19	1.25
	1V2	1.18	0.25	0.09	**0.19**	0.45
	GYR	1.23	0.14	0.19	0.41	**0.55**

From data obtained in Table 3.8, we concluded that all SphK1 protein structures analyzed could be used for docking (since in all cases the RMSD values are below 2 Å). In addition, it was found that the 3VZD protein structure showed the best results for cross-docking. Hence, this structure was chosen to predict the best pose and the interactions of new SphK1 inhibitors by docking.

3.3.3.2. *Docking and binding prediction for the compounds designed.*

The virtual interaction predictions between an enzyme and any ligand are usually obtained by docking. Thus, following the procedure described above, the docking was carried out selecting our compounds and the protein structure from 3VZD, since it provided the best results of RMSD. Furthermore, the known SphK1 inhibitor, *N*,*N*-dimethylsphingosine (DMS) was used as a reference to compare with our compounds.

In this sense, DMS presented a hydrogen bond and a salt bridge interaction with aspartic acid 178 (Asp 178) and a hydrogen bond with leucine 268 (Leu 268) (Figure 3.4).

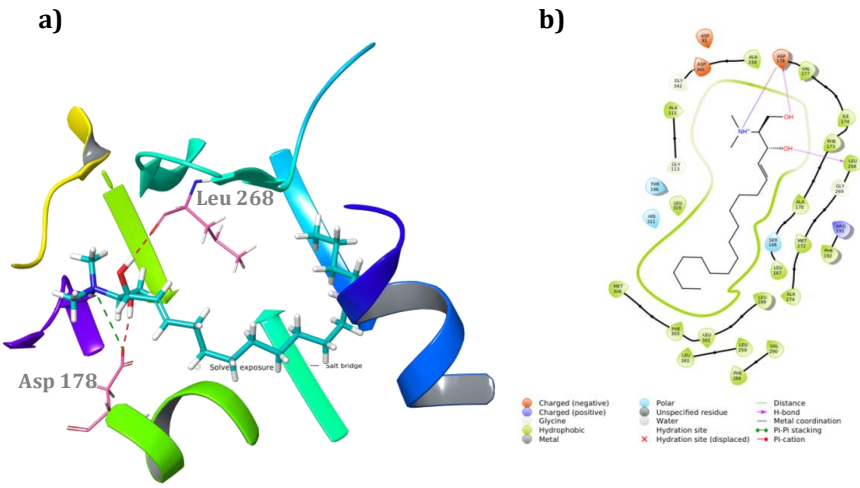


Figure 3.4. **a)** Hydrogen bonds and salt bridge predicted for **DMS** and the binding pocket of SphK1. Hydrogen bonds and salt bridges are shown as red and green dashed lines, respectively. DMS ligand is represented in blue and amino acid residues Leu 268 and Asp 178 in pink. **b)** Ligand interaction diagram of DMS with 3VZD.

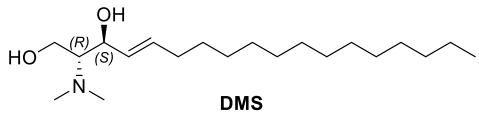
Considering that our compounds have similar structure regarding to DMS, it is logical to think that these interactions should be also predicted to our compounds. However, the introduction of hydrazine moiety in the skeleton of sphingosine means that new hydrogen bonds might appear between the added nitrogen and some amino acid residue. In similar way, it could not be discarded the formation of some π-π stacking bonds between the azo- moiety or unsaturated bonds with some phenylalanine residue from the binding site.

On the other hand, we were also interested in contrasting the affinity of each ligand on the binding site through GlideScore value. This score is used to rank the different poses predicted by docking, showing the lowest value for the best pose. This is an empirical scoring function which approximates the ligand binding free energy and includes force field contributions (electrostatic, van der Waals) and terms rewarding or penalizing interactions known to influence ligand binding.

As aforementioned, DMS is predicted to have interaction with Leu 268 and Asp 178 and besides presents a GlideScore of -7.920 Kcal/mol. We thought that the introduction of new nitrogen to the molecule might increase the number of interactions with the binding site. Furthermore, we also envisioned that the new nitrogen might contribute with diminishing the GlideScore value since better it is, more negative value is obtained. This can be explained by considering that GlideScore provides a binding free energy and that tighter binders are related to more negative values.

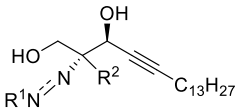
Comparable results to DMS were obtained in all cases screened since only hydrogen bonds were predicted for the interaction of the hydroxyl groups or amino moieties with three principal residues including Leu 268, Asp 81 and Asp 178. GlideScore values neither were as good as expected. In fact, the target compounds of this work were predicted to exhibit practically the same GlideScore value and with the same order of magnitude than DMS (Table 3.9). Importantly, only ligands with the same configuration than DMS and Sph (*R,S*) are described in the table. The data for another enantiomer (*S,R*) have been omitted.

Table 3.9. Glide score for the compounds designed.

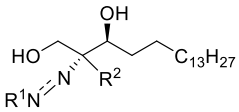


DMS

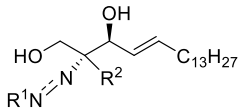
GlideScore = -7.920 Kcal/mol



3.146, R^1 = ^{i}Pr; R^2 = Me
3.152, R^1 = ^{i}Pr; R^2 = Et
3.165, R^1 = $(CH_3)_2$; R^2 = Me
3.167, R^1 = $(CH_3)_2$; R^2 = Et



3.180, R^1 = ^{i}Pr; R^2 = Me
3.181, R^1 = ^{i}Pr; R^2 = Et
3.168, R^1 = $(CH_3)_2$; R^2 = Me
3.188, R^1 = $(CH_3)_2$; R^2 = Et



3.182, R^1 = ^{i}Pr; R^2 = Me
3.183, R^1 = ^{i}Pr; R^2 = Et
3.172, R^1 = $(CH_3)_2$; R^2 = Me
3.189, R^1 = $(CH_3)_2$; R^2 = Et

Ligand (*R,S*)[a]	Glide Score (Kcal/mol)	H-Bond[b]	Ligand (*R,S*)[a]	Glide Score (Kcal/mol)	H-Bond[b]
3.146	-7.366	Leu 268 Asp 81	**3.168**	-6.992	Leu 268
3.152	--[c]	--	**3.188**	-7.170	Leu 268 Asp81
3.165	-7.160	Leu 268 Asp 81	**3.182**	-5.422	Leu 268
3.167	-7.403	Leu 268 Asp 178	**3.183**	-6.986	Asp 81
3.180	--[c]	--	**3.172**	-7.267	Leu 268 Asp 178
3.181	-7.541	Asp 81	**3.189**	-6.275	Asp 81

[a] Ligand with configuration (*R,S*). [b] Hydrogen bonds predicted between the ligand and the protein. [c] Enantiomer not predicted.

Figure 3.5 shows these interactions for compound **(*R,S*)-3.189** and **(*S,R*)-3.189**, containing an ethyl group in the quaternary position and including a double bond and *N,N*-dimethyl moiety in the polar head. Interaction with Asp 81 was predicted to **(*R,S*)-3.189**, whereas Leu 268 and Asp 178 showed virtual interaction with **(*S,R*)-3.189**.

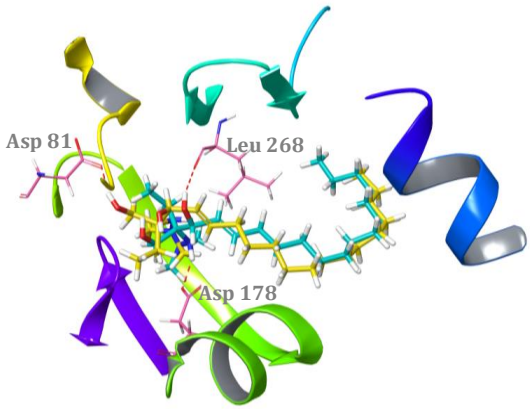


Figure 3.5. Overlay of compounds **(*R,S*)-3.189** and **(*S,R*)-3.189**. Compound **(*R,S*)-3.189** in yellow, compound **(*S,R*)-3.189** in blue and residues Asp 178, Asp 81 and Leu 268 in pink. Hydrogen bonds are represented as red dashed lines.

The overlay of *N,N*-dimethyl derivatives **(*R,S*)-3.165**, **(*R,S*)-3.168** and **(*R,S*)-3.172** bearing triple, single and double bonds respectively exhibited different poses and interactions with amino acids residues. In spite of that, all of them virtually interacted with Leu 268. Besides, compound **(*R,S*)-3.165** was also predicted to perform hydrogen bond with Asp 81 and the compound **(*R,S*)-3.172** with Asp 178 (Figure 3.6a). On the other hand, the superposition of compounds **(*R,S*)-3.146** and **(*R,S*)-3.165** bearing a triple bond an azo- and *N,N*-dimethyl moieties respectively displayed interaction with Leu 268 and Asp 81 in both cases. That means that despite having different groups, the best pose predicted does not show significant differences between both compounds (Figure 3.6b).

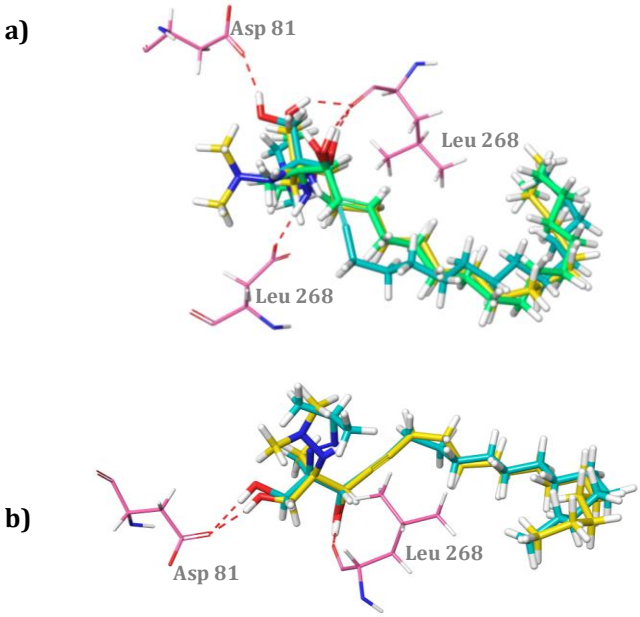


Figure 3.6. a) Overlay of compounds **(*R,S*)-3.165**, **(*R,S*)-3.168** and **(*R,S*)-3.172**. Compound **(*R,S*)-3.165** in blue, **(*R,S*)-3.168** in green, **(*R,S*)-3.172** in yellow and amino acid residues Asp 81, Asp 178 and Leu 268 in pink. Hydrogen bonds are represented as red dashed lines. b) Superposition of compounds **(*R,S*)-3.146** and **(*R,S*)-3.165**. Compound **(*R,S*)-3.146** in blue, **(*R,S*)-3.165** in yellow and amino acid residues Asp 81 and Leu 268 in pink. Hydrogen bonds are represented as red dashed lines.

3.3.4. Biological evaluation: *In vitro* sphingosine kinase inhibitory activity determination mediated by fluorescent-based immunoassay.

Several methods have been developed to measure the inhibitory effect of drugs in a direct way. In fact, radiolabelling, characterized by utilizing ATP and/or sphingosine as substrates in this kind of assay, is commonly used to this purpose.[59] Despite there being different protocols based on this method, they are not able to monitor the reaction in real time and require radioactive materials.[60] In similar way, bioluminescence assay cannot do it either although it examines the SphK activity through indirect manner, measuring the ADP formed.[61]

Another useful kind of assay consists in the specific binding between a conjugated antibody with a long-life time lanthanide and a phosphorylated product of the sphingosine kinase reaction. This method is known as time resolved fluorescence energy transfer (TR-FRET) and it is resistant to matrix components which generate interfering signals.[62] In spite of that, these interferences do not affect to the measurement since they have lifetimes several orders of magnitudes shorter than the lanthanide-specific signal.[63] Additionally, this kind of assay is extremely sensitive to ADP formation and the changes on the signals take place in the first 10-20 % conversion of ATP to ADP favouring its use for low-activity kinases. Furthermore, it is suitable for a wide range of ATP concentrations (1-500 μM).

To achieve the desired signal this kit works in two-step manner. Firstly, the selected kinase (SphK1 or SphK2), ATP, sphingosine and the inhibitor are incubated for 60 minutes to form ADP and sphingosine-1-phosphate (S1P). Then, a detection solution of Europium labelled antibody together with a fluorescent tracer and EDTA (to quench the reaction) are added to the mixture. ADP generated in the first reaction will displace the tracer from the antibody producing a TR-FRET signal. If the inhibitor is high in potency, big amounts of ADP will remove the tracer from the antibody resulting in a low TR-FRET signal. Otherwise, if the inhibitor is moderate in potency low amount of tracer will be dislodged. As consequence, high response by fluorescence will be obtained.

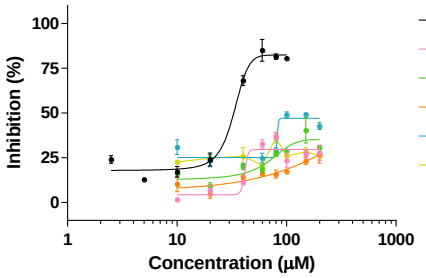
3.3.4.1. Biological tests.

Direct assays to measure the inhibition potency of our compounds designed were carried out in collaboration with Dr. Raúl Beltrán from the Department of Biochemistry and Biotechnology of the Universidad Rovira i Virgili. In this sense, both kinases were examined following the procedure previously described and expressing the inhibitory activity in IC_{50} values.

For this kind of assays, *N,N*-dimethylsphingosine (DMS) is usually used as a reference inhibitor, performing the biological tests in DMS working range (10-100 μM).[64] Thus, first we investigated our compounds based on this range of concentrations (Figure 3.7).

Sphingosine Kinase 1

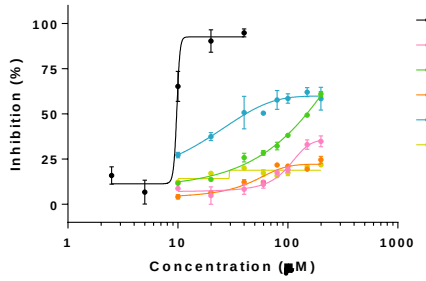
a)



b)

Compound	IC_{50} (μM)
DMS	29.0
3.180	N/A
3.168	72.1
3.188	N/A
3.167	N/A
3.181	N/A

Sphingosine Kinase 2



Compound	IC_{50} (μM)
DMS	9.2
3.180	106.0
3.168	>100
3.188	N/A
3.167	32.5
3.181	N/A

Figure 3.7. Preliminary TR-FRET assays for compounds **DMS**, **3.180**, **3.168**, **3.188**, **3.167** and **3.181** against SphK1 and SphK2. a) Inhibitory curves of sphingosine analogues **DMS**, **3.180**, **3.168**, **3.188**, **3.167** and **3.181**. b) Half maximal inhibitory concentration (IC_{50}) values for each sphingosine derivative.

Apparently, the lack of insaturations in the molecule is closely linked to the inhibitory potency. No inhibition or IC_{50} values higher than 100 μM were observed in the compounds **3.168**, **3.180**, **3.181** and **3.188** for both isoforms although different polar heads were tested. In this preliminary assays, we also found that *N,N*-dimethylhydrazino compound **3.167** bearing an ethyl and alkyne was selective for SphK2 displaying 32.5 μM as IC_{50} value. On the contrary, no inhibitory activity was detected against SphK1.

Remarkably, the rest of the compounds exhibited encouraging results. Therefore, we decided to repeat the assays decreasing the concentration of the inhibitors in order to obtain the IC_{50} values. In the same way, the inhibition of DMS for both kinases was also assayed again and the IC_{50} values are shown in Figure 3.8 and Figure 3.9.

N,N-dimethylhydrazino analogues **3.165** and **3.188** showed interesting data (Figure 3.8). Whereas compound **3.188** was effective for both kinases, compound **3.165** only showed inhibitory potency against SphK2, being selective for this isoform.

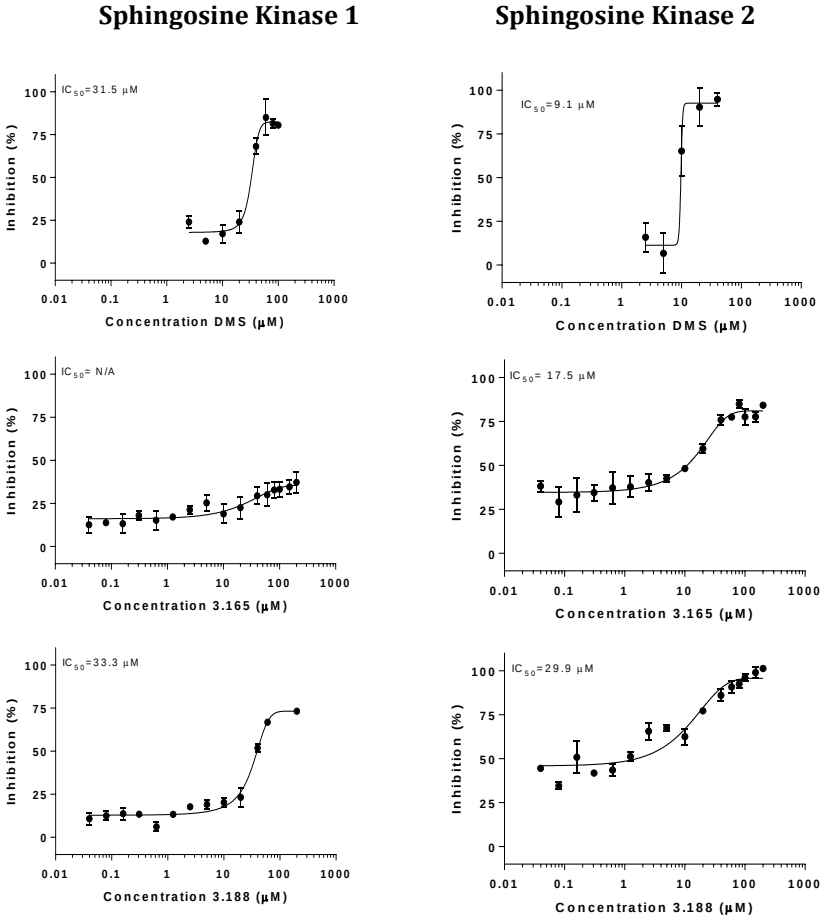


Figure 3.8. Inhibitory potency of compounds **DMS** and **3.165** and **3.188** against SphK1 and SphK2.

On the other hand, azo- derivatives **3.146**, **3.152** and **3.182** were not selective for any kinase and showed moderate inhibitory potency for both isoforms (Figure 3.9).

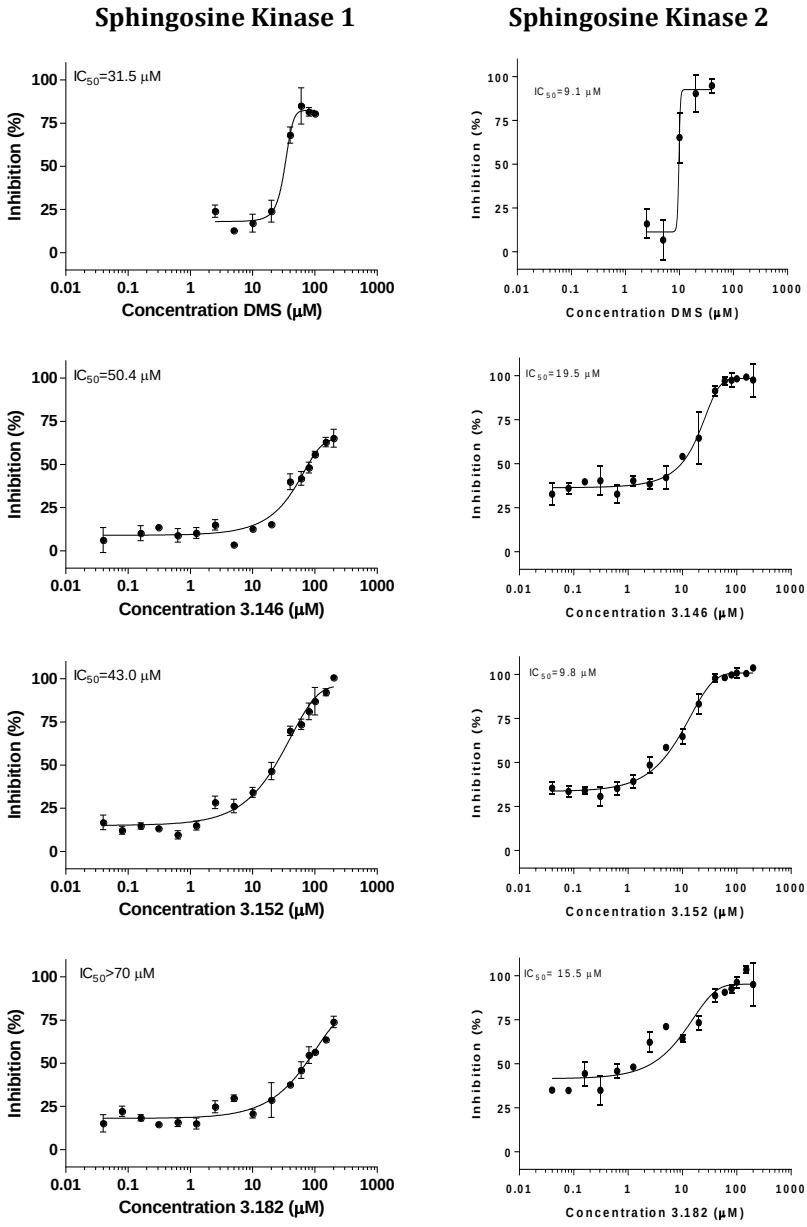


Figure 3.8. Inhibitory potency of compounds **DMS**, **3.146**, **3.152** and **3.182** against SphK1 and SphK2.

In general terms, compounds with completely saturated chain showed no inhibition or inhibition in high concentrations whereas those bearing unsaturated tail displayed different results depending on the polar head. Thus, azo-sphingosine derivatives led to compounds with dual inhibition while those containing *N,N*-dimethylhydrazino groups resulted to be selective for SphK2 except for the case of **3.188**, which showed inhibition for both enzymes. The selectivity for SphK2 could be explained taking into account the homology modelling studies between SphK1 and SphK2. These studies have suggested that the J-channel forming the substrate binding site of SphK2 presents regions of postulated compression at the stem and at the heel of the channel and expansion at the toe of the cavity relative to those in SphK1. In this sense, compounds **3.165** and **3.167** bearing an alkyne framework in the lipophilic tail might drive to a more extended structure that could fit better in the longer and narrower J-channel of SphK2 compared to that of SphK1.[65] Furthermore, the presence of a basic *N,N*-dimethylhydrazino group (probably as its *N,N*-dimethylhydrazinium cation) could also contribute to increase the highly organized polar interaction network surrounding the polar head.

3.4. CONCLUSIONS.

The syntheses of novel sphingosine derivatives have been carried out. The conclusions extracted from the preparation of these compounds are:

i) Sphingoid skeleton can be synthesized from the 1-pentadecyne by formylation followed by Horner-Wadsworth-Emmons olefinantion.

ii) The installation of a quaternary position can be done during the olefinitation and by selecting the appropriate stabilised phosphonate.

iii) Hydrazino- and azo- groups as poly-nitrogenated moieties were introduced as a novel modifications in the polar head in an efficient manner.

iv) Changes in the lipophilic tail were also performed by installing triple, double or saturated bonds at the region of the double bond of the sphingosine.

v) Interactions with Leu 268, Asp 81 and Asp 178 were predicted in most of cases when docking studies were performed between our designed compounds and SphK1.

vi) *In vitro* assays revealed that hydrazine derivatives are selective for SphK2, azo- analogues show dual inhibitory potency against SphK and the lack of insaturations is close related to no inhibition.

3.5. EXPERIMENTAL SECTION

3.5.1. General methods.

All reagents were purchased from Sigma Aldrich or Alfa Aesar chemical companies. Dichloromethane (CH_2Cl_2) was distilled from CaH_2, THF was distilled from sodium and Et_3N was stored with activated 4Å M.S. 4Å M.S. were activated by heating under high vacuum at 260 °C for 10 h and then were stored at 165 °C. Dioxane, CH_3CN and ethyl acetate were used without any distillation. ^1H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 or on a Bruker® Avance Ultrashield (400 MHz and 100.6 MHz respectively) spectrometer. NMR signals were fully assigned by COSY, HSQC, NOESY and HMBC experiments. All chemical shifts are quoted on the δ scale in ppm using the residual solvent as internal standard (^1H NMR: $CDCl_3$ = 7.26; ^{13}C NMR: $CDCl_3$ = 77.16; ^1H NMR: MeOD = 3.31; ^{13}C NMR: MeOD = 49.00). Coupling constants (J) are reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Infrared (IR) spectra were recorded on

a JASCO FTIR-600 plus Fourier Transform Infrared Spectrophotometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Melting points (m.p.) were recorded with Reichert apparatus. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck® aluminium backed sheets coated with 60 F_{254} silica gel. Visualization of the silica plates was achieved using a UV lamp (λmax = 254 nm) and/or by heating plates that were dipped in an anisaldehyde solution. Flash chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh). The biological assays were run on a CLARIOstar® BMG LABTECH's instrument using Corning® 384 low volume well plates.

3.5.2. General procedures.

3.5.2.1. General procedure for the preparation of α,β-unsaturated esters.

The compounds **3.105**, **3.107** and **3.109** were synthesized as reported[26] with minor changes during work-up.

A solution of *n*-BuLi in hexanes (5.28 mmol) was slowly added to a solution of 1-pentadecyne (4.80 mmol) in THF (19.2 mL) at -23 °C. After 2 h, the reaction was allowed to warm at room temperature and it was stirred for other 2 h before cooling at 0 °C. Then, 1-formylpiperidine (5.38 mmol) was added to the pentadecynyllithium suspension at 0 °C and it was stirred at room temperature for 2h. The reaction was quenched with 20 mL of 10 % aqueous $NaHSO_4$ solution and the product was extracted with Et_2O (4 x 20 mL). The organic layer was washed with 10 % aqueous $NaHSO_4$, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude alkynal was directly submitted to a Horner-Wadsworth-Emmons olefination without previous purification.

To a solution of LiBr (20.90 mmol) in THF (100 mL), the corresponding phosphonate (4.88 mmol) was added at room temperature. After 10 min, Et_3N (6.34 mmol) was introduced into the reaction mixture and it was allowed to stir for 15 min. Then, the freshly

synthesized alkynal was dissolved in 20 mL of THF and added to the solution. Once the reaction was completed, the reaction mixture was filtered through silica gel to remove the precipitate formed during the reaction. The pad was washed with 200 mL of hexane/AcOEt 60:40 and the solvent was then removed under reduced pressure. The crude obtained was purified by flash chromatography using hexane/Et_2O (99:1).

*3.5.2.2. Gene*ral *procedure for aziridination.*

The compounds **3.126**, **3.127** and **3.128** were synthesized as reported[35] with minor changes during work-up.

A solution of (diacetoxi)iodobenzene (1.50 mmol) in CH_2Cl_2 was added to a suspension of *N*-aminophthalimide (2.00 mmol) and the corresponding alkenyl (1.00 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred at room temperature monitored by TLC until completion. The, it was quenched by using a saturated $NaHCO_3$ solution and filtered over celite. The mixture was then extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude was purified by flash chromatography on silica gel using hexane/ AcOEt (95:5).

3.5.2.3. General procedure for ring-opening of aziridines.

The compounds **3.134**, **3.135**, **3.136** were synthesized with minor changes during work-up.

To a solution of aziridine (0.50 mmol) in dioxane/water 1:1 (6.8 mL), *p*-toluensulfonic acid (0.55 mmol) was added at room temperature and the reaction mixture was heated under reflux until completion observed by TLC. Then, the mixture was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash chromatography using hexane/AcOEt mixtures.

3.5.2.4. General procedure for over-reduction of alkynes to obtain saturated compounds.

The compounds **3.169** and **3.170** were synthesized with minor changes during work-up.

To a solution of alkyne (0.69 mmol) in AcOEt (22.0 mL) in a Fischer-porter reactor, palladium on carbon (30 or 40 wt %) was added. Then, the reactor was charged with hydrogen (2 or 5 bar) and the reaction was stirred for 16 or 48 h at room temperature. The reaction mixture was filtered through celite, washed with AcOEt (3x15 mL) and the solvent was removed under reduced pressure. The crude was purified using hexane/AcOEt (80:20).

3.5.2.5. General procedure for hydrosilylation/desilylation of alkynes catalyzed by [Ru].[47b,51]

The compounds **3.174** and **3.175** were synthesized with minor changes during the work-up.

In a flame-dried schlenk tube containing a solution of alkyne (0.87 mmol) and $[Cp^*RuCl]_4$ (0.04 mmol) in degassed CH_2Cl_2 (5.0 mL), $(EtO)_3SiH$ (1.57 mmol) was slowly added at room temperature. The resulting mixture was stirred until complete consumption of starting material and the solvent was removed under reduced pressure. Then, a suspension of AgF (0.013 mmol) in a mixture of THF/MeOH/H_2O (5.0:0.3:0.03 mL) was introduced into the schlenck tube and the mixture was stirred for 1.5 h in darkness at room temperature. The solvent was removed under reduced pressure and the crude was purified by flash chromatography using hexane/AcOEt (80:20).

3.5.2.6. General procedure for hydrazine deprotection and synthesis of hydrazones.

The compounds **3.139**, **3.141**, **3.143** and **3.1766-3.179** were synthesized as previously reported[39b] with minor changes during work-up.

Methylhydrazine (0.75 mmol) was added to a solution of the ring-opened product (0.50 mmol) in THF (3.3 mL) at -20 °C. The solution was stirred at that temperature for 30 min and it was then allowed to warm to room temperature until completion controlled by TLC. The solvent was removed under vacuum and the concentrated crude was redissolved in AcOEt and filtered through cotton to remove the *N*-methyl phthalhydrazide by-product generated during the reaction. Then, the filtrate was evaporated and the residue was redissolved in acetone at room temperature. The solution was stirred until complete formation of the hydrazone and it was then concentrated and purified by flash chromatography using hexane/AcOEt (80:20).

3.5.2.7. General procedure for formation of azo-compounds and ester reductions.

The compounds **3.146**, **3.149** and **3.152**, and **3.180**-**3.183** were synthesized as previously reported[29b,43] with minor changes during work-up.

Acetic acid (0.95 mmol) was added to a solution of hydrazone (0.50 mmol) and $NaBH_3CN$ (1.40 mmol) in THF (5.8 mL) at 0 °C. Then, the solution was allowed to warm at room temperature and stirred until the starting material was consumed. The reaction was quenched with a saturated solution of $NaHCO_3$ and extracted with AcOEt (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under vacuum. The resulting crude containing a mixture of hydrazine and azo- compounds was directly submitted to the next reduction without previous purification.

The crude was redissolved in CH_2Cl_2 (1.2 mL) and the solution was cooled to -40 °C. A solution of DIBAL (1.25 mmol) was added dropwise and the mixture was stirred at -40 °C until completion monitored by TLC. Then, the mixture was quenched with a solution of NaOH 1M, filtered through celite using $CHCl_3$ and extracted with $CHCl_3$ (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. To ensure the formation of *E*-azo-compound, the crude was allowed to stir in air and in CH_2Cl_2 (2.0 mL) overnight under light. The crude was purified by silica gel chromatography using hexane/AcOEt mixtures.

3.5.2.8. General procedure for hydrazine deprotection and further dimethylation.

The compounds **3.157**, **3.160**, **3.163**, **3.171** and **3.185-3.187** were synthesized as previously reported[39b,66] with minor changes during work-up.

Methylhydrazine (0.75 mmol) was added to a solution of the ring-opened product (0.50 mmol) in THF (3.3 mL) at -20 °C. The solution was stirred at the same temperature for 30 min and it was then allowed to warm to room temperature until completion monitored by TLC. The solvent was removed under vacuum and the crude was redissolved in AcOEt and filtered through cotton to get rid of the *N*-methyl phthalhydrazide by-product generated during the reaction. Then, the filtrate was evaporated and the residue was redissolved in MeOH (13.8 mL). After cooling at 0 °C, $NaBH_3CN$ (1.00 mmol) and paraformaldehyde (2.00 mmol) were added to the reaction mixture and it was then allowed to warm at room temperature and stirred for 24 or 48 h. The solvent was removed under reduced pressure and the crude was redissolved in AcOEt and filtered through a pad of celite. The filtrate was then evaporated and the residue was purified by silica gel chromatography using hexane/AcOEt mixtures.

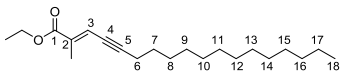
3.5.2.9. General procedure for obtaining alcohols from reduction of esters.

The compounds **3.124**, **3.165**-**3.168**, **3.172**, **3.188** and **3.189** were synthesized as previously reported[29b] with minor changes during work-up.

A solution of DIBAL (0.25 mmol) was added dropwise to a solution of *N,N*-dimethylhydrazino compound (0.10 mmol) in CH_2Cl_2 (0.26 mL) at -40 °C. Once the reaction was completed, the mixture was quenched with a solution of NaOH 1M, filtered through celite using $CHCl_3$ and extracted with $CHCl_3$ (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography using hexane/AcOEt mixtures.

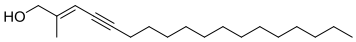
3.5.3. Synthetic procedures and characterization data.

Ethyl (*E*)-2-methyloctadec-2-en-4-ynoate (3.107):



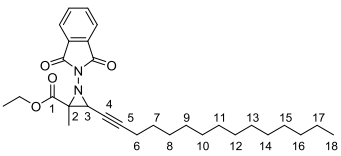
The reaction was performed as described in general procedure 3.5.*2.1.* by using 1-pentadecyne (1.26 mL, 4.80 mmol) and triethyl 2-phosphonopropionate (1.15 mL, 4.88 mmol) to afford a mixture of esteroisomers *cis/trans* (7:93). After purification the *trans* product **3.107** was achieved in 57 % yield as a yellowish oil (877.0 mg, 2.74 mmol, 57 %) over two steps. IR (neat): 2924, 2854, 2213, 1713, 1465, 1344, 1258, 1119, 631 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (m, 1H, H_3), 4.19 (q, *J* = 7.1 Hz, 2H, $CH_3\underline{CH_2}O$), 2.40 (td, *J* = 7.0, 2.2 Hz, 2H, H_6), 2.02 (d, *J* = 1.3 Hz, 3H, $C\underline{H_3}$), 1.55 (m, 2H, H_7), 1.40 (m, 2H, H_8), 1.28 – 1.20 (m, 21H, $\underline{CH_3}CH_2O$, H_9 to H_{17}), 0.87 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5 (C_1), 137.9 (C_3), 120.5 (C_2), 103.9 (C_5), 77.7 (C_4), 60.9 ($CH_3\underline{C}H_2O$), 32.0 (CH_2), 29.9 (CH_2), 29.8 (2xCH_2), 29.7(CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.0 (C_{10}), 28.7 (C_7), 22.8 (CH_2), 20.0 (C_6), 15.2 ($\underline{C}H_3$), 14.3 (C_{18}), 14.2 ($\underline{C}H_3CH_2O$). HR ESI-TOF MS for [M+Na^+] $C_{21}H_{36}NaO_2^+$ (m/z): 343.2608; found: 343.2613.

(*E*)-2-methyloctadec-2-en-4-yn-1-ol (3.124):



Compound **3.107** (332 mg, 1.00 mmol) was reacted with DIBAL (2.6 mL, 2.60 mmol, 1.0 M in dichloromethane) in CH_2Cl_2 (2.6 mL) following the procedure described to obtain alcohols. After work-up, the crude was purified using hexane/AcOEt (90:10) to afford **3.124** (237.8mg, 0.85 mmol, 85 %) as white solid. m.p. 37-38 °C. IR (neat): 3340, 2922, 2852, 2361, 1464, 1375, 1075, 1014 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.53 (s, 1.6 Hz, 1H, H_3), 4.08 (s, 2H, H_1), 2.34 (td, *J* = 7.0, 1.6 Hz, 2H, H_6), 1.87 (s, 3H, $C\underline{H}_3$), 1.59 – 1.49 (m, 2H, H_7), 1.46 – 1.35 (m, 2H, H_8), 1.27 (bs, 18H, H_9 to H_{17}), 0.87 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3 (C_2), 105.7 (C_3), 94.7 (C_5), 77.6 (C_4), 67.2 (C_1), 32.1 (CH_2), 29.8 (4xCH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (C_7), 29.0 (C_8), 22.8 (CH_2), 19.7 (C_6), 16.4 ($\underline{C}H_3$), 14.3 (C_{18}). HR ESI-TOF MS for [M+Na^+] $C_{19}H_{34}NaO^+$ (m/z): 301.2502; found: 301.2504.

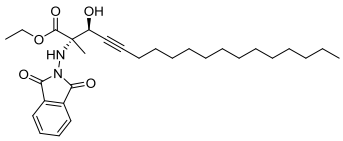
Ethyl [1-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-methyl-3-(pentadec-1-yn-1-yl)aziridine]-2-carboxylate (3.126):



Compound **3.107** (880.0 mg, 2.74 mmol) was treated with *N*-aminophthalimide (588.6 mg, 5.48 mmol) and (diacetoxy)iodobenzene (1323.8 mg, 4.11 mmol) following the general procedure for aziridination. After the work-up, the crude was purified by flash chromatography by using hexane/AcOEt (95:5) getting the aziridine **3.126** as a yellow oil in quantitative yield.[67] IR (neat): 2927, 2855, 2220, 1715, 1261, 1121, 746, 631 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H, H_{ar}), 7.66 (dd, *J* = 5.5, 3.0 Hz, 2H, H_{ar}), 4.14 – 4.04 (m, 2H, $CH_3\underline{CH_2}O$), 4.02 (t, *J* = 1.8 Hz, 1H, H_3), 2.27 (td, *J* = 7.1, 1.8 Hz, 2H, H_6), 1.74 (s, 3H, $C\underline{H}_3$), 1.59 – 1.48 (m, 2H, H_7), 1.44 – 1.33 (m, 2H, H_8), 1.33 – 1.22 (bs, 18H, H_9 to H_{17}), 1.19 (t, *J* = 7.1 Hz, 3H, $\underline{CH_3}CH_2O$), 0.87 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2 (C_1), 164.5 (2xC_{ar}), 134.1 (2xC_{ar}), 130.4 (2xC_{ar}), 123.2 (2xC_{ar}), 87.0 (C_5), 72.8 (C_4), 62.4 ($CH_3\underline{C}H_2O$), 49.9

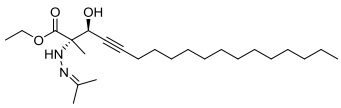
(C_2), 43.9 (C_3), 32.0 (CH_2), 29.8 (4xCH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.0 (C_7), 28.5 (C_8), 22.8 (CH_2), 19.0 (C_6), 15.5 ($\underline{C}H_3$), 14.3 (C_{18}), 14.0 ($\underline{C}H_3CH_2O$). HR ESI-TOF MS for [2M+Na$^+$] $C_{58}H_{80}N_4NaO_8^+$ (m/z): 983.5868; found: 983.5875.

Ethyl 2-((1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)amino)-3-hydroxy-2-methyloctadec-4-ynoate (3.134):



Compound **3.134** was prepared following the general procedure for the ring-opening aziridines, starting from alkynylaziridine **3.126** (1300.0 mg, 2.70 mmol) and *p*-toluensulfonic acid (511.4 mg, 2.97 mmol). After the work-up, the crude was purified by flash chromatography by using hexane/AcOEt (from 90:10 to 80:20) to give **3.134** as a yellow oil (1102.0 mg, 2.21 mmol, 82 %). IR (neat): 3448, 3230, 2924, 2853, 2223, 1788, 1725, 1466, 1378, 1259, 713, 631 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H, H_{ar}), 7.76 (dd, *J* = 5.4, 3.1 Hz, 2H, H_{ar}), 5.77 (s, 1H, H_{NH}), 4.42 (dt, *J* = 10.9, 2.0 Hz, 1H, H_3), 4.38 – 4.18 (m, 2H, $CH_3\underline{CH_2}O$), 4.19 (d, *J* = 10.9 Hz, 1H, H_{OH}), 2.17 (td, *J* = 7.1, 2.0 Hz, 2H, H_6), 1.52 – 1.40 (m, 2H, H_7), 1.39 – 1.17 (m, 26H, H_8 to H_{17}, $\underline{CH_3}CH_2O$, $C\underline{H_3}$), 0.87 (t, *J* = 6.8 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2 (C_1), 167.8 (2xC_{ar}), 134.7 (2xC_{ar}), 129.9 (2xC_{ar}), 123.9 (2xC_{ar}), 87.4 (C_5), 77.5 (C_4) 68.2 (C_3), 67.8 (C_2), 62.2 ($CH_3\underline{C}H_2O$), 32.0 (CH_2), 29.8 (3xCH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 28.9 (C_7), 28.6 (C_8), 22.8 (CH_2), 18.8 (C_6), 17.4 ($\underline{C}H_3$), 14.3 (C_{18}), 14.2 ($\underline{C}H_3CH_2O$). HR ESI-TOF MS for [M+Na$^+$] $C_{29}H_{42}N_2NaO_5^+$ (m/z): 521.2986; found: 521.2982.

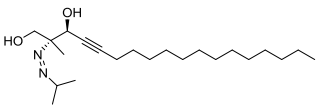
Ethyl 3-hydroxy-2-methyl-2-(2-(propan-ylidene)hydrazinyl)octadec-4-ynoate (3.139):



The reaction was performed as described in general procedure for synthesis of hydrazones starting from **3.134** (250.0 mg, 0.50 mmol) and methylhydrazine (40 µL, 0.75 mmol) in THF (1.1 mL). After filtration, the resulting crude was redissolved in 3 mL of acetone,

stirred for 16 h and purified by flash chromatography using hexane/AcOEt (80:20) to accomplish hydrazone **3.139** (63.0 mg, 0.16 mmol, 62 % over two steps) as a colorless oil. IR (neat): 2929, 2850, 2359, 1714, 1262, 1122, 742, 630 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.57 (bs, 1H, H_{NH}), 4.61 (bs, 1H, H_3), 4.30 – 4.09 (m, 3H, $CH_3\underline{CH_2}O$, H_{OH}), 2.17 (td, *J* = 7.0, 1.8 Hz, 1H, H_6), 1.90 (s, 3H, $(\underline{CH_3})_2C$), 1.79 (s, 3H, $(\underline{CH_3})_2C$), 1.56 (s, 3H, $C\underline{H_3}$), 1.49 – 1.39 (m, 2H, H_7), 1.39 – 1.15 (m, 23H, $\underline{CH_3}CH_2O$, H_8 to H_{17}), 0.87 (t, *J* = 6.8 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6 (C_1), 148.8 ($(CH_3)_2\underline{C}$), 87.3 (C_5), 77.7 (C_4), 68.6 (C_3), 66.2 (C_2), 61.5 ($CH_3\underline{C}H_2O$), 32.0 (CH_2), 29.8 (4xCH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3(CH_2), 29.0 (C_8), 28.8 (C_7), 25.5($(\underline{C}H_3)_2C$), 22.8 (CH_2), 19.6 ($\underline{C}H_3$), 18.8 (C_6), 15.8($(\underline{C}H_3)_2C$), 14.3(C_{18}), 14.2 ($\underline{C}H_3CH_2O$). HR ESI-TOF MS for $[M+H^+]$ $C_{24}H_{45}N_2O_3^+$ (m/z): 409.3425; found: 409.3426.

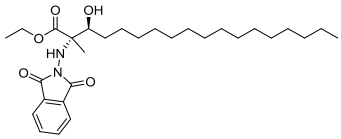
2-(isopropyldiazenyl)-2-methyloctadec-4-yne-1,3-diol (3.146):



Hydrazone **3.139** (60.0 mg, 0.15 mmol) was treated with $NaBH_3CN$ (26.4 mg, 0.42 mmol) and AcOH (20 μL, 0.28 mmol) in 4mL of THF following the procedure previously described for reduction of hydrazone and ester moieties. Once the hydrazone was reduced, the reaction mixture was filtered over celite and the solvent was removed. The resulting crude was redissolved in CH_2Cl_2 (0.38 mL) and the solution was cooled at -40 °C before DIBAL (0.38 mL, 1 M in dichloromethane, 0.38 mmol) was slowly added. The reaction was quenched and the crude was purified by column chromatography using hexane/AcOEt (80:20) to give **3.146** as a brownish oil (18.7 mg, 0.05 mmol, 34 % over two steps). IR (neat): 3380, 2923, 2853, 2362, 1465, 1275, 1041, 749 cm^{-1}. ^1H NMR (400 MHz $CDCl_3$) δ 4.78 (bs, 1H, H_3), 4.12 (d, *J* = 12.0 Hz, 1H, H_1), 3.89 (d, *J* = 12.0 Hz, 1H, $H_{1'}$), 3.77 – 3.63 (m, 1H, $(CH_3)_2\underline{CH}$), 3.25 (s, 1H, H_{OH}), 2.77 (s, 1H, H_{OH}), 2.22 (td, *J* = 7.1, 2.1 Hz, 2H, H_6), 1.50 (m, 2H, H_7), 1.43 – 1.13 (m, 29H, H_8 to H_{17}, $C\underline{H_3}$, $\underline{(CH_3)_2}CH$), 0.87 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 87.9 (C_5), 77.9 (C_4), 74.2 (C_2), 68.8 ($(CH_3)_2\underline{C}H$), 68.0 (C_3), 66.1 (C_1), 32.0 (CH_2), 29.8 (4xCH_2), 29.7 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.7 (C_7), 22.8 (CH_2), 20.6 ($(\underline{C}H_3)_2CH$), 20.5 ($(\underline{C}H_3)_2CH$),

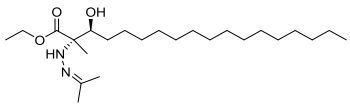
18.9 (C_6), 18.1 ($\underline{C}H_3$), 14.3 (C_{18}). HR ESI-TOF MS for [M+H$^+$] $C_{22}H_{43}N_2O_2^+$ (m/z): 366.3319; found: 366.3317.

Ethyl 2-((1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)amino)-3-hydroxy -2-methyloctadecanoate (3.169):



Compound **3.169** was synthesized following the general procedure described for over-reduction of alkynes starting from **3.134** (341.6 mg, 0.69 mmol), palladium on carbon (102.5 mg, 30 wt%) and hydrogen (5 bar). After stirring for 16 h, the reaction mixture was filtered and purified to afford **3.169** (286.8 mg, 0.57 mmol, 83 % yield) as a white solid. m.p. 59 °C. IR (neat): 3475, 3325, 2923, 2852, 1800, 1725, 1467, 1378, 1260, 1200 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H, H_{ar}), 7.76 (dd, *J* = 5.4, 3.1 Hz, 2H, H_{ar}), 5.67 (s, 1H, H_{NH}), 4.34 – 4.17 (m, 2H, $CH_3\underline{CH_2}O$), 3.62 – 3.42 (m, 2H, H_3, H_{OH}), 1.66 – 1.52 (m, 2H, H_4), 1.34 – 1.23 (m, 32H, H_5 to H_{17}, $\underline{CH_3}CH_2O$, $C\underline{H_3}$), 0.87 (t, *J* = 6.8 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 (C_1), 168.2 (2xC_{ar}), 134.7 (2xC_{ar}), 130.0 (2xC_{ar}), 123.8 (2xC_{ar}), 76.0 (C_3), 68.2 (C_2), 62.0 ($CH_3\underline{C}H_2O$), 32.2 (CH_2), 32.1 (CH_2), 29.8 (8xCH_2), 29.7 (CH_2), 29.5 (CH_2), 26.6 (C_4), 22.8 (CH_2), 17.7 ($\underline{C}H_3$), 14.3 (C_{18}), 14.2 ($\underline{C}H_3CH_2O$). HR ESI-TOF MS for [M+H$^+$] $C_{29}H_{47}N_2O_5^+$ (m/z): 503.3479; found: 503.3479.

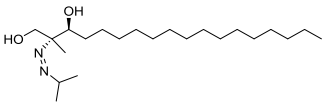
Ethyl 3-hydroxy-2-(2-(propan-2-ylidene)hydrazinyl)-2-methyloctadecanoate (3.176):



The reaction was performed as described in general procedure for synthesis of hydrazones starting from **3.169** (225 mg, 0.45 mmol) and methylhydrazine (35.3 μL, 0.67 mmol) in THF (3.3 mL). After filtration, the resulting crude was redissolved in 2.5 mL of acetone, stirred for 16 h and purified by flash chromatography using hexane/AcOEt (90:10) to accomplish **3.176** (122.9 mg, 0.31 mmol, 69 % over two steps) as a colorless oil. IR (neat): 3649, 2961, 2924, 2853,

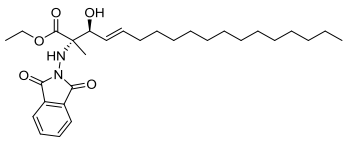
2362, 1733, 1457, 1260, 1088, 799, 630 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.32 (s, 1H, H_{NH}), 4.18 (q, *J* = 7,1 Hz, 2H, $CH_3\underline{CH_2}O$), 3.93 (bd, *J* = 7.6 Hz, 1H, H_{OH}), 3.82 (m, 1H, H_3), 1.90 (s, 3H, $\underline{(CH_3)_2}CH$), 1.77 (s, 3H, $\underline{(CH_3)_2}CH$), 1.65 – 1.52 (m, 1H, H_4), 1.51 – 1.18 (m, 33H, H_5 to H_{17}, $\underline{CH_3}CH_2O$, $H_{4'}$, $C\underline{H_3}$), 0.87 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0 (C_1), 147.7 ($(CH_3)_2\underline{C}$), 76.6 (C_3), 66.2 (C_2), 61.2 ($CH_3\underline{C}H_2O$), 32.6 (CH_2), 32.0 (CH_2), 29.8 (8xCH_2), 29.7 (CH_2), 29.5 (CH_2), 26.6 (C_4), 25.5 ($(\underline{CH_3})_2C$), 22.8 (CH_2), 20.7 ($\underline{C}H_3$), 15.6 ($(\underline{CH_3})_2C$), 14.3 ($\underline{C}H_3CH_2O$, C_{18}). HR ESI-TOF MS for $C_{24}H_{49}N_2O_3$ [M+H^+]: 413.3738; found: 413.3729.

2-(2-(propan-2-ylidene)hydrazinyl)-2-methyloctadecane-1,3-diol (3.180):



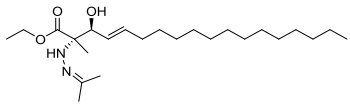
Hydrazone **3.176** (122.9 mg, 0.31 mmol) was treated with $NaBH_3CN$ (58.1 mg, 0.92 mmol) and AcOH (35.1 µL, 0.49 mmol) in 5.5 mL of THF following the procedure previously described for reduction of hydrazone and ester moieties. Once the hydrazones was reduced, the reaction mixture was filtered over celite and the solvent was removed. The resulting crude was redissolved in CH_2Cl_2 (0.71 mL) and the solution was cooled at -40 °C before DIBAL (0.71 mL, 1 M in dichloromethane, 0.71 mmol) was slowly added. The reaction was quenched and the crude was purified by column chromatography using hexane/AcOEt (80:20) to give **3.180** (37 mg, 0.10 mmol, 35 % over two steps) as a yellow oil. IR (neat): 3393, 2921, 2852, 2365, 1464, 1378, 1044 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 4.02 – 3.97 (m, 1H, H_4), 3.82 (d, *J* = 11.2 Hz, 1H, H_2), 3.69 (d, *J* = 11.2 Hz, 1H, $H_{2'}$), 3.62 (dt, *J* = 13.0, 6.5 Hz, 1H, $(CH_3)_2\underline{CH}$), 1.56 (bs, 2H, H_4), 1.40 – 1.19 (m, 32H, H_5 to H_{17}, $(\underline{CH_3})_2C$), 1.04 (s, 3H, $C\underline{H_3}$), 0.90 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, MeOD) δ 76.8 (C_2), 74.7 (C_3), 69.6 ($(CH_3)_2\underline{C}H$), 67.3 (C_1), 33.1 (CH_2), 32.0 (CH_2), 30.8 (6xCH_2), 30.7 (2xCH_2), 30.6 (CH_2), 30.5 (CH_2), 27.6 (C_5), 23.8 (CH_2), 20.7 ($(\underline{C}H_3)_2C$), 14.5 ($\underline{C}H_3$), 14.2 (C_{18}). HR ESI-TOF MS for $C_{22}H_{47}N_2O_2$ [M+H^+]: 371.3632; found: 371.3625.

Ethyl (*E*)-2-((1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)amino)-3-hydroxy-2-methyloctadec-4-enoate (3.174):



Compound **3.174** was prepared following the hydrosilylation/desilylation procedure catalyzed by [Ru] starting from alkyne **3.134** (435 mg, 0.87 mmol), $[Cp^*RuCl]_4$ (11.8 mg, 0.04 mmol) and $SiH(OEt)_3$ (0.29 mL, 1.57 mmol). After complete silylation, a suspension of AgF (166 mg, 0.013 mmol) in a mixture of THF/MeOH/H_2O (5.0:0.3:0.03 mL) was introduced into the schlenck and the mixture was stirred for 1.5 h in darkness at room temperature. The resulting crude was purified by flash chromatography using hexane/AcOEt (80:20) to afford compound **3.174** as a yellow oil (230.9 mg, 0.46 mmol, 53%). IR (neat): 3461, 3296, 2922, 2852, 2368, 2324, 1788, 1722, 1467, 1378, 1260, 1200, 1104 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.82 (m, 2H, H_{ar}), 7.82 – 7.74 (m, 2H, H_{ar}), 5.81 – 5.67 (m, 2H, H_5, H_{NH}), 5.62 (dd, *J* = 15.5, 5.9 Hz, 1H, H_4), 4.35 – 4.16 (m, 2H, $CH_3\underline{CH_2}O$), 4.06 – 3.99 (m, 2H, H_3, H_{OH}), 2.03 (m, 2H, H_6), 1.42 – 1.16 (m, 28H, H_7 to H_{17}, $C\underline{H_3}$, $\underline{CH_3}CH_2O$), 0.87 (t, *J* = 6.8 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 (C_1), 168.0 (2xC_{ar}), 135.3 (C_5), 134.7 (2xC_{ar}), 129.9 (2xC_{ar}), 127.5 (C_4), 123.8 (2xC_{ar}), 77.2 (C_3), 68.1 (C_2), 62.0 ($CH_3\underline{C}H_2O$), 32.4 (CH_2), 32.0 (C_6), 29.8 (4xCH_2), 29.7 (2xCH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 22.8 (C_7), 17.7 ($\underline{C}H_3$), 14.2 ($\underline{C}H_3CH_2O$, C_{18}). HR ESI-TOF MS for $[M+Na^+]$ $C_{29}H_{44}N_2NaO_5^+$ (m/z): 523.3142; found: 523.3142.

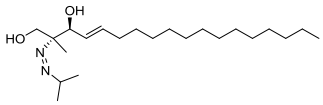
Ethyl (*E*)-3-hydroxy-2-(2-(propan-2-ylidene)hydrazinyl)-2-methyloctadec-4-enoate (3.178):



The reaction was performed as described in general procedure for synthesis of hydrazones starting from **3.174** (230.8 mg, 0.46 mmol) and methylhydrazine (36.4 μL, 0.69 mmol) in THF (3.3 mL). After filtration, the resulting crude was redissolved in 3 mL of acetone, stirred for 16 h and purified by flash chromatography using hexane/AcOEt (90:10) to accomplish **3.178** (136 mg, 0.33 mmol, 72 %

over two steps) as a colorless oil. IR (neat): 3371, 3312, 2922, 2853, 2367, 2324, 1731, 1463, 1367, 1234, 1142, 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.69 (dt, *J* = 15.2, 6. Hz, 1H, H_5), 5.52 (dd, *J* = 15.2, 7.5 Hz, 1H, H_4), 5.37 (bs, 1H, H_{NH}), 4.44-4.27 (m, 2H, H_3, H_{OH}), 4.25 – 4.12 (q, *J* = 7.1 Hz, 2H, $CH_3\underline{CH_2}O$), 2.04 (m, 2H, H_6), 1.90 (s, 3H, $(\underline{CH_3})_2C$), 1.77 (s, 3H, $(\underline{CH_3})_2C$), 1.42 (s, 3H, $C\underline{H_3}$), 1.41 – 1.16 (m, 25H, H_9 to H_{19}, $\underline{CH_3}CH_2O$), 0.87 (t, *J* = 6.8 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5 (C_1), 147.9 ($(CH_3)_2\underline{C}$), 134.7 (C_5), 128.1 (C_4), 78.1 (C_3), 66.1 (C_2), 61.2 ($CH_3\underline{C}H_2O$), 32.5 (CH_2), 32.1 (C_6), 29.8 (6xCH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.5 ($(\underline{C}H_3)_2C$), 22.8 (CH_2), 20.7 ($\underline{C}H_3$), 15.6 ($(\underline{C}H_3)_2C$), 14.3 ($\underline{C}H_3CH_2O$, C_{18}). HR ESI-TOF MS for [M+H$^+$] $C_{24}H_{47}N_2O_5^+$ (m/z): 411.3581; found: 411.3585.

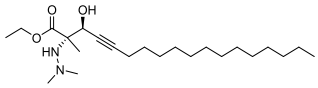
(*E*)-2-(2-(propan-2-ylidene)hydrazinyl)-2-methyloctadec-4-ene-1,3-diol (3.182):



Hydrazone **3.178** (136.0 mg, 0.33 mmol) was treated with $NaBH_3CN$ (41.6 mg, 0.66 mmol) and AcOH (37.7 μL, 0.53 mmol) in 3.8 mL of THF following the procedure previously described for reduction of hydrazone and ester moieties. After completion of the reaction, the mixture was filtered over celite and the solvent was removed. The resulting crude was redissolved in CH_2Cl_2 (0.83 mL) and the solution was cooled at -40 °C before DIBAL (0.83 mL, 1 M in dichloromethane, 0.83 mmol) was slowly added. The reaction was quenched and the crude was firstly purified by flash chromatography using $CHCl_3$/MeOH (96:4) and then repurified using hexane/AcOEt (80:20) to give **3.182** (10.3 mg, 0.03 mmol, 8 % over two steps) as a colorless oil. IR (neat): 3334, 2927, 2852, 2358, 2342, 1716, 1675, 1464, 1261, 1097, 1050 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 5.67 (dt, *J* = 13.6, 6.5 Hz, 1H, H_5), 5.50 – 5.39 (m, 1H, H_6), 4.50 (d, *J* = 7.1 Hz, 1H, H_3), 3.88 (d, *J* = 11.3 Hz, 1H, H_1), 3.74 (d, *J* = 11.3 Hz, 1H, $H_{1'}$), 3.66 (dt, *J* = 10.4, 6.5 Hz, 1H, $(CH_3)_2\underline{CH}$), 2.05 (dd, *J* = 13.5, 6.5 Hz, 2H, H_6), 1.48 – 1.20 (m, 28H, H_7 to H_{17}, $(\underline{CH_3})_2CH$), 1.06 (s, 3H, $C\underline{H_3}$), 0.92 (t, *J* = 6.8 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, MeOD) δ 134.5 (C_5), 129.8 (C_4), 76.4 (C_2, C_3), 69.5 $(CH_3)_2\underline{C}H$), 67.0 (C_1), 33.3 (CH_2), 33.1

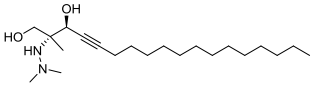
(C_6), 30.8 (4xCH_2), 30.7 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 23.7 (CH_2), 20.8 (($\underline{C}H_3$)$_2$CH), 15.4 ($\underline{C}H_3$), 14.4 (C_{18}). HR ESI-TOF MS for [M+Na$^+$] $C_{22}H_{44}N_2NaO_2^+$ (m/z): 391.3295; found: 391.3309.

Ethyl 2-(2,2-dimethylhydrazinyl)-3-hydroxy-2-methyloctadec-4-ynoate (1.157):



The reaction was carried out as described in general procedure for synthesis of dimethyl hydrazines starting from **3.134** (139.4 mg, 0.28 mmol) and methylhydrazine (22.1 µL, 0.42 mmol) in THF (1.8 mL). After filtration, the resulting crude was redissolved in 7.8 mL of MeOH and paraformaldehyde (42.0 mg, 1.40 mmol) was added to the reaction mixture. After cooling at 0 °C, $NaBH_3CN$ (105.6 mg, 1.68 mmol) was added and the resulting solution was stirred for 48 h at room temperature. The crude was purified by flash chromatography using hexane/AcOEt (from 95:5 to 90:10) to give **1.157** (69 mg, 0.17 mmol, 62 % over two steps) as a colorless oil. IR (neat): 3615, 3420, 2926, 2855, 2360, 1715, 1456, 1264, 1122, 888, 740, 631 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (dd, *J* = 2.5, 1.5 Hz, 1H, H_3), 4.29 – 4.09 (m, 2H, $CH_3\underline{CH_2}O$), 2.47 (s, 6H, $N(\underline{CH_3})_2$), 2.26 – 2.10 (m, 2H, H_6), 1.54 – 1.39 (m, 5H, H_7, $C\underline{H_3}$), 1.39 – 1.12 (m, 23H, H_8 to H_{17}, $\underline{CH_3}CH_2O$), 0.86 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3 (C_1), 87.4 (C_5), 78.1 (C_4), 68.0 (C_3), 66.8 (C_2), 61.4 ($CH_3\underline{C}H_2O$), 50.1 ($N(\underline{C}H_3)_2$), 32.0 (CH_2), 29.8 (4xCH_2), 29.7 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.7 (C_8), 22.8 (C_7), 19.4 ($\underline{C}H_3$), 18.8 (C_6), 14.3 (C_{18}), 14.2 ($\underline{C}H_3CH_2O$). HR ESI-TOF MS for [M+H$^+$] $C_{23}H_{45}N_2O_3^+$ (m/z): 397.3425; found: 397.3431.

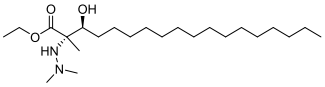
2-(2,2-dimethylhydrazinyl)-2-methyloctadec-4-yne-1,3-diol 3.165):



Dimethyl hydrazine **3.157** (69.0 mg, 0.17 mmol) was treated with a solution of DIBAL (0.43 mL, 1 M in dichloromethane, 0.43 mmol) in CH_2Cl_2 (0.43 mL) at -40 °C according to the procedure described for reduction of ester moieties. The crude was purified by silica gel chromatography using hexane/AcOEt (from 90:10 to 80:20) to yield **3.165** (52.1 mg,

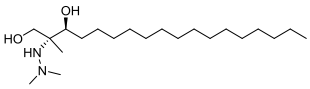
0.15 mmol, 84 %) as a white solid. m.p. 35 °C. IR (neat): 3735, 3381, 2953, 2853, 2366, 2354, 2340, 1467, 1042, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.61 (t, *J* = 2.0 Hz, 1H, H_3), 3.82 (d, *J* = 11.1 Hz, 1H, H_1), 3.69 (m, 2H, $H_{1'}$, H_{NH}), 2.50 (s, 6H, $N(\underline{C}H_3)_2$), 2.23 (td, *J* = 7.1, 2.0 Hz, 2H, H_6), 1.56 – 1.42 (m, 2H, H_7), 1.42 – 1.17 (m, 20H, H_8 to H_{17}), 1.05 (s, 3H, $C\underline{H}_3$), 0.87 (t, *J* = 6.8 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 87.9 (C_5), 78.6 (C_4), 67.0 (C_3), 66.6 (C_1), 61.3 (C_2), 50.7 ($N(\underline{C}H_3)_2$), 32.0 (CH_2), 29.8 (4xCH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.8 (C_8), 22.8 (C_7), 18.9 (C_6), 18.4 ($\underline{C}H_3$), 14.3 (C_{18}) . HR ESI-TOF MS for $[M+H^+]$ $C_{21}H_{43}N_2O_2^+$ (m/z): 355.3319; found: 355.331.

Ethyl 2-(2,2-dimethylhydrazinyl)-3-hydroxy-2-methyloctadecanoate (3.185):



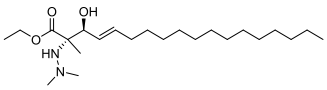
The reaction was carried out as described in general procedure for synthesis of dimethyl hydrazines starting from **3.169** (150.0 mg, 0.28 mmol) and methylhydrazine (17.3 µL, 0.33 mmol) THF (2.2 mL). After reaction completion, the crude was filtered and the resulting crude was redissolved in 8.3 mL of MeOH and paraformaldehyde (44.7 mg, 1.49 mmol) was added. After cooling at 0 °C, $NaBH_3CN$ (112.4 mg, 1.79 mmol) was introduced the resulting solution was stirred at room temperature for 24 h. The crude was purified by flash chromatography using hexane/AcOEt (from 90:10 to 80:20) to give **3.185** (54.4 mg, 0.14 mmol, 46 % over two steps) as a colorless oil. IR (neat): 3735, 3512, 2923, 2853, 2770, 2362, 2342, 1731, 1457, 1107, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 – 4.22 (m, 2H, $CH_3\underline{CH}_2O$), 3.64 (dd, *J* = 9.9, 2.0 Hz, 1H, H_3), 3.47 (bs, 1H, H_{OH}), 2.44 (s, 6H, $N(\underline{C}H_3)_2$), 1.59 (bs, 2H, H_4), 1.52 – 1.39 (m, 2H, H_5), 1.37 – 1.13 (m, 30H, H_6 to H_{17}, $\underline{C}H_3CH_2O$, $C\underline{H}_3$), 0.87 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8 (C_1), 75.9 (C_3), 67.0 (C_2), 61.1 ($CH_3\underline{C}H_2O$), 50.2 ($N(\underline{C}H_3)_2$), 32.2 (CH_2), 32.1 (C_5), 29.8 (8xCH_2), 29.7 (CH_2), 29.5 (CH_2), 26.8 (C_4), 22.9 (CH_2), 19.6 ($\underline{C}H_3$), 14.3 ($\underline{C}H_3CH_2O$, C_{18}). HR ESI-TOF MS for $[M+H^+]$ $C_{23}H_{49}N_2O_3^+$ (m/z): 401.3738; found: 401.3735.

2-(2,2-dimethylhydrazinyl)-2-methyloctadecane-1,3-diol (3.168):



Dimethyl hydrazine **3.185** (50.9 mg, 0.13 mmol) was treated with a solution of DIBAL (0.32 mL, 1 M in dichloromethane, 0.32 mmol) in CH_2Cl_2 (0.32 mL) at -40 °C according to the procedure described for reduction of esters. The crude was purified by silica gel chromatography using hexane/AcOEt (80:20) to accomplish **3.168** (30.6 mg, 0.09 mmol, 66 %) as a white solid. m.p. 62 °C. IR (neat): 3734, 2921, 2853, 2366, 1457, 1260, 1033, 799, 749 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 3.71 (d, *J* = 10.9 Hz, 1H, H_1), 3.55 (m, 2H, $H_{1'}H_3$), 2.48 (s, 6H, $N(\underline{CH_3})_2$), 1.59 (bs, 2H, H_4), 1.33 (bs, 26H, H_5 to H_{17}), 0.91 (m, 6H, H_{18}, $C\underline{H_3}$). ^{13}C NMR (100 MHz, MeOD) δ 77.2 (C_3), 65.0 (C_1), 62.2 (C_2), 50.5 ($N(\underline{C}H_3)_2$), 33.1 (CH_2), 32.5 (C_4), 30.8 ($9xCH_2$), 30.5 (CH_2), 28.0 (CH_2), 23.8 (CH_2), 18.5 ($\underline{C}H_3$), 14.4 (C_{18}). HR ESI-TOF MS for $[M+H^+]$ $C_{21}H_{47}N_2O_2^+$ (m/z): 359.3632; found: 359.3631.

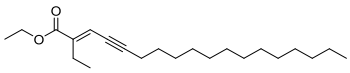
Ethyl (*E*)-2-(2,2-dimethylhydrazinyl)-3-hydroxy-2-methyloctadec-4-enoate (3.171):



The reaction was carried out as described in the general procedure for the synthesis of dimethyl hydrazines starting from **3.174** (131.4 mg, 0.26 mmol) and methylhydrazine (20.7 μL, 0.39 mmol) THF (1.9 mL). After reaction completion the reaction crude was filtered. The resulting crude was redissolved in 7.2 mL of MeOH and paraformaldehyde (31.5 mg, 1.05 mmol) was added to the solution mixture. After cooling at 0 °C, $NaBH_3CN$ (32.9 mg, 0.52 mmol) was introduced into the mixture and the solution was stirred at room temperature for 48 h. The crude was purified by flash chromatography using hexane/AcOEt (from 90:10 to 80:20) to give **3.171** (40 mg, 0.10 mmol, 38 % over two steps) as a colorless oil. IR (neat): 3500, 3448, 2922, 2852, 2770, 2367, 1730, 1465, 1370, 1224, 1108 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 5.68 (dt, *J* = 14.8, 6.8 Hz, 1H, H_5), 5.48 (dd, *J* = 14.8, 7.2 Hz, 1H, H_4), 4.19 – 4.10 (m, 2H, $CH_3\underline{CH_2}O$), 4.03 (d, *J* = 7.2 Hz, 1H, H_3), 2.41 (s, 6H, $N(\underline{CH_3})_2$), 2.04 (m, 2H, H_6), 1.42 – 1.20 (m, 30H, $\underline{CH_3}CH_2O$, H_7 to H_{17}, $C\underline{H_3}$), 0.89 (t, *J* = 6.9 Hz,

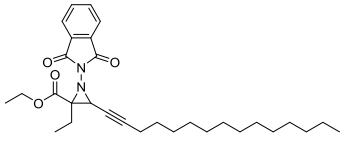
3H, H_{18}). ^{13}C NMR (100 MHz, MeOD) δ 176.0 (C_1), 135.2 (C_5), 129.6 (C_4), 77.4 (C_3), 68.9 (C_2), 61.9 ($CH_3\underline{C}H_2O$), 50.1 ($N(\underline{C}H_3)_2$), 33.4 (CH_2), 33.1 (C_6), 30.8 ($5xCH_2$), 30.6 (CH_2), 30.5 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 23.8 (CH_2), 18.5 ($\underline{C}H_3$), 14.6 (C_{18}), 14.5 ($\underline{C}H_3CH_2O$). HR ESI-TOF MS for [M+H$^+$] $C_{23}H_{47}N_2O_3^+$ (m/z): 399.3581; found: 399.3587.

Ethyl (*E*)-2-ethyloctadec-2-ene-5-ynoate (3.109):



The reaction was performed as described in general procedure *3.5.2.1* by using 1-pentadecyne (1.26 mL, 4.80 mmol) and triethyl 2-phosphonobutyrate (1.16 mL, 4.88 mmol) to afford a mixture of two esteroisomers *cis/trans* (12:88). The *trans* product was purified using hexane/Et_2O (95:5) to achieve **3.109** (1141 mg, 3.31 mmol, 69 % over two steps) as a yellow oil. IR (neat): 2923, 2853, 5357, 2212, 1712, 1609, 1463, 1309, 1238, 1129 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.59 (t, *J* = 2.3 Hz, 1H, H_3), 4.20 (q, *J* = 7.1 Hz, 2H, $CH_3\underline{CH_2}O$), 2.50 (q, *J* = 7.5 Hz, 2H, $CH_3\underline{CH_2}$), 2.41 (td, *J* = 7.0, 2.3 Hz, 2H, H_6), 1.62 – 1.49 (m, 2H, H_7), 1.49 – 1.35 (m, 2H, H_8), 1.35 – 1.17 (m, 21H, H_9 to H_{17}, $\underline{CH_3}CH_2O$), 1.06 (t, *J* = 7.5 Hz, 3H, $\underline{CH_3}CH_2$), 0.88 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2 (C_1), 144.0 (C_2), 120.0 (C_3), 103.5 (C_5), 77.4 (C_4), 60.8 ($CH_3\underline{C}H_2O$), 32.0 (CH_2), 29.8 ($4xCH_2$), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.0 (C_8), 28.7 (C_7), 22.9 (CH_2), 22.8 ($CH_3\underline{C}H_2$), 20.1 (C_6), 14.4 ($\underline{C}H_3CH_2O$), 14.3 (C_{18}), 13.5 ($\underline{C}H_3CH_2$). HR ESI-TOF MS for [M+H$^+$] $C_{22}H_{39}O_2^+$ (m/z): 335.2945; found: 335.2950.

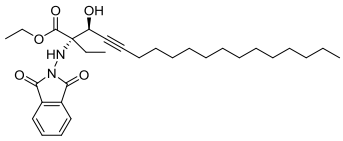
Ethyl [1-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-ethyl-3-(pentadec-1-yn-1-yl)aziridine]-2-carboxylate (3.128):



Compound **3.109** (1000.0 mg, 2.90 mmol) was treated with *N*-aminophthalimide (940.0 mg, 5.80 mmol) and (diacetoxi)iodobenzene (1400.0 mg, 4.35 mmol) following the general procedure for aziridination. After the work-up, the crude was purified by flash chromatography by using hexane/AcOEt (95:5) getting the aziridine **3.128** as a yellow oil

(1277.0 mg, 2.58 mmol, 89 %). IR (neat): 3337, 2923, 2853, 2360, 1718, 1466, 1377, 1301, 1237, 1153, 705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H, H_{ar}), 7.65 (dd, *J* = 5.5, 3.0 Hz, 2H, H_{ar}), 4.15 – 4.05 (m, 2H, $CH_3\underline{CH_2}O$), 4.01 (t, *J* = 1.8 Hz, 1H, H_3), 2.32 – 2.19 (m, 2H, H_6), 1.92 (dq, *J* = 14.6, 7.2 Hz, 2H, $CH_3\underline{CH_2}$), 1.59 – 1.47 (m, 2H, H_7), 1.44 – 1.33 (m, 2H, H_8), 1.33 – 1.22 (m, 21H, H_9 to H_{17}, $\underline{CH_3}CH_2O$), 1.19 (t, *J* = 7.2 Hz, 3H, $\underline{CH_3}CH_2$), 0.87 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C_1), 164.5 ($2xC_{ar}$), 134.1 ($2xC_{ar}$), 130.3 ($2xC_{ar}$), 123.1 ($2xC_{ar}$), 86.7 (C_5), 72.9 (C_4), 62.3 ($CH_3\underline{C}H_2O$), 54.1 (C_2), 43.7 (C_3), 32.1 (CH_2), 29,8 ($4xCH_2$), 29.7 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.0 (C_8), 28.5 (C_7), 23.6 ($CH_3\underline{C}H_2$), 22.8 (CH_2), 19.0 (C_6), 14.3 (C_{18}), 14.0 ($\underline{C}H_3CH_2O$), 9.8 ($\underline{C}H_3CH_2$). HR ESI-TOF MS for [M+H$^+$] $C_{30}H_{43}N_2O_4^+$ (m/z): 495.3217; found: 495.3218.

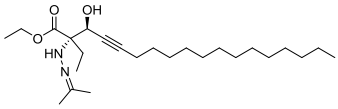
Ethyl 2-((1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)amino)-3-hydroxy-2-ethyloctadec-4-ynoate (3.136):



Compound **3.136** was prepared following the general procedure for the ring-opening aziridines, starting from **3.128** (310.7 mg, 0.628 mmol) and *p*-toluensulfonic acid (131.4 mg, 0.69 mmol). After the work-up, the crude was purified by flash chromatography by using hexane/AcOEt (from 90:10 to 80:20) to give a mixture of regioisomers (77:13). The desired product **3.136** was obtained as a yellow oil (122.4 mg, 0.23 mmol, 37 %). IR (neat): 3446, 3312, 2924, 2853, 2363, 1725, 1450, 1378, 1237 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H, H_{ar}), 7.76 (dd, *J* = 5.5, 3.1 Hz, 2H, H_{ar}), 5.66 (s, 1H, H_{NH}), 4.53 (s, 2H, H_3, H_{OH}), 4.35 – 4.17 (m, 2H, $CH_3\underline{CH_2}O$), 2.09 (t, *J*=7.0 Hz, 2H, H_6), 1.96 (dq, *J* = 14.8, 7.4 Hz, 1H, $CH_3\underline{CH_2}$), 1.63 (dq, *J* = 14.8, 7.4 Hz, 1H, $CH_3\underline{CH_2}$), 1.46 – 1.34 (m, 2H, H_7), 1.34 – 1.17 (m, 23H, H_8 to H_{17}, $\underline{CH_3}CH_2O$), 1.02 (t, *J* = 7.4 Hz, 3H, $\underline{CH_3}CH_2$), 0.86 (t, *J* = 6.6 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5 (C_1), 168.1 ($2xC_{ar}$), 134.7 ($2xC_{ar}$), 130.0 ($2xC_{ar}$), 123.8 ($2xC_{ar}$), 87.2 (C_5), 77.6 (C_4), 71.5 (C_2), 65.5 (C_3), 61.9 ($CH_3\underline{C}H_2O$), 32.0 (CH_2), 29.8 ($4xCH_2$), 29.7 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 28.6 (C_7), 24.7 ($CH_3\underline{C}H_2$), 22.8 (CH_2), 18.8 (C_6),

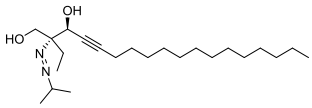
14.3 (C_{18}), 14.2 ($\underline{C}H_3CH_2O$), 8.3 ($\underline{C}H_3CH_2$). HR ESI-TOF MS for [M+H$^+$] $C_{30}H_{45}N_2O_5^+$ (m/z): 513.3323; found: 513.3324.

Ethyl 2-ethyl-3-hydroxy-2-(2-propan-2-ylidene)hydrazinyl)octadec-4-ynoate (3.143):



The reaction was performed as described in general procedure for synthesis of hydrazones starting from **3.136** (250.0 mg, 0.49 mmol) and methylhydrazine (38.5 µL, 0.73 mmol) in THF (3.7 mL). After filtration, the resulting crude was redissolved in 3 mL of acetone, strirred for 16 h and purified by flash chromatography using hexane/AcOEt (90:10) to accomplish **3.143** (139.3 mg, 0.32 mmol, 68 % over two steps) as a colorless oil. IR (neat): 3393, 2923, 2853, 2364, 1734, 1463, 1234, 1147, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (s, 1H, H_{NH}), 5.21 (d, *J* = 9.1 Hz, 1H, H_{OH}), 4.68 (dt, *J* = 9.1, 7.0 Hz, 1H, H_3), 4.28 – 4.16 (m, 2H, $CH_3\underline{CH_2}O$), 2.25 (dq, *J* = 14.9, 7.5 Hz, 1H, $CH_3\underline{CH_2}$), 2.16 (td, *J* = 7.0, 2.0 Hz, 2H, H_6), 1.98 – 1.85 (m, 4H, $CH_3\underline{CH_2}$, $(\underline{CH_3})_2C$), 1.82 (s, 3H, $(\underline{CH_3})_2C$), 1.53 – 1.38 (m, 2H, H_7), 1.37 – 1.19 (m, 23H, H_8 to H_{17}, $\underline{CH_3}CH_2O$), 0.86 (m, 6H, H_{18}, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 (C_1), 147.9 ($(CH_3)_2\underline{C}$), 87.0 (C_5), 78.3 (C_4), 69.7 (C_3), 69.3 (C_2), 61.5 ($CH_3\underline{C}H_2O$), 32.0 (CH_2), 29.8 (3xCH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.9 (CH_2, C_7), 26.3 ($CH_3\underline{CH_2}$), 25.5 ($(\underline{C}H_3)_2C$), 22.8 (CH_2), 18.9 (C_6), 15.7 ($(\underline{C}H_3)_2C$), 14.3 ($\underline{C}H_3CH_2O$, C_{18}), 8.41 ($\underline{C}H_3CH_2$). HR ESI-TOF MS for [M+H$^+$] $C_{25}H_{47}N_2O_3^+$ (m/z): 423.3581; found: 423.3691.

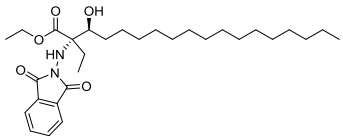
2-ethyl-2-(isopropyldiazenyl)octadec-4-yne-1,3-diol (3.152):



Hydrazone **3.143** (139.3 mg, 0.32 mmol) was treated with $NaBH_3CN$ (47.6 mg, 0.66 mmol) and AcOH (37.6 µL, 0.52 mmol) in THF (3.9 mL) following the procedure previously described for reduction of hydrazone and ester moieties. Once the hydrazones was reduced, the reaction mixture was filtered over celite and the solvent was removed. The resulting crude was redissolved in CH_2Cl_2 (0.83 mL) and the solution

was cooled at -40 °C before DIBAL (0.83 mL, 1M in dichloromethane, 0.83 mmol) was slowly added. The reaction was quenched and the crude was purified by using CH_2Cl_2/hexane (90:10) to give **3.152** (13.9 mg, 0.04 mmol, 11 % over two steps) as a yellowish oil. IR (neat): 3334, 3162, 2923, 2853, 2360, 2327, 1262, 1033, 746 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 4.80 (s, 1H, H_3), 3.96 (d, *J* = 11.6 Hz, 1H, H_1), 3.87 (d, *J* = 11.6 Hz, 1H, $H_{1'}$), 3.73 – 3.62 (m, 1H, $(CH_3)_2\underline{CH}$), 2.20 (t, *J* = 6.7 Hz, 2H, H_6), 1.93 (td, *J* = 15.0, 7.5 Hz, 1H, $CH_3\underline{CH_2}$), 1.81 (td, *J* = 15.0, 7.5 Hz, 1H, $CH_3\underline{CH_2}$), 1.57 – 1.19 (m, 28H, H_7 to H_{17}, $\underline{(CH_3)_2}CH$), 0.90 (t, *J* = 6.6 Hz, 3H, H_{18}), 0.81 (t, *J* = 7.5 Hz, 3H, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, MeOD) δ 86.2 (C_5), 78.4 (C_4), 75.6 (C_2), 68.5 ($(CH_3)_2\underline{C}H$), 65.0 (C_3), 62.6 (C_1), 31.7 (CH_2), 29.4 (CH_2), 29.3 (3xCH_2), 29.1 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 28.3 (C_8), 23.4 (C_7), 22.3 ($CH_3\underline{C}H_2$), 19.6 (CH_2), 19.5 ($\underline{(C}H_3)_2CH$), 18.0 (C_6), 13.0 ($\underline{C}H_3CH_2$), 6.2 (C_{18}). HR ESI-TOF MS for [M+Na^+] $C_{23}H_{44}N_2NaO_2^+$ (m/z): 403.3295; found: 403.3290.

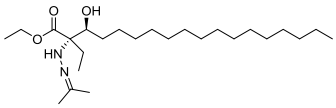
Ethyl 2-((1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)amino)-3-hydroxy -2-ethyloctadecanoate (3.170):



Compound **3.170** was synthesized following the general procedure described for over-reduction of alkynes starting from **3.136** (240.0 mg, 0.47 mmol), palladium on carbon (96.0 mg, 40 wt %) and hydrogen (2 bar). After stirring for 48 h at 40 °C, the reaction mixture was filtered and purified to afford **3.170** (189.9 mg, 0.37 mmol, 78 %) as a yellow oil. IR (neat): 3477, 3295, 2922, 2852, 2368, 1788, 1719, 1467, 1377, 1233, 1200 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H, H_{ar}), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H, H_{ar}), 5.75 (s, 1H, H_{NH}), 4.26 (qd, *J* = 7.1, 1.2 Hz, 2H, $CH_3\underline{CH_2}O$), 3.88 (d, *J* = 9.2 Hz, 1H, H_{OH}), 3.68 – 3.58 (m, 1H, H_3), 1.87 (dq, *J* = 14.6, 7.3 Hz, 1H, $CH_3\underline{CH_2}$), 1.77 – 1.56 (m, 2H, H_4), 1.50 (dq, *J* = 14.6, 7.3 Hz, 1H, $CH_3\underline{CH_2}$), 1.44 – 1.17 (m, 29H, H_5 to H_{17}, $\underline{CH_3}CH_2O$), 1.01 (t, *J* = 7.3 Hz, 3H, $\underline{CH_3}CH_2$), 0.86 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 (C_1), 168.4 (2xC_{ar}), 134.7 (2xC_{ar}), 130.1 (2xC_{ar}), 123.8 (2xC_{ar}), 74.0 (C_3), 71.9 (C_2), 61.8 ($CH_3\underline{C}H_2O$), 32.2 (CH_2), 32.1 (C_4),

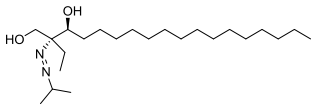
29.8 (9xCH_2), 29.50 (CH_2), 26.8 (CH_2), 24.2 (CH_2), 22.8 ($CH_3\underline{C}H_2$), 14.3 ($\underline{C}H_3CH_2O$, C_{18}), 8.5 ($\underline{C}H_3CH_2$). HR ESI-TOF MS for [M+H$^+$] $C_{30}H_{49}N_2O_5^+$ (m/z): 517.3636; found: 517.3641.

Ethyl -3-hydroxy-2-(2-(propan-2-ylidene)hydrazinyl) 2-ethyloctadecanoate (3.177):



The reaction was performed as described in general procedure for synthesis of hydrazones starting from **3.170** (168.7 mg, 0.33 mmol) and methylhydrazine (25.8 µL, 0.49 mmol) THF (2.4 mL). After filtration, the resulting crude was redissolved in 3 mL of acetone, stirred for 16 h and purified by flash chromatography using hexane/AcOEt (87:13) to accomplish **3.177** (118 mg, 0.28 mmol, 85 % over two steps) as a yellow oil. IR (neat): 3408, 2921, 2852, 2359, 2842, 1730, 1457, 1367, 1234, 1142 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (s, 1H, H_{NH}), 4.67 (bs, 1H, H_3), 4.20 (dq, *J* = 7.1, 2.8, 2H, $CH_3\underline{CH_2}O$), 3.87 (d, *J* = 9.7 Hz, 1H, H_{OH}), 2.18 (dq, *J* = 14.9, 7.5 Hz, 1H, $CH_3\underline{CH_2}$), 1.92 – 1.80 (m, 4H, $CH_3\underline{CH_2}$, $(\underline{CH_3})_2C$), 1.79 (s, 3H, $(\underline{CH_3})_2C$), 1.59 – 1.43 (m, 2H, H_4), 1.37 – 1.16 (m, 29H, H_5 to H_{17}, $\underline{CH_3}CH_2O$), 0.87 (t, *J* = 6.8 Hz, 3H, H_{18}), 0.76 (t, *J* = 7.4 Hz, 3H, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 (C_1), 146.2 ($(CH_3)_2\underline{C}$), 77.0 (C_3), 69.2 (C_2), 61.2 ($CH_3\underline{C}H_2O$), 33.6 (C_4), 32.1 (CH_2), 29.8 (9xCH_2), 29.5 (CH_2), 27.2 ($CH_3\underline{C}H_2$), 26.6 (CH_2), 25.6 ($(\underline{C}H_3)_2C$), 22.8 (CH_2), 15.3 ($(\underline{C}H_3)_2C$), 14.3 ($\underline{C}H_3CH_2O$, C_{18}), 8.0 ($\underline{C}H_3CH_2$). HR ESI-TOF MS for [M+H$^+$] $C_{25}H_{51}N_2O_3^+$ (m/z): 427.3894; found: 427.3883.

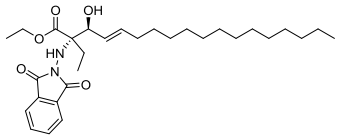
2-(isopropyldiazenyl)-2-ethyloctadecane-1,3-diol (3.181):



Hydrazone **3.177** (126.6 mg, 0.30 mmol) was treated with $NaBH_3CN$ (37.3 mg, 0.59 mmol) and AcOH (33.8 µL, 0.47 mmol) THF (3.4 mL) following the procedure previously described for reduction of hydrazone and ester moieties. Once the hydrazones was reduced, the reaction mixture was filtered over celite and the solvent was removed. The resulting crude was redissolved in CH_2Cl_2 (0.74 mL) and the solution was cooled at -40 °C before DIBAL (0.74 mL, 1 M in dichloromethane,

0.74 mmol) was slowly added. The reaction was quenched and the crude was purified by using hexane/AcOEt (95:5) to give **3.181** (11.1 mg, 0.03 mmol, 10 % over two steps) as a colorless oil. IR (neat): 3397, 2921, 2852, 2360, 2300, 1727, 1464, 1379, 1049 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 3.92 (dd, *J* = 10.3, 1.7 Hz, 1H, H_3), 3.80 (bs, 2H, H_1), 3.65 (dt, *J* = 13.0, 6.5 Hz, 1H, $(CH_3)_2\underline{CH}$), 1.91 – 1.74 (m, 2H, $CH_3\underline{CH_2}$), 1.51 (m, 2H, H_4), 1.44 – 1.17 (m, 32H, H_5 to $H_{17,}$ $(\underline{CH_3})_2CH$), 0.89 (t, *J* = 6.9 Hz, 3H, H_{18}), 0.78 (t, *J* = 7.5 Hz 3H, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, MeOD) δ 77.1 (C_2), 75.6 (C_3), 69.9 ($(CH_3)_2\underline{C}H$), 64.2 (C_1), 33.1 (CH_2), 32.3 (C_5), 30.8 ($8xCH_2$), 30.7 (CH_2), 30.5 (CH_2), 27.8 (CH_2), 24.0 (CH_2), 23.8 ($CH_3\underline{C}H_2$), 20.9 ($(\underline{C}H_3)_2CH$), 14.5 (C_{18}), 7.8 ($\underline{CH_3}CH_2$). HR ESI-TOF MS for [M+H⁺] $C_{23}H_{49}N_2O_2^+$ (m/z): 385.3789; found: 385.3793.

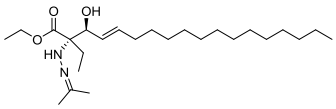
Ethyl (*E*)-2-((1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)amino)-3-hydroxy-2-ethyloctadec-4-enoate (3.175):



Compound **3.175** was prepared following the hydrosilylation/desilylation procedure catalyzed by [Ru] starting from alkyne **3.136** (400 mg, 0.88 mmol), $[Cp^*RuCl]_4$ (12.0 mg, 0.04 mmol) and $SiH(OEt)_3$ (0.29 mL, 1.57 mmol). After complete silylation, a suspension of AgF (167 mg, 0.013 mmol) in a mixture of THF/MeOH/H_2O (5.0:0.3:0.03 mL) was introduced into the schlenck and the mixture was stirred for 1.5 h in darkness at room temperature. The resulting crude was purified by flash chromatography using hexane/AcOEt (85:15) to afford **3.175** (283.1 mg, 0.55 mmol, 63%) as a yellow oil. IR (neat): 3448, 3299, 2922, 2852, 2770, 2367, 2324, 1730, 1465, 1371, 1224, 1108 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.5, 3.0 Hz, 2H, H_{ar}), 7.77 (dd, *J* = 5.5, 3.0 Hz, 2H, H_{ar}), 5.72 – 5.62 (m, 3H, H_4, $H_{5,}$ H_{NH}), 4.37 (bs, 1H, H_{OH}), 4.27 (q, *J* = 7.1 Hz, 2H, $\underline{C}H_3CH_2O$), 4.06 (bs, 1H, H_3), 2.11 – 1.95 (m, 2H, H_6), 1.85 (dq, *J* = 14.6, 7.3 Hz, 1H, $CH_3\underline{CH_2}$), 1.44 (dq, *J* = 14.6, 7.3 Hz, 1H, $CH_3\underline{CH_2}$), 1.36 – 1.19 (m, 25H, H_1, H_7 to H_{17}), 1.04 (t, *J* = 7.3 Hz, 3H, $\underline{CH_3}CH_2$), 0.87 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9 (C_1), 168.5 ($2xC_{ar}$), 135.4 (C_5), 134.8 ($2xC_{ar}$), 130.1 ($2xC_{ar}$), 127.7 (C_4), 123.9 ($2xC_{ar}$), 75.4

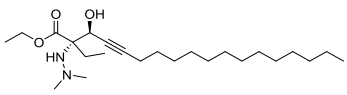
(C_3), 72.2 (C_2), 61.8 ($CH_3\underline{C}H_2O$), 32.5 (CH_2), 32.1 (C_6), 29.8 ($5xCH_2$), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 24.7 ($CH_3\underline{C}H_2$), 22.8 (CH_2), 14.3 ($\underline{C}H_3CH_2O$, C_{18}), 8.4 ($\underline{C}H_3CH_2$). HR ESI-TOF MS for [M+Na$^+$] $C_{30}H_{46}N_2NaO_5^+$ (m/z): 537.3299; found: 537.3300.

Ethyl (*E*)-3-hydroxy-2-(2-(propan-2-ylidene)hydrazinyl)-2-ethyloctadec-4-enoate (3.179):



The reaction was performed as described in general procedure for synthesis of hydrazones starting from **3.175** (247.0 mg, 0.48 mmol) and methylhydrazine (37.9 µL, 0.72 mmol) in 3.5 mL of THF. After filtration, the resulting crude was redissolved in 3.0 mL of acetone, stirred for 16 h and purified by flash chromatography using hexane/AcOEt (90:10) to accomplish **3.179** (165.3 mg, 0.39 mmol, 81 % over two steps) as a colorless oil. IR (neat): 3372, 3325, 2922, 2853, 2354, 2312, 1731, 1463, 1367, 1234, 1142 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 – 5.59 (m, 1H, H_5), 5.54 (dd, *J* = 15.3, 7.4 Hz, 1H, H_4), 5.48 (bs, 1H, H_{NH}), 5.09 (bs, 1H, H_{OH}), 4.35 (d, *J* = 7.4 Hz, 1H, H_3), 4.19 (q, *J* = 7.1 Hz, 2H, $CH_3\underline{CH_2}O$), 2.13 (td, *J* = 14.8, 7.4 Hz, 1H, $CH_3\underline{CH_2}$), 2.06 – 1.95 (m, 2H, H_6), 1.92 (s, 3H, $(\underline{CH_3})_2C$), 1.90 – 1.82 (m, 1H, $CH_3\underline{CH_2}$), 1.79 (s, 3H, $(\underline{CH_3})_2C$), 1.39 – 1.17 (m, 25H, $\underline{CH_3}CH_2O$, H_7 to H_{17}), 0.87 (t, *J* = 6.8 Hz, 3H, H_{18}), 0.79 (t, *J* = 7.4 Hz, 3H, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 (C_1), 146.4 (C_{23}), 134.2 (C_7), 128.8 (C_6), 78.6 (C_5), 69.3 (C_4), 61.1 (C_2), 32.4 (CH_2), 32.0 ($(CH_3)_2\underline{C}$), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.9 ($CH_3\underline{C}H_2$), 25.4 ($(\underline{C}H_3)_2C$), 22.7 (CH_2), 15.3 ($(\underline{C}H_3)_2C$), 14.3 ($\underline{C}H_3CH_2O$), 14.2 (C_{18}), 8.0 ($\underline{C}H_3CH_2$). HR ESI-TOF MS for [M+Na$^+$] $C_{25}H_{48}N_2NaO_3^+$ (m/z): 447.3557; found: 447.3555.

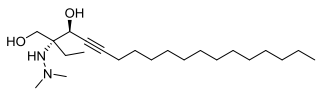
Ethyl 2-(2,2-dimethylhydrazinyl)-3-hydroxy-2-ethyloctadec-4-ynoate (3.163):



The reaction was carried out as described in general procedure for synthesis of dimethyl hydrazines starting from **3.136** (145.0 mg, 0.28 mmol) and methylhydrazine (22.3 µL, 0.42 mmol) THF (2.1 mL). After filtration, the

resulting crude was redissolved in 7.8 mL of MeOH and paraformaldehyde (34.0 mg, 1.13 mmol) was added. The reaction mixture was cooled at 0 °C and $NaBH_3CN$ (35.6 mg, 0.57 mmol) was added. The temperature was allowed to warm to room temperature and the solution was stirred for 48 h. The crude was purified by flash chromatography using hexane/AcOEt (95:5) to give **3.163** (43.5 mg, 0.11 mmol, 35 % over two steps) as yellowish oil. IR (neat): 3437, 2923, 2853, 2360, 1735, 1457, 1374, 1231, 1025 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 4.57 (s, 1H, H_3), 4.24 – 4.10 (m, 2H, $CH_3\underline{CH_2}O$), 2.49 (s, 6H, $N(\underline{CH_3})_2$), 2.30 – 2.14 (m, 2H, H_6), 1.99 – 1.90 (m, 2H, $CH_3\underline{CH_2}$), 1.57 – 1.20 (m, 25H, H_7 to H_{17}, $\underline{CH_3}CH_2O$), 0.97 – 0.84 (m, 6H, H_{18}, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, MeOD) δ 173.5 (C_1), 87.9 (C_5), 79.8 (C_4), 71.2 (C_2), 68.1 (C_3), 62.0 ($CH_3\underline{C}H_2O$), 50.2 ($N(\underline{C}H_3)_2$), 33.1 (CH_2), 30.8 (5xCH_2), 30.5 (CH_2), 30.3 (CH_2), 29.9 (C_8), 29.7 (C_7), 26.2 (CH_2), 23.8 ($CH_3\underline{C}H_2$), 19.4 (C_6), 14.6 ($\underline{C}H_3CH_2O$), 14.5 (C_{18}), 8.7 ($\underline{C}H_3CH_2$). HR ESI-TOF MS for [M+H^+] $C_{24}H_{47}N_2O_3^+$ (m/z): 411.3581; found: 411.3588.

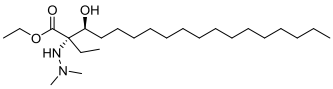
2-(2,2-dimethylhydrazinyl)-2-ethyloctadec-4-yne-1,3-diol (3.167):



Dimethyl hydrazine **3.163** (45.5 mg, 0.11 mmol) was treated with a solution of DIBAL (0.28 mL, 1 M in dichloromethane, 0.28 mmol) in CH_2Cl_2 (0.28 mL) at -40 °C according to the procedure described for reduction of ester moieties. The crude was purified by silica gel chromatography using $CHCl_3$:MeOH:NH_4OH (99.5:0.5:0.1) to accomplish the sphingosine derivative **3.167** (17.6 mg, 0.05 mmol, 43 %) as a yellow oil. IR (neat): 3305, 2923, 2853, 2775, 2358, 2320, 1464, 1045 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 4.54 (t, *J* = 2.1 Hz, 1H, H_3), 3.80 (d, *J* = 11.0 Hz, 1H, H_1), 3.65 (d, *J* = 11.0 Hz, 1H, $H_{1'}$), 2.51 (s, 6H, $N(\underline{CH_3})_2$), 2.26 (td, *J* = 6.8, 2.1 Hz, 2H, H_6), 1.68 – 1.38 (m, 6H, H_7, H_8, $CH_3\underline{CH_2}$), 1.31 (bs, 19H, H_9 to H_{17}), 0.97 – 0.88 (m, 6H, H_{18}, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, MeOD) δ 87.9 (C_5), 80.1 (C_4), 67.6 (C_2), 64.7 (C_3), 63.7 (C_1), 50.5 ($N(\underline{C}H_3)_2$), 33.1 (CH_2), 30.8 (5xCH_2), 30.7 (CH_2), 30.5 (CH_2), 30.3 (CH_2), 29.9 (C_8), 29.8 (C_7), 25.1 (CH_2), 23.8 ($CH_3\underline{C}H_2$), 19.4 (C_6), 14.5 (C_{18}), 7.8 ($\underline{C}H_3CH_2$).

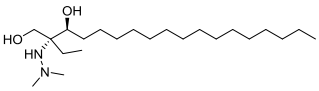
HR ESI-TOF MS for $[M+H^+]$ $C_{22}H_{45}N_2O_2^+$ (m/z): 369.3476; found: 369.3475.

Ethyl 2-(2,2-dimethylhydrazinyl)-3-hydroxy-2-ethyloctadecanoate (3.186):



The reaction was carried out following the general procedure for the synthesis of dimethyl hydrazines starting from **3.170** (183.3 mg, 0.36 mmol) and methylhydrazine (28.2 μL, 0.54 mmol) in 2.7 mL of THF. After filtration, the resulting crude was redissolved in 9.8 mL of MeOH and paraformaldehyde (42.6 mg, 1.42 mmol) was added. The reaction mixture was cooled at 0 °C and $NaBH_3CN$ (44.6 mg, 0.71 mmol) was added. The temperature was allowed to warm to room temperature and the solution was stirred for 48 h. The crude was purified by flash chromatography using hexane/Et_2O (87:13) to give **3.186** (54.3 mg, 0.13 mmol, 37 % over two steps) as a yellow oil. IR (neat): 3368, 2923, 2852, 2773, 2365, 2327, 1466, 1276, 1054 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 – 3.98 (m, 2H, $CH_3\underline{CH_2}O$), 3.76 (dd, *J* = 10.2, 1.9 Hz, 1H, H_3), 2.48 (s, 6H, $N(\underline{CH_3})_2$), 2.03 – 1.71 (m, 2H, $CH_3\underline{CH_2}$), 1.64 – 1.42 (m, 2H, H_4), 1.35 – 1.08 (m, 29H, H_5 to H_{17}, $\underline{CH_3}CH_2O$), 0.93 – 0.74 (m, 6H, H_{18}, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 (C_1), 76.3 (C_3), 69.4 (C_2), 60.9 ($CH_3\underline{C}H_2O$), 50.3 ($N(\underline{C}H_3)_2$), 33.3 (CH_2), 32.0 (CH_2), 29.8 (7xCH_2), 29.7 (2xCH_2), 29.5 (CH_2), 26.8 ($CH_3\underline{C}H_2$), 26.4 (CH_2), 22.8 (C_4), 14.3 ($\underline{C}H_3CH_2O$), 14.2 (C_{18}), 8.0 ($\underline{C}H_3CH_2$). HR ESI-TOF MS for $[M+H^+]$ $C_{24}H_{51}N_2O_3^+$ (m/z): 415.3894; found: 415.3882.

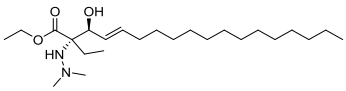
2-(2,2-dimethylhydrazinyl)-2-ethyloctadecane-1,3-diol (3.188):



Dimethyl hydrazine **3.186** (54.3 mg, 0.13 mmol) was treated with a solution of DIBAL (0.33 mL, 1 M in dichloromethane, 0.33 mmol) in CH_2Cl_2 (0.33 mL) at -40 °C according to the procedure described for reduction of ester moieties. The crude was purified by silica gel chromatography using hexane/AcOEt (60:40) to accomplish the sphingosine derivative **3.188** (44.6 mg, 0.12 mmol, 91 %) as a yellowish oil. IR (neat): 3368,

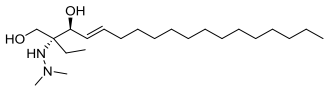
2923, 2852, 2773, 2365, 2326, 1465, 1054, 749 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 3.70 (d, *J* = 10.9 Hz, 1H, H_1), 3.60 (dd, *J* = 10.3, 1.5 Hz, 1H, H_3), 3.53 (d, *J* = 10.9 Hz, 1H, $H_{1'}$), 2.46 (s, 6H, $N(\underline{CH_3})_2$), 1.66 – 1.40 (m, 4H, H_4, $CH_3\underline{CH_2}$), 1.40 – 1.22 (m, 26H, H_5 to H_{17}), 0.92 – 0.79 (m, 6H, H_{18}, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, MeOD) δ 76.0 (C_3), 64.2 (C_2), 63.2 (C_1), 50.5 ($N(\underline{C}H_3)_2$), 33.1 (CH_2), 32.4 (CH_2), 30.8 ($9xCH_2$), 30.5 (CH_2), 27.9 ($CH_3\underline{C}H_2$), 25.3 (C_4), 23.8 (CH_2), 14.5 (C_{18}), 7.7 ($\underline{C}H_3CH_2$). HR ESI-TOF MS for $[M+H^+]$ $C_{22}H_{49}N_2O_2^+$ (m/z): 373.3789; found: 373.3782.

Ethyl (*E*)-2-(2,2-dimethylhydrazinyl) -3-hydroxy-2-ethyloctadec-4-enoate (3.187):



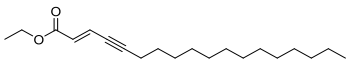
The reaction was carried out following the general procedure for the synthesis of dimethyl hydrazines starting from the corresponding ring-opened substrate **3.175** (169.1 mg, 0.33 mmol) and methylhydrazine (25.8 µL, 0.49 mmol) in 2.4 mL of THF. After filtration, the resulting crude was redissolved in 9.0 mL of MeOH and paraformaldehyde (39.4 mg, 1.31 mmol) was added. The reaction mixture was cooled at 0 °C and $NaBH_3CN$ (41.2 mg, 0.66 mmol) was added. The temperature was allowed to warm to room temperature and the solution was stirred for 48 h. The crude was purified by flash chromatography using hexane/Et_2O (80:20) to give **3.187** (46.8 mg, 0.11 mmol, 35 % over two steps) as a yellow oil. IR (neat): 3450, 3387, 2954, 2853, 2366, 1731, 1465, 1225, 1024 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 – 5.49 (m, 2H, H_4, H_5), 4.27 (d, *J* = 6.8 Hz, 1H, H_3), 4.16 (q, *J* = 7.1 Hz, 2H, $CH_3\underline{CH_2}O$), 2.50 (s, 6H, $N(\underline{CH_3})_2$), 2.03 (ddd, *J* = 13.8, 6.8, 3.0 Hz, 2H, H_6), 1.84 (qd, *J* = 14.3, 7.4 Hz, 2H, $CH_3\underline{CH_2}$), 1.36 – 1.17 (m, 25H, $\underline{CH_3}CH_2O$, H_6 to H_{17}), 0.90 – 0.81 (m, 6H, H_{18}, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6 (C_1), 134.5 (C_5), 129.0 (C_4), 78.0 (C_3), 69.7 (C_2), 61.0 ($CH_3\underline{C}H_2O$), 50.3 ($N(\underline{C}H_3)_2$), 32.6 (CH_2), 32.0 (C_6), 29.8 ($5xCH_2$), 29.6 (CH_2), 29.5 (CH_2), 29.3 ($2xCH_2$), 26.7 ($CH_3\underline{C}H_2$), 22.8 (CH_2), 14.3 ($\underline{C}H_3CH_2O$, C_{18}), 8.1 ($\underline{C}H_3CH_2$). HR ESI-TOF MS for $[M+H^+]$ $C_{24}H_{49}N_2O_3^+$ (m/z): 413.3738; found: 413.3757.

(*E*)-2-(2,2-dimethylhydrazinyl)-2ethyloctadec-4-ene-1,3-diol (3.189):



Dimethyl hydrazine **3.187** (28.0 mg, 0.07 mmol) was treated with a solution of DIBAL (0.16 mL, 1M in dichloromethane, 0.16 mmol) in CH_2Cl_2 (0.16 mL) at -40 °C according to the procedure described for reduction of ester moieties. The crude was purified by silica gel chromatography using hexane/AcOEt (80:20) to accomplish the sphingosine derivative **3.189** (16.2 mg, 0.05 mmol, 67 %) as a yellowish oil. IR (neat): 3362, 3266, 2921, 2852, 2358, 2342, 1464, 1260, 1100, 1024, 802, 970 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 5.69 (dt, *J* = 15.3, 6.8 Hz, 1H, H_5), 5.57 (ddt, *J* = 15.3, 7.5, 1.1 Hz, 1H, H_4), 4.10 (d, *J* = 7.5 Hz, 1H, H_3), 3.66 (d, *J* = 11.1 Hz, 1H, H_1), 3.48 (d, *J* = 11.1 Hz, 1H, $H_{1'}$), 2.49 (s, 6H, $N(\underline{CH_3})_2$), 2.06 (dd, *J* = 14.0, 6.8 Hz, 2H, H_6), 1.61 – 1.49 (m, 2H, $CH_3\underline{CH_2}$), 1.44 – 1.22 (m, 22H, H_7 to H_{17}), 0.89 (t, *J* = 7.1, Hz, 3H, H_{18}), 0.88 (t, *J* = 7.5, Hz, 3H, $\underline{CH_3}CH_2$). ^{13}C NMR (100 MHz, MeOD) δ 134.8 (C_5), 130.0 (C_4), 77.3 (C_3), 64.0 (C_2), 63.2 (C_1), 50.4 ($N(\underline{C}H_3)_2$), 33.4 (CH_2), 33.1 (C_6), 30.8 (CH_2), 30.6 (6xCH_2), 30.5 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 25.3 ($CH_3\underline{C}H_2$), 23.8 (CH_2), 14.5 (C_{18}), 7.9 ($\underline{C}H_3CH_2$). HR ESI-TOF MS for $[M+H^+]$ $C_{22}H_{47}N_2O_2^+$ (m/z): 371.3632; found: 371.3634.

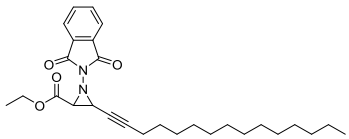
Ethyl *(E)*-octadec-2-ene-4-ynoate (3.105):



The reaction was performed as described in general procedure 1.2.1. by using 1-pentadecyne (1.89 mL, 7.20 mmol) and triethyl phosphonoacetate (1.6 mL, 8.1 mmol) to afford a mixture of two esteroisomers *cis/trans* (1:6.5). The *trans* product **3.105** was achieved (1278.1 mg, 4.17 mmol, 58 % over two steps) as a yellowish oil. IR (neat): 2922, 2853, 2358, 2214, 1716, 1619, 1465, 1299, 1155, 1035, 630 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (dt, *J* = 15.8, 2.2 Hz, 1H, H_3), 6.12 (d, *J* = 15.8 Hz, 1H, H_2), 4.19 (q, *J* = 7.1 Hz, 2H, $CH_3\underline{CH_2}O$), 2.35 (td, *J* = 7.0, 2.2 Hz, 2H, H_6), 1.66 – 1.46 (m, 2H, H_7), 1.43 – 1.32 (m, 2H, H_8), 1.32 – 1.17 (m, 21H, H_9 to H_{17}, $\underline{CH_3}CH_2O$), 0.87 (t, *J* = 6.8 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3 (C_1), 129.4 (C_3), 126.3 (C_2), 101.0 (C_5), 78.0 (C_4), 60.7 ($CH_3\underline{C}H_2O$),

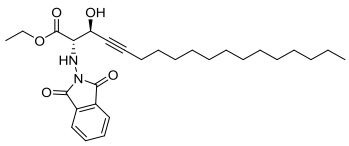
32.1 (CH_2), 29.8 (4xCH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.5 (C_8), 22.8 (C_7), 19.9 (C_6), 14.4 ($\underline{C}H_3CH_2O$), 14.3 (C_{18}). HR ESI-TOF MS for [M+Na$^+$] $C_{20}H_{34}NaO_2^+$ (m/z): 329.2457; found: 329.2458.

Ethyl [1-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)- 3-(pentadec-1-yn-1-yl)aziridine]-2-carboxylate (3.127):



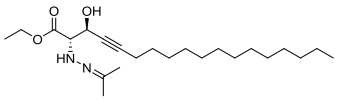
Compound **3.105** (1278.1 mg, 4.17 mmol) was treated with *N*-aminophthalimide (1352.0 mg, 8.34 mmol) and (diacetoxi)iodobenzene (2014.0 mg, 6.26 mmol) following the general procedure for aziridination. After the work-up, the crude was purified by flash chromatography by using hexane/AcOEt (95:5) to afford **3.127** as a mixture of invertomers (78:22) (1128.6 mg, 2.41 mmol, 88 %) as a white solid. m.p. 63 °C. IR (neat): 2924, 2853, 2360, 2290, 1724, 1373, 1222, 1190, 891, 708, 632 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (major, dd, *J* = 5.5, 3.0 Hz, 1.56H, H_{ar}), 7.75 (minor, dd, *J* = 5.5, 3.0 Hz, 0.44H, H_{ar}), 7.70 (major, dd, *J* = 5.5, 3.0 Hz, 1.56 H, H_{ar}), 7.66 (minor, dd, *J* = 5.5, 3.0 Hz, 0.44H, H_{ar}), 4.34 – 4.23 (major, m, 1.56H, $CH_3\underline{CH_2}O$), 4.13 (minor, q, *J* = 7.1 Hz, 0.44H, $CH_3\underline{CH_2}O$'), 3.94 (major, d, *J* = 4.8 Hz, 0.78H, H_2), 3.79 (minor, dt, *J* = 4.9, 1.8 Hz, 0.22H, H_3), 3.42 (major, dt, *J* = 4.8, 1.9 Hz, 0.78H, $H_{3'}$), 3.35 (minor, d, *J* = 4.9 Hz, 0.22H, $H_{2'}$), 2.22 (minor, td, *J* = 7.1, 1.8 Hz, 0.44H, $H_{6'}$), 2.01 (major, tt, *J* = 6.9, 1.9 Hz, 1.56H, H_6), 1.50 (minor, m, 0.44H, $H_{7'}$), 1.43 – 0.93 (m, 35H, H_7 to H_{17}, H_1, $H_{6'}$ to $H_{17'}$, $\underline{CH_3}CH_2O$'), 0.86 (m, 4H, H_{18}, $H_{18'}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6 (C_1), 165.4 ($C_{1'}$), 164.6 (2xC_{ar}), 164.3 (2x$C_{ar'}$), 134.2 (2xC_{ar}), 134.1 (2x$C_{ar'}$), 130.1 (4xC_{ar}), 123.2 (4xC_{ar}), 87.7 (C_5), 85.3 ($C_{5'}$), 73.9 ($C_{4'}$), 71.9 (C_4), 62.2 ($CH_3\underline{C}H_2O$'), 62.1 ($CH_3\underline{C}H_2O$), 45.7 (C_2), 45.5 ($C_{2'}$), 37.3 ($C_{3'}$), 37.1 (C_3), 31.9 (CH_2), 29.7 (2xCH_2, 2x$CH_{2'}$), 29.6 (4xCH_2, 5x$CH_{2'}$), 29.5 ($CH_{2'}$), 29.4 (CH_2), 29.1 ($CH_{2'}$), 29.0 (CH_2), 28.9 ($CH_{2'}$), 28.6 (CH_2), 28.2 ($CH_{2'}$), 28.0 (C_7), 22.7 (CH_2), 18.8 ($\underline{C}H_3CH_2O$'), 18.6 ($\underline{C}H_3CH_2O$), 14.1 (C_{18}), 13.9 ($C_{18'}$). HR ESI-TOF MS for [M+Na$^+$] $C_{28}H_{38}N_2NaO_4^+$ (m/z): 489.2724; found: 489.2728.

Ethyl 2-((1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)amino)-3-hydroxy-octadec-4-ynoate (3.135):



Compound **3.135** was prepared following the general procedure for the ring-opening aziridines, starting from **3.127** (750.0 mg, 1.61 mmol) and *p*-toluensulfonic acid (336.0 mg, 1.77 mmol). After the work-up, the crude was purified by flash chromatography by using hexane/AcOEt (form 90:10 to 80:20) to give a mixture of regioisomers (84:16). The desired product **3.135** was obtained (351.1 mg, 0.72 mmol, 45 %) as a yellow solid. m.p. 83 °C. IR (neat): 3444, 3242, 2922, 2852, 2359, 2341, 1746, 1709, 1465, 1200 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H, H_{ar}), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H, H_{ar}), 5.55 (d, *J* = 4.32 Hz, 1H, H_{NH}), 4.69 (ddt, *J* = 11.2, 4.1, 2.0 Hz, 1H, H_3), 4.40 – 4.21 (m, 2H, $CH_3\underline{CH_2}O$), 4.08 (d, *J* = 11.2 Hz, 1H, H_{OH}), 3.77 (t, *J* = 4.2 Hz, 1H, H_2), 2.18 (td, *J* = 7.1, 2.0 Hz, 2H, H_6), 1.55 – 1.40 (m, 2H, H_7), 1.39 – 1.15 (m, 23H, H_8 to H_{17}, $\underline{CH_3}CH_2O$), 0.87 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0 (C_1), 166.9 ($2xC_{ar}$), 134.7 ($2xC_{ar}$), 130.0 ($2xC_{ar}$), 123.9 ($2xC_{ar}$), 87.6 (C_5), 76.6 (C_4), 68.4 (C_2), 63.2 (C_3), 62.3 ($CH_3\underline{C}H_2O$), 32.1 (CH_2), 29.8 ($4xCH_2$), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 28.6 (C_7), 22.8 (CH_2), 18.8 (C_6), 14.3 ($\underline{C}H_3CH_2O$, C_{18}). HR ESI-TOF MS for $[M+Na^+]$ $C_{28}H_{40}N_2NaO_5^+$ (m/z): 507.2829; found: 507.2834.

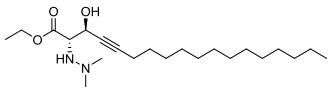
Ethyl -3-hydroxy-2-(2-(propan-2-ylidene)hydrazinyl) 3-hydroxyoctadec-4-ynoate (3.141):



The reaction was carried out following the general procedure for the synthesis of hydrazone starting from **3.135** (161.4 mg, 0.33 mmol) and methylhydrazine (26.3 µL, 0.50 mmol) in THF (2.5 mL). After filtration, the resulting crude was redissolved in 3 mL of acetone and the reaction was stirred until complete consumption of starting material. The crude was purified by flash chromatography using hexane/AcOEt (90:10 to 80:20) to give **3.141** (109.2 mg, 0.276 mmol, 83 % over two steps) as a yellowish oil. IR (neat): 3433 2923, 2854,

2366, 1740, 1466, 1371, 1194, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 (d, *J* = 8.8 Hz, 1H, H_{NH}), 4.76 (bs, 1H, H_3), 4.31 – 4.12 (m, 3H, H_2, $CH_3\underline{CH_2}O$), 3.69 (bs, 1H, H_{OH}), 2.17 (td, *J* = 7.0, 1.8 Hz, 2H, H_6), 1.92 (s, 3H, $(\underline{CH_3})_2C$), 1.84 (s, 3H, $(\underline{CH_3})_2C$), 1.53 – 1.40 (m, 2H, H_7), 1.38 – 1.21 (m, 23H, H_8 to H_{17}, $\underline{CH_3}CH_2O$), 0.87 (t, *J* = 6.8 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (C_1), 149.9 ($(CH_3)_2\underline{C}$), 87.7 (C_5), 77.0 (C_4), 66.6 (C_2), 63.5 (C_3), 61.5 ($CH_3\underline{C}H_2O$), 32.1 (CH_2), 29.8 (CH_2), 29.7 (4xCH_2), 29.5 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 25.4 ($(\underline{C}H_3)_2C$), 22.8 (CH_2), 18.8 (C_6), 16.0 ($(\underline{C}H_3)_2C$), 14.3 (C_{18}, $\underline{C}H_3CH_2O$). HR ESI-TOF MS for [M+H^+] $C_{23}H_{43}N_2O_3^+$ (m/z): 395.3274; found: 395.3257.

Ethyl 2-(2,2-dimethylhydrazinyl)-3-hydroxyoctadec-4-ynoate (3.160):



The reaction was carried out following the general procedure for the synthesis of dimethyl hydrazines starting from **3.135** (161.4 mg, 0.33 mmol) and methylhydrazine (26.3 µL, 0.50 mmol) in THF (2.5 mL). After filtration, the resulting crude was redissolved in 8.9 mL of MeOH and paraformaldehyde (48.5 mg, 1.61 mmol) was added to the solution mixture. The reaction mixture was cooled at 0 °C and $NaBH_3CN$ (121.8 mg, 1.96 mmol) was added. The temperature was allowed to warm to room temperature and the solution was stirred for 48 h. The crude was purified by flash chromatography using hexane/AcOEt (from 95:5 to 80:20) to give **3.160** (25.2 mg, 0.07 mmol, 20 % over two steps) as a yellowish oil. IR (neat): 3315, 2923, 2853, 2363, 2328, 1735, 1645, 1457, 1027 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.79 (dt, *J* = 3.9, 2.0 Hz, 1H, H_3), 4.31 – 4.15 (m, 2H, $CH_3\underline{CH_2}O$), 3.89 (d, *J* = 3.9 Hz, 1H, H_2), 2.51 (s, 6H, $N(\underline{CH_3})_2$), 2.20 (td, *J* = 7.1, 2.0 Hz, 2H, H_6), 1.54 – 1.42 (m, 2H, H_7), 1.40 – 1.20 (m, 23H, H_8 to H_{17}, $\underline{CH_3}CH_2O$), 0.89 (t, *J* = 6.9 Hz, 3H, H_{18}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C_1), 87.1 (C_5), 77.6 (C_4), 64.5 (C_3), 63.9 (C_2), 61.6 ($CH_3\underline{C}H_2O$), 47.8 ($N(\underline{C}H_3)_2$), 32.1 (CH_2), 29.8 (5xCH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (C_8), 29.0 (C_7), 28.8 (CH_2), 22.8 (C_6), 18.9 ($\underline{C}H_3CH_2O$), 14.3 (C_{18}). HR ESI-TOF MS for [M+H^+] $C_{22}H_{43}N_2O_3^+$ (m/z): 383.6238; found: 383.6254.

3.5.4. Computational details.

Docking was carried out using the software Maestro "molecular modeling interface", Version 3.2.017, Release 2015-4, Platform Linux-x86_64 created by Schrödinger®.

For the protein preparation hydrogen atoms were added (removing the originals). The missing side chains and missing loops were filled using Prime and other subunits different from A were deleted. The best protonation state at pH 7 were set using PROPKA (pK_a predictor). The waters molecules were removed and the structure were minimized. Other parameters were set as default. To increase the reliability of the results of the structure of each crystal data from PDB, the proteins (3VZB, 3VZC, 3VZD, 4L02, 4V24) were aligned using the default parameters of the task "Protein Structure Alignment". After the alignment of the proteins, the process for docking procedure was continued.

The receptor grid generation was constructed by identifying the co-crystallized ligand in the receptor; the size of the enclosing box was similar in size to the binding site and other parameters was set as default.

The files used for ligand preparation was .smi. The ligand docking was performed with all the parameters set to their default values based on characterization of the binding pocket. It was chosen to write out at most 32 poses per ligand (32 poses per ligand included). All the parameters for the docking run were set to their default values, and the GlideScore was employed for ranking the molecules.

To validate the RMSD valued in was compared the values obtained using the interface of the software (Ligand docking→core) using core comparison, otherwise, it was used the script: "$SCHRODINGER/run rmsd.py -m a.sdf b.sdf -c output.csv." in where a is the crystallized ligand and b the ligand prepare from .smi files.

The top-ranked docking conformations were determined using GlideScore values with help of the ligand interaction diagram. After self-docking and cross-docking, the protein used for the docking of new proposed ligands was the 3VZD grid.

3.5.5. Biological evaluation protocol.

In order to quantify the inhibitory activity of synthesized compounds, Adapta™ Universal Kinase Assay (Invitrogen, Carlsbad, CA, USA) was used. Inhibitors were dissolved in 100% DMSO at a final concentration of 50 mM (100 x solution). Several dilutions were performed at 20, 15, 10, 8, 6, 4, 2, 1 and 0.5 mM also in DMSO. Compounds were then pre-diluted to 4x in 1x Kinase Buffer A provided in the kit and plated in Corning white round-bottom 384 microplates. Each sample was analyzed in triplicate. The assay was performed following strictly the indications provided by the manufacturer. SphK1 and SphK2 were used at final concentrations of 0.025 ng/µl and 0.8 ng/µl. ATP present in the reaction was at 1µM and sphingosine at 5 µM. The reaction was stopped after 60 minutes of reaction with 10 mM EDTA, 3.6 nM ADP tracer and 2 nM anti-ADP antibody.

TR-FRET was read after 30 minutes in a CLARIOstar microplate reader (BMG Labtech, Biogen Científica SL, Madrid, Spain) using the following parameters: Ex = 340 nm; Em1 = 620/10; Em2 = 665/10; delay = 100 µs; integration time = 200 µs; Focal height = 11 mm. All steps were developed at room temperature.

Results of each condition were calculated as ratio EM_{665nm}/EM_{620nm} and expressed as % of inhibition using the following expression:

$$\%\ inhibition = \frac{(Ratio_{SAMPLE} - Ratio_{0\%\ INHIBITION})}{(Ratio_{100\%\ INHIBITION} - Ratio_{0\%\ INHIBITION})} \cdot 100$$

IC_{50} of each compound was calculated fitting the data to a sigmoidal dose-response curve with variable slope.

The 0 % of inhibition value is obtained from an inhibitor-less well plate. By contrast, the 100 % value is obtained from a saturated concentration well plate (kinase-less experiment).

3.6. REFERENCES.

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CHAPTER 4

Synthesis of β-fluoroamines mediated by ring-opening of aziridines

UNIVERSITAT ROVIRA I VIRGILI
NOVEL STRATEGIES FOR THE SYNTHESES OF SPHINGOSINE KINASE INHIBITORS, B-FLUOROAMINES AND ENANTIOENRICHED ALLENES
Macarena Corro Morón

4.1. INTRODUCTION

The incorporation of fluorine into molecules to generate organofluorinated compounds leads to important changes in their physical, chemical and biological properties.[1] These changes are often produced by the replacement of hydrogen by fluorine although exchanges by oxygen also occur. Actually, the van der Waals radius of C-F bond (1.41 Å) falls between C-O bond (1.43 Å) and C-H (1.09 Å), making it a versatile element for bioisosteric replacement.[2] Thus, it is no wonder that fluorinated compounds have great relevance in pharmaceutical, agrochemical or medicinal investigations.[3]

Among different fluoroamine units, the β-fluoroamine motif is especially remarkable in medicinal chemistry.[3b] The electron-withdrawing β-fluoro group is able to decrease the pK_a of the amine, improving the bioavailability and increasing the blood-brain barrier penetration.[4] Furthermore, the β-fluoroamine moiety is also involved in improvements in metabolic stability and binding affinity, thereby constituting an important building block in drugs with anticancer,[5] anticholinergic and anti-inflammatory properties[6] besides in therapeutic β-peptides.[7]

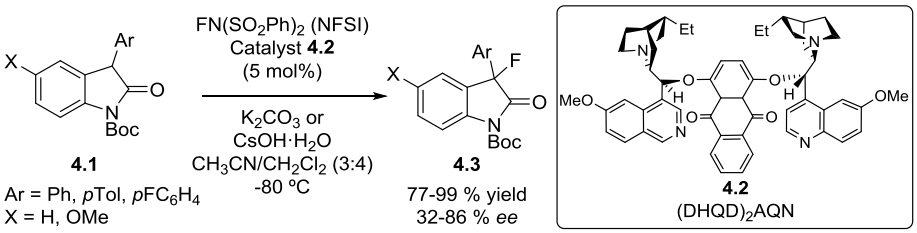
In this sense, the interest in preparing new compounds possessing this scaffold in their structures has increased during the last years. As a result, a variety of achiral and chiral approaches have been reported.

4.1.1. Approaches in the syntheses of vicinal fluoroamine motives.

4.1.1.1. *Organocatalytic syntheses of β-fluoroamines*.

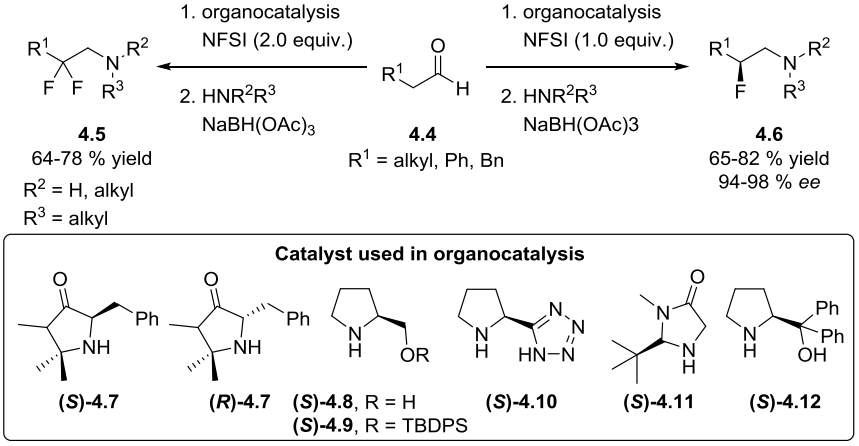
Organocatalysis has emerged as an important resource in the synthesis of β-fluoroamine moiety. In fact, this unit is easily accessible through different methods that rely on the α-fluorination of carbonyl compounds through their enol form or one-pot α-fluorination/reductive amination protocols.

In 2008, Shibata described the enantioselective fluorination of oxindoles **4.1** with *N*-fluorobenzenesulfonimide (NFSI) (Scheme 4.1).[8] 3-Fluoroindoles **4.3** were afforded in good to excellent yields and moderate to excellent enantioselectivity.



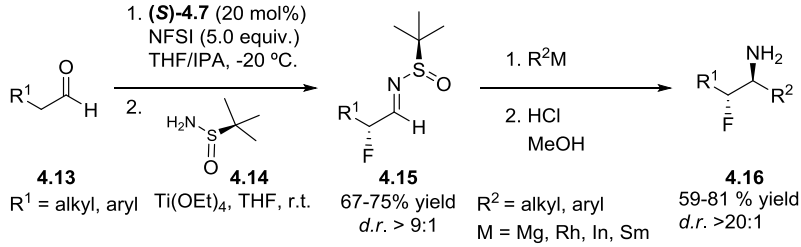
Scheme 4.1. Enantioselective synthesis of fluoroamines with the chiral catalyst $(DHQD)_2AQN$ (**4.2**) and NFSI.

One year later and extending the methodology described by MacMillan for the enantioselective α-fluorination of aldehydes,[9] Lindsley reported the synthesis of enantioenriched β-fluoroamines **4.6** catalyzed by organocatalysts **4.7-4.12** *via* one-pot α-fluorination/reductive amination sequence in excellent yields and enantioselectivities.[10] In addition, slightly modifications in this process provided access to β,β-difluoroamines **4.5** in good yields (Scheme 4.2).



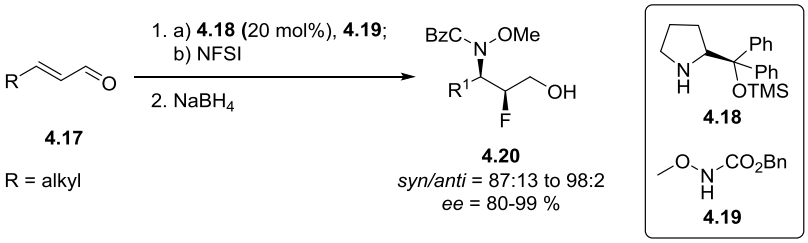
Scheme 4.2. Organocatalytic synthesis of β- and β-β-difluoroamines.

Highly diastereoselective primary β-fluoroamines **4.16** were also prepared by the same author. In this case, fluoroamines were achieved following a sequence involving α-fluorination of aldehyde **4.13**, transformation of the aldehyde into *N*-sulfinyl aldimine **4.15** by reaction with NFSI/**(S)-4.7**, and nucleophilic addition of organometallic species, and deprotection (Scheme 4.3).[11]



Scheme 4.3. Diastereoselective preparation of primary β-fluoroamines **4.16**.

The treatment of achiral α,β-unsaturated aldehydes **4.17** with amine **4.19** as nucleophile and *N*-fluorosulfonamide (NFSI) as electrophile source led to **4.20** through an asymmetric olefin aminofluorination reaction. This process was conducted by an organocascade sequence in which the amine was first introduced by conjugated addition to the iminium intermediate, followed by trapping of the the enamine formed with an electrophilic fluorine source (Scheme 4.4).[12] Products were obtained in excellent diastereo- and enantioselectivity.

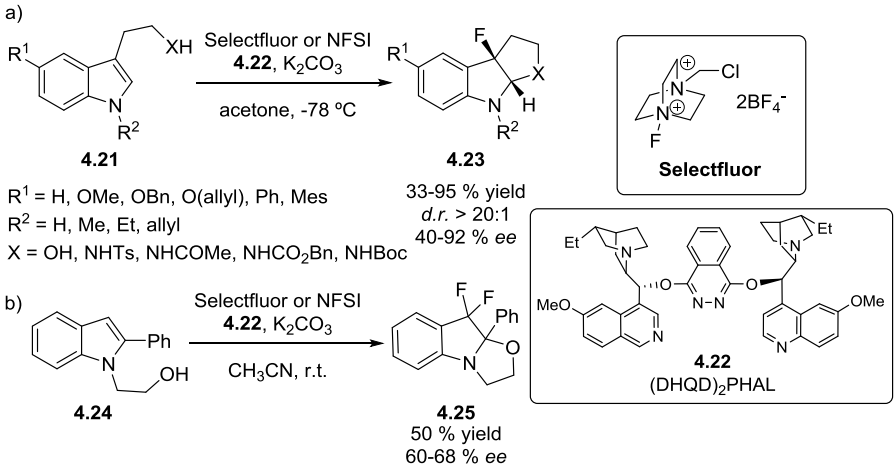


Scheme 4.4. Highly enantioselective organocatalytic synthesis of fluoroamines.

4.1.1.2. Lewis base- and anionic phase-transfer-catalyzed syntheses of vicinal fluoroamines.

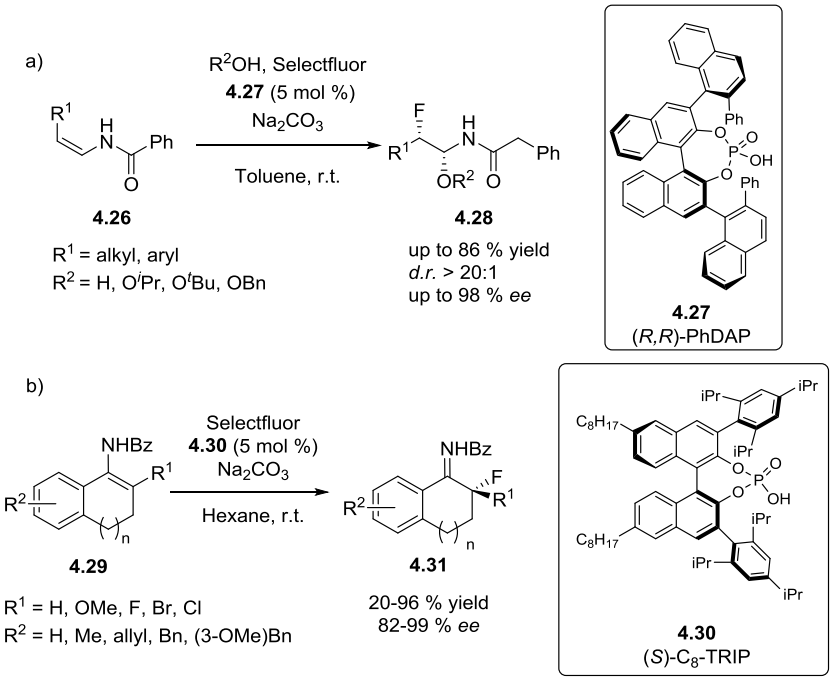
Fluoroamines can be also prepared from indoles and amides using fluorinated source such as 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) in combination with Lewis basic or anionic phase-transfer catalysts.

In this regard, Governeur published the first organocatalytic synthesis of fluorinated heterocyclic products where the fluorine was installed on a quaternary benzylic center starting from prochiral indoles (a, Scheme 4.5).[13] Additionally, dihalocyclization of indoles was also carried out containing the *gem*-difluoro motif (b, Scheme 4.5).



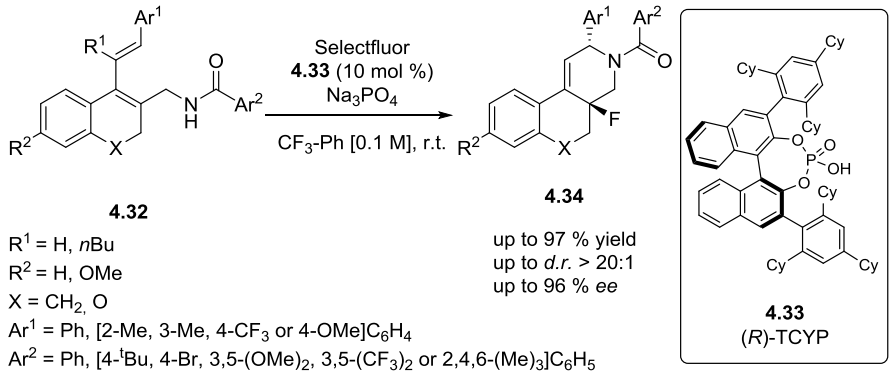
Scheme 4.5. Enantioselective synthesis of β-fluoroamines **4.23** and **4.25** assisted by the Lewis base $(DHQD)_2PHAL$ (**4.22**).

Toste described another procedure for the enantioselective synthesis of fluoroamines such as **4.28** from **4.26** by using Selectfluor and a chiral phosphoric acid catalyst in a tandem oxyfluorination of enamides (a, Scheme 4.6).[14] Furthermore, this strategy was extended to cyclic enamides affording excellent enantioselectivities and yields in most cases.[15] The chiral catalyst controls the fluorination reaction through an anion phase-transfer besides the addition to the imine (b, Scheme 4.6).



Scheme 4.6. Tandem oxyfluorination of enamides **4.29** and **4.31**.

The use of similar conditions led to the formation of enantioenriched 1,4-aminofluoro derivatives from conjugated dienes.[16] In this case, the replacement of Na_2CO_3 by Na_3PO_4 as a base and the change of the substituents in the phosphoric acid, provided the desired compounds in excellent yields and enantioselectivities albeit in moderate to good diastereoselectivities (Scheme 4.7).

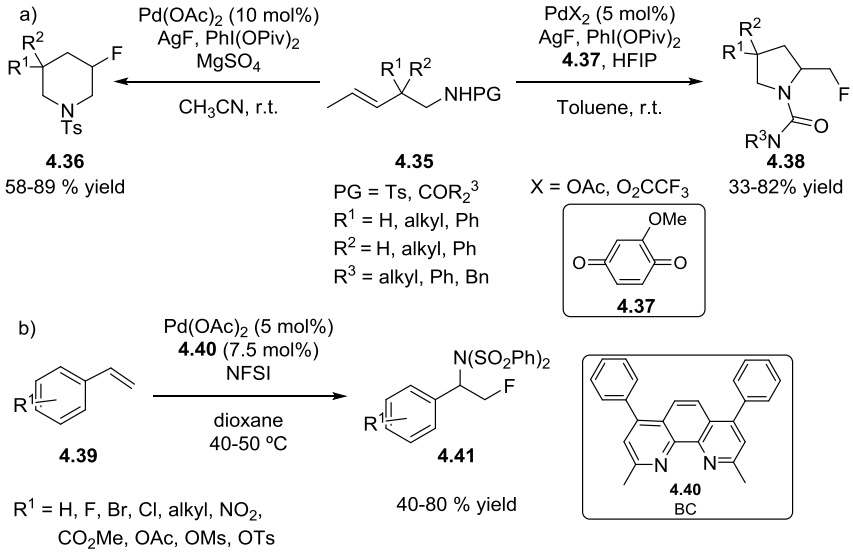


Scheme 4.7. Enantioselective synthesis of 1,4-aminofluoro derivatives **4.34** from **4.32** by chiral anion Phase-Transfer.

4.1.1.3. Metal-catalyzed intra- and intermolecular aminofluorination.

Different approaches for the formation of fluoroamines have been described employing transition-metal catalysts based on palladium, copper, iron and silver.

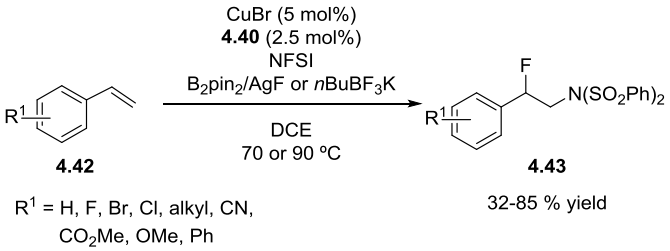
Liu *et al.* developed methods of intra- and intermolecular aminofluorination for unactivated alkenes. The processes were catalyzed by Pd(II) species in combination with strong oxidants and fluorine sources.[17] Specifically, compound **4.36** was synthesized from **4.35** in the presence of $Pd(OAc)_2$, $PhI(OPiv)_2$ as oxidant and AgF as fluorinating reagent whereas the synthesis of **4.38** was afforded by changing $Pd(OAc)_2$ by PdX_2 catalyst (a, Scheme 4.8). On the other hand, the catalytic system $Pd(OAc)_2$/**4.40** catalyzed the addition of NFSI to styrene derivatives **4.39** to provide fluoroamines **4.41** (b, Scheme 4.8).[18] High regioselectivity was obtained in both cases.



Scheme 4.8. Palladium-catalyzed intra- and intermolecular fluoroamination of unactivated alkenes **4.35** and styrene derivatives **4.39**.

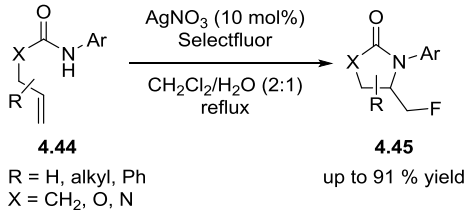
Zhang reported the first radical aminofluorination of styrenes, with regioselectivity opposite to that obtained by Liu.[19] In this study he

employed copper as catalyst and NSFI as double radical nitrogen and fluorine source (Scheme 4.9).



Scheme 4.9. Copper-catalyzed fluoroamination of styrenes **4.42**.

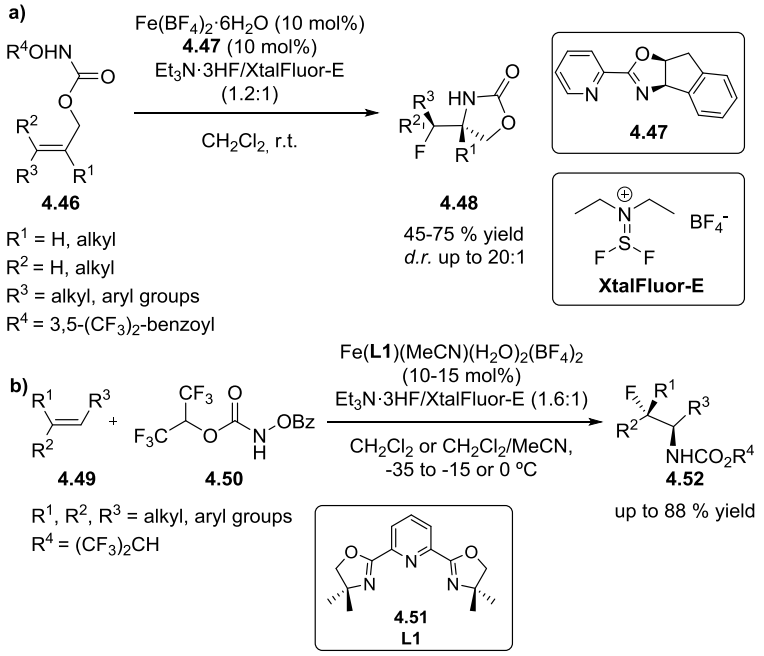
The silver-assisted radical aminofluorination of unactivated alkenes in aqueous media was reported by Li in 2013.[20] This kind of reaction was catalyzed by $AgNO_3$ and Selectfluor played the role of oxidant and fluorine source. As a result, *N*-cyclic amides **4.45** carrying fluorine in β-position were prepared in moderate to good yields (Scheme 4.10).



Scheme 4.10. Synthesis of β-fluoroamines **4.45** from **4.44** in aqueous media catalyzed by Ag(I).

Fe(II) catalysts were also used in the intra- and intermolecular aminofluorination of active and unactivated alkenes. Styrenes **4.46** bearing a carbamate function treated with the catalytic system Fe(II)/**4.47**, $Et_3N{\cdot}HF$ as fluorine source and XTalFluor-E (*N*,*N*-diethyl-*S*,*S*-difluorosulfiliminium tetrafluoroborate) as carboxylate trapping reagent to suppress the aminohydroxylation, underwent an intramolecular reaction to afford *syn* and *anti*-fluorooxazolidinones **4.48** (a, Scheme 4.11).[21] Besides, β-fluoro amino acids were also synthesized upon further derivatizations. Conversely, unfunctionalized alkenes were intermolecularly aminofluorinated in the presence of Fe(II), $Et_3N{\cdot}HF$ and

XTalFluor-E. The amino moiety was installed starting from a benzoate **4.50** bearing a carbamate functionalization (b, Scheme 4.11).[22] According to mechanistic studies, the reaction might take place through nitrenoid intermediate.



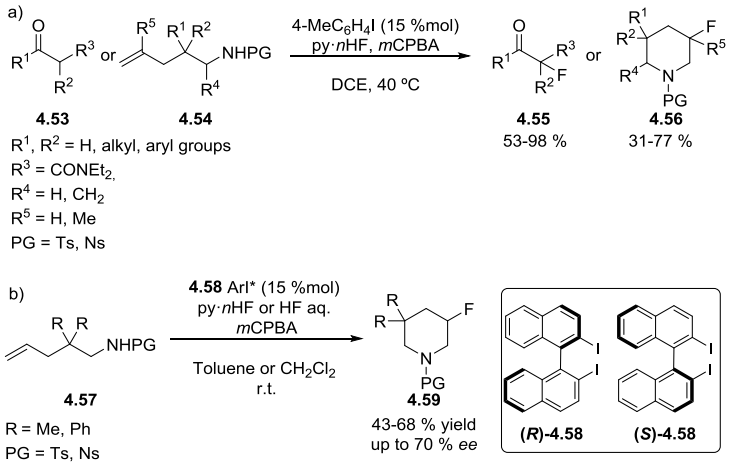
Scheme 4.11. Intra- and intermolecular Fe (II)-catalyzed fluoroamination of alkenes **4.46** and **4.49**.

4.1.1.4. Metal free aminofluorination-mediated by hypervalent I(III).

Hypervalent I(III) reagents has been widely used as fluorine source in the difluorination of alkenes leading to 1,1[23] or 1,2[24] derivatives regarding to the double bond and in the fluorination of alkenes,[25] alkynes,[26] β-ketoesteres[27] and β-dicarbonyl compounds.[28] However, its use is not only exclusive of this kind of processes but it is also used in the achiral and/or enantioselective synthesis of β-fluoroamines.

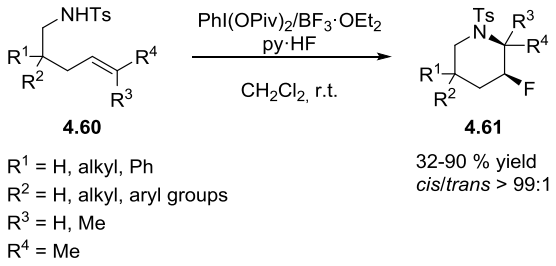
Actually, Shibata reported the intramolecular aminofluorination of ketones **4.53** and ω-amino-alkenes **4.54** catalyzed by a hypervalent

iodo(III) reagent generated *in situ* from the iodoarene, Olah's reagent (py·HF) as fluorine source and *m*CPBA as oxidant (a, Scheme 4.12).[28b] The enantioselective synthesis of piperidines **4.59** was accomplished by treating **4.57** with chiral I(III) reagents derived from **4.58** under similar conditions (b, Scheme 4.12).



Scheme 4.12. Hypervalent I(III)-mediated synthesis of a-fluoro-ketones **4.55** and β-fluoro-piperidines **4.56** and **4.59**.

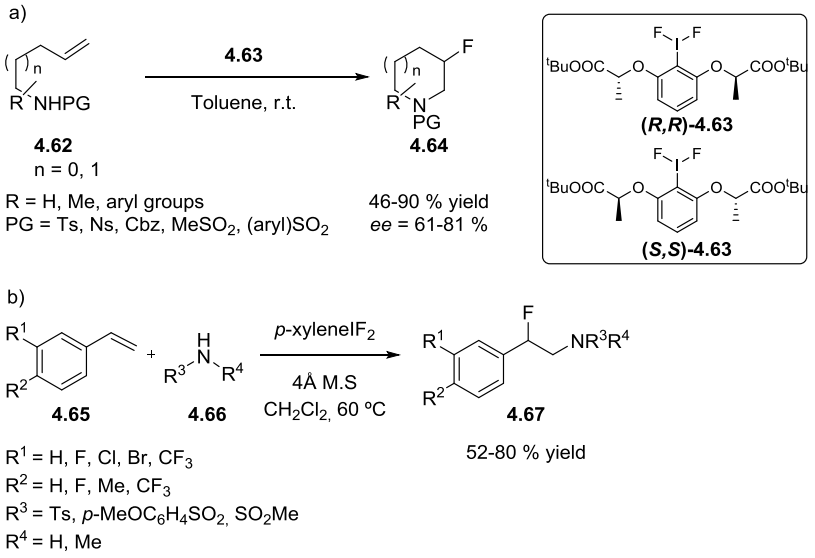
Meng described a related intramolecular aminofluorination of alkenes mediated by hypervalent I(III)/py·HF system in the presence of $BF_3{\cdot}OEt_2$ (Scheme 13).[29] Piperidines **4.61** were obtained in moderate to good yield and excellent diastereoselectivity from aminoalkenes **4.60**.



Scheme 4.13. Intramolecular synthesis of β-fluoroamines type **4.61**.

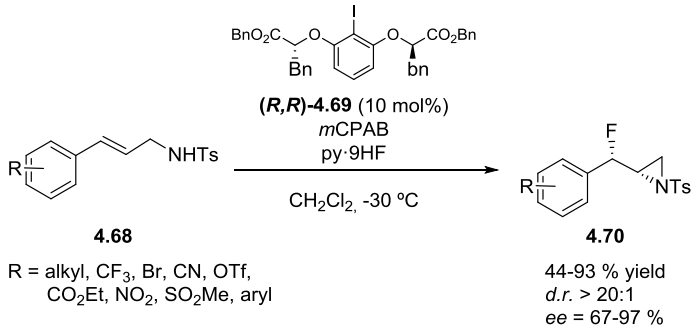
An asymmetric version of this transformation was disclosed by Nevado using chiral $ArIF_2$ reagents. Thus, the reaction of aminoalkene **4.62** with the chiral I(III) reagent **4.63** afforded piperidines **4.64** with

high enantioselectivity (a, Scheme 4.14).[30] Furthermore, the regioselective synthesis of 2-fluoro-2-phenylethanamines was described using *p*-xyleneIF$_2$ as fluoride source (b, Scheme 4.14).



Scheme 4.14. Fluoroamination of unactivated alkenes in intra- and intermolecular way.

Very recently, Jacobsen and co-workers developed a highly enantio- and diastereoselective *syn* aminofluorination of cinnamyl amine derivatives.[31] β-Fluoroaziridines **4.70** were obtained by treating the cinnamyl derivatives **4.68** with the chiral hypervalent I(III) catalysts **4.69**, *m*CPBA and py·9HF. Presumably, this reaction occurs through the nucleophilic addition of fluoride, which generates an intermediate with C(sp^3)-I(III) bond in *anti* disposition with respect to fluorine. Another nucleophilic attack by amine would then provide the corresponding *syn* β-fluoroaziridines (Scheme 4.15).

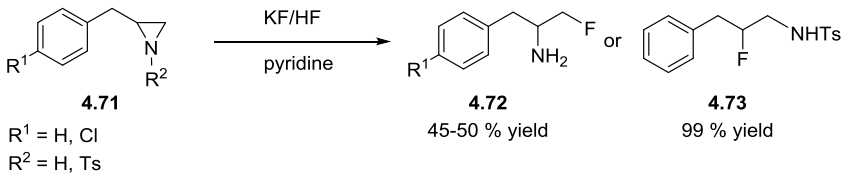


Scheme 4.15. Enantioselective preparation of β-fluoroaziridines **4.70** from amines **4.68** with chiral hypervalent I(III) catalyst **4.69**.

4.1.1.5. Aziridines as key intermediate in the synthesis of β-fluoroamines.[32]

The ring-opening of small cycles can provide fluoroamines in an elegant manner. In fact, aziridines have been chosen as key intermediates to generate this kind of motif since eighties.

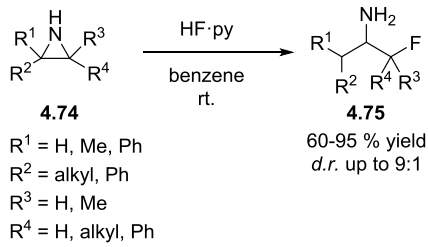
In 1980, Coutts and co-workers reported the synthesis of fluoroamines starting from aziridines using py·HF/KF.[33] They found that when activated aziridines **4.71** (R^2 = Ts) were used, fluoride attacked the more substituted carbon to give **4.73** in quantitative yield, whereas, non-activated aziridines (R^2 = H) led to the opposite regioselectivity in moderate yields (Scheme 4.16).



Scheme 4.16. Ring-opening of aziridines as strategy to afford *β*-fluoroamines.

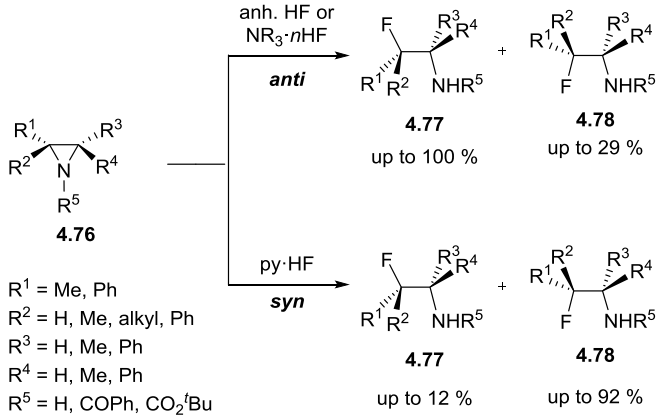
The same year, Wade also prepared β-fluoroamines **4.75** in a regioselective fashion by treating **4.74** with the Olah's reagent, although a mixture of diastereoisomers was obtained in most cases.[34] He explained that the low diastereoselectivity could arise from an S_N1-type

mechanism with formation of a carbocation prior to the nucleophilic attack (Scheme 4.17).



Scheme 4.17. Olah's reagent-assisted ring opening of aziridines **4.75**.

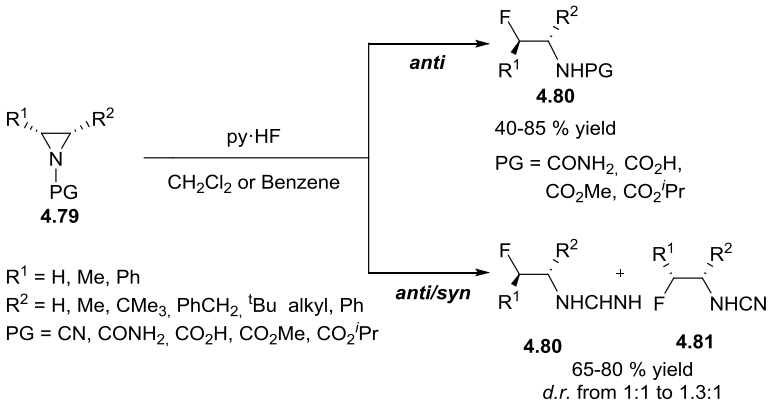
Laurent and co-workers investigated the ring-opening of aziridines with different fluorine reagents.[35] They discovered that the treatment of aziridines with anhydrous HF or $NR_3{\cdot}n$HF led to the formation of *anti* fluoroamines as major products. However, the use of py·HF mainly enhanced the *syn* products (Scheme 4.18). They rationalized these results by the formation of a carbocation besides they explained that the stereoselectivity was highly dependent on the substrate and the fluorinated reagent used.



Scheme 4.18. *Syn* or *anti* ring-opening of aziridines **4.76** depending on the fluoride source.

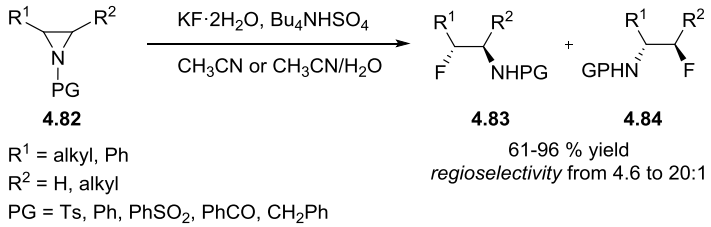
Anti-β-fluoro-α-amino acids **4.80** were regio- and stereoselectively prepared from *cis*-2-amidoaziridines **4.79** by reacting these compounds with Olah's reagent (py·HF) and further hydrolysis.[36]

Interestingly, the ring-opening of *cis*-2-cyanoaziridines provided a mixture of *syn/anti* products which was explained by S_N1 mechanism. Whereas, the high stereoselectivity observed for the first case was attributed to S_N2 pathway (Scheme 4.19).



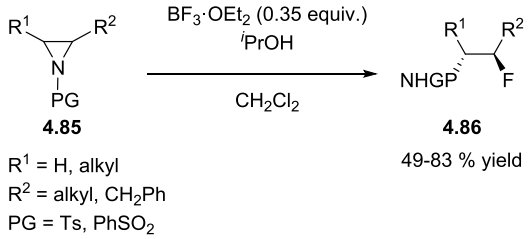
Scheme 4.19. Stereoselective ring-opening of aziridines **4.79** controlled by *N*-protecting group.

Activated and non-activated aziridines were easily opened using $KF{\cdot}H_2O$ in the presence of Bu_4NHSO_4.[37] An exchange of ions between KF and Bu_4NHSO_4 evolved towards the formation of the nucleophilic species Bu_4NF, which efficiently opened the aziridine **4.82** in *anti*-manner providing **4.83** and **4.84** (Scheme 4.20).



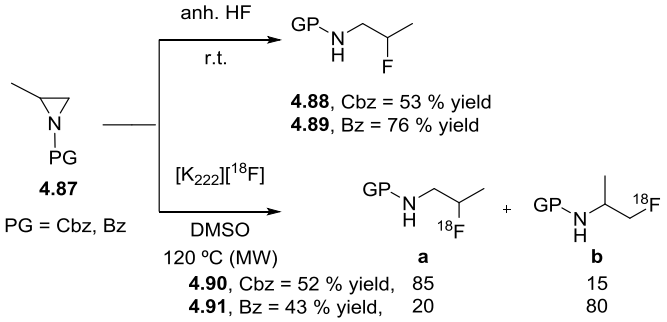
Scheme 4.20. Preparation of β-fluoroamines by ring-opening of aziridines **4.82**.

Moderate to good yields were achieved in the synthesis of β-fluoroamines **4.86** starting from activated aziridines **4.85** and in the presence of $BF_3{\cdot}OEt$ as fluorine source (Scheme 4.21).[38]



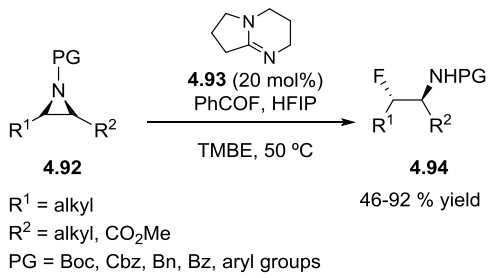
Scheme 4.21. Direct opening of activated aziridines **4.85** with $BF_3{\cdot}OEt_2$ to form β-fluoroamines **4.86**.

2-Fluoropropanamines **4.88** y **4.89** were regioselectively prepared from *N*-benzoyl (Bz) and *N*-benzyloxycarbonyl (Cbz) 2-methylaziridines **4.87** with anhydrous hydrogen fluoride.[39] Besides, the ring-opening of theses aziridines in the presence of [^{18}F]-fluoride was first reported in a regioselective way. The source of labeled fluoride selected for this reaction was potassium cryptand fluoride ([K222][^{18}/^{19}F]) where the 2-fluoropropanamine and 1-fluoro-2-propanamine **4.90** and **4.91** were obtained as major products (Scheme 4.22).



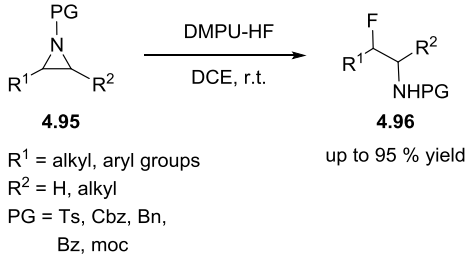
Scheme 4.22. Regioselective fluoroamination of activated aziridines **4.87** with anhydrous HF and [^{18}F]-labelled fluoride.

Hydrofluorination of different protected aziridines was promoted by the action of a fluorinating reagent generated in situ using benzoyl fluoride and a non-nucleophilic alcohol (HFIP).[40] The synthesis of this reagent was catalyzed by a Lewis base. As a result, β-fluoroamines **4.94** were prepared from aziridines **4.92** in high regio- and diastereoselectivity and in moderate to excellent yields (Scheme 4.23).



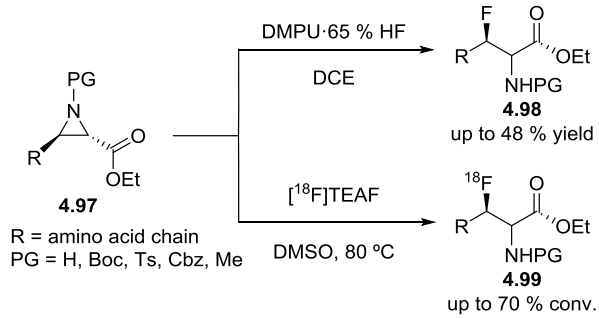
Scheme 4.23. Hydrofluoroamination of aziridines **4.92** assisted by Lewis base catalyst.

A series of β-fluoroamines **4.96** were accomplished in a regio- and stereoselective manner under acidic conditions.[41] The reaction conditions proved to have good functional group tolerance and it was established that the substituents contained in the carbons of the aziridines were crucial for the stereoselectivity of the products Quasi-S_N2, quasi- S_N1 and quasi- S_Ni mechanisms were proposed to explain the different products obtained (Scheme 4.24).



Scheme 4.24. Regio- and diastereoselective synthesis of fluoroamines in acid medium.

Aziridines protected with *N*-tosyl, *N*-Boc, *N*-Cbz and *N*-methyl groups were submitted to ring-opening reaction in the presence of non-acidic [$^{18}F/^{19}F$] fluoride source.[42] Poor to moderate yields were observed in the formation of the corresponding β-fluoroamines, affording the best result for *N*-tosylaziridines. Likewise, moderate results were obtained when the aziridines were treated in non-radioactive experiments and using DMPU/HF as fluoride source (Scheme 4.25).



Scheme 4.25. Stereoselective synthesis of fluoroamines **4.98** and **4.99** using DMPU/HF system and [^{18}F]-TEAF, respectively.

4.2. OUTLOOK AND OBJECTIVES

As seen in Chapter 3, the alkene aziridination and the ring-opening of aziridines constitute key steps in the synthesis of sphingosine kinase inhibitors (SphKIs). In this regard, we were interested in exploring this strategy in the fluoroamination of conjugated dienylcarbamates using $ArIF_2$ as a fluorine source and oxidant source. Towards the ultimate goal of developing the fluoroamination of dienylcarbamates, we decided first to perform a preliminary study on the synthesis of β-fluoroamines starting from simpler cinammyl carbamates in a tandem intramolecular aziridination/ring-opening reaction, aiming to explore the different procedures of generating the fluorinating reagent and the behavior of the reaction. More specifically, the goals of this chapter are:

i) To synthesize cinnamyl alcohols by reduction of the corresponding cinnamic acids.

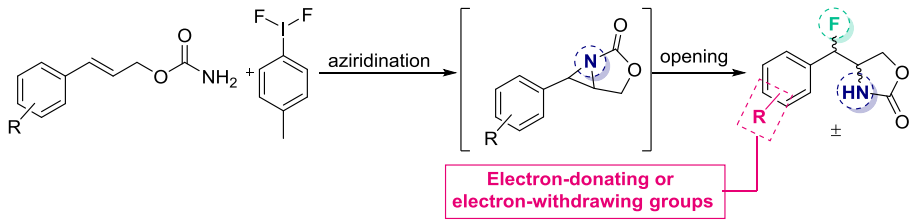
ii) To prepare carbamates using as starting material the freshly cinnamyl alcohols.

iii) To evaluate different fluoride sources in the preparation of the hypervalent iodoarene difluoride.

iv) To optimize a tandem intramolecular aziridination/ring-opening reaction to generate β-fluoroamines using 4-MePhIF$_2$ as oxidant and fluoride source.

v) To expand the scope of the process applying the optimal conditions on other substituted cinnamyl carbamates.

vi) To detect or isolate some intermediate which may gain insight on the mechanism of the reaction including the stereochemical outcome.



4.3. RESULTS AND DISCUSSION.

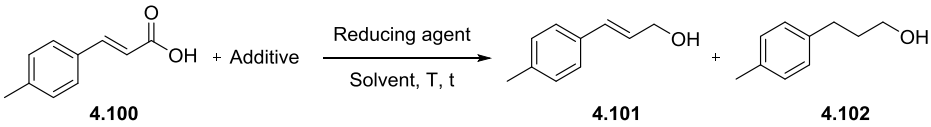
4.3.1. Synthesis of cinnamyl alcohols and subsequent carbamates.

Cinammyl alcohols were chosen as starting materials for the syntheses of β-fluoroamines. These alcohols are intended to be further transformed into carbamates, intramolecularly aziridinated and ring-opened.

4.3.1.1. Syntheses of cinnamyl alcohols by reduction of their corresponding acids.

Different strategies involving direct reduction[43] or reduction in two steps including previous conversion from acid to ester[44] were tested in the preparation of cinnamyl alcohol **4.101** starting from cinnamic acids (Table 4.1).

Table 4.1. Reduction of cinnamic acids.



4.100 **4.101** **4.102**

Entry	Additive	Reducing agent	Solvent	T (°C)	t (h)	Selectivity (4.99:4.100)[e]	Yield (%)[f]
1[a]	--	BH_3	THF	r.t	20	--	--
2[b]	--	DIBAL	Toluene	-5	16	99:1	30
3[c]	MeI	DIBAL	DMF/ CH_2Cl_2	r.t. to -40	30	99:1	19
4[d]	Ethyl chloroformate	$NaBH_4$	THF	-5	1	88:12	53

[a] Conditions: acid (0.18 mmol), BH_3·THF (0.81 mmol), THF (3.7 mL). [b] Conditions: acid (0.30 mmol), DIBAL (0.78 mmol), toluene (0.78 mL). [c] Conditions: i) acid (0.30 mmol), MeI (0.6 mmol), K_2CO_3 (0.45 mmol), DMF (0.7 mL); ii) DIBAL (0.75 mmol), CH_2Cl_2 (0.75 mL). [d] Conditions: acid (0.30 mmol), ethyl chloroformate (0.30 mmol), Et_3N (43 µL), THF (0.5 mL); ii) $NaBH_4$ (1.14 mmol), MeOH (0.33 mL). [e] Determined by ^1H NMR. [f] Isolated yield for **4.101**.

When we explored the direct reduction of compound *p*-methylcinnamic acid **4.100** in the presence of an excess of BH_3, no reaction was observed (entry 1). The replacement of BH_3 by DIBAL as reducing agent proceeded with excellent chemoselectivity towards **4.101** although in poor yield (entry 2). In view of these results, we decided, first, to transform the acid into ester and then, reduce it. The treatment of **4.100** in basic medium with MeI to form the corresponding ester followed by its reduction provided the compound **4.101** in only 19 % over two steps but in excellent chemoselectivity (entry 3). However, better yield was afforded when ethyl chloroformate was reacted with **4.100** to form the acyl carbonate and its subsequent reduction in the presence of $NaBH_4$ (entry 4). In this case, the chemoselectivity slightly decreased and the product derived from reduction of double bond was also observed as a consequence of the use of a softer reducing agent (chemoselectivity = 88:12).

Even though the reaction was not completely chemoselective, it rendered better yields and, hence, we selected this method for the reduction of the rest of cinnamic acids. Yields between 40-80% and chemoselectivities among 82:12 and 93:7 were obtained in the syntheses of alcohols **4.103-4.108** (Figure 4.1).

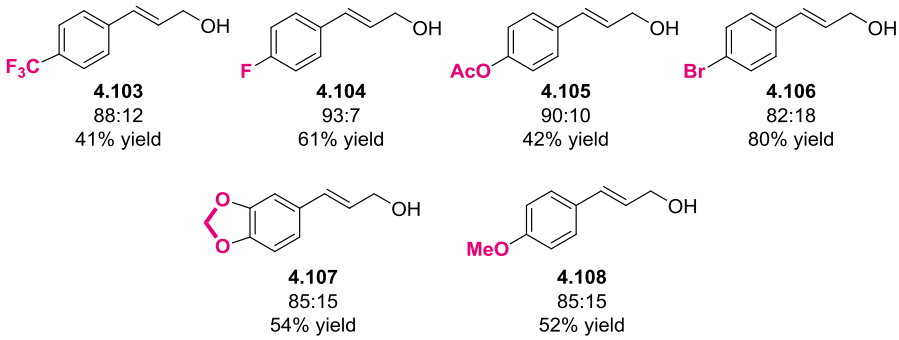
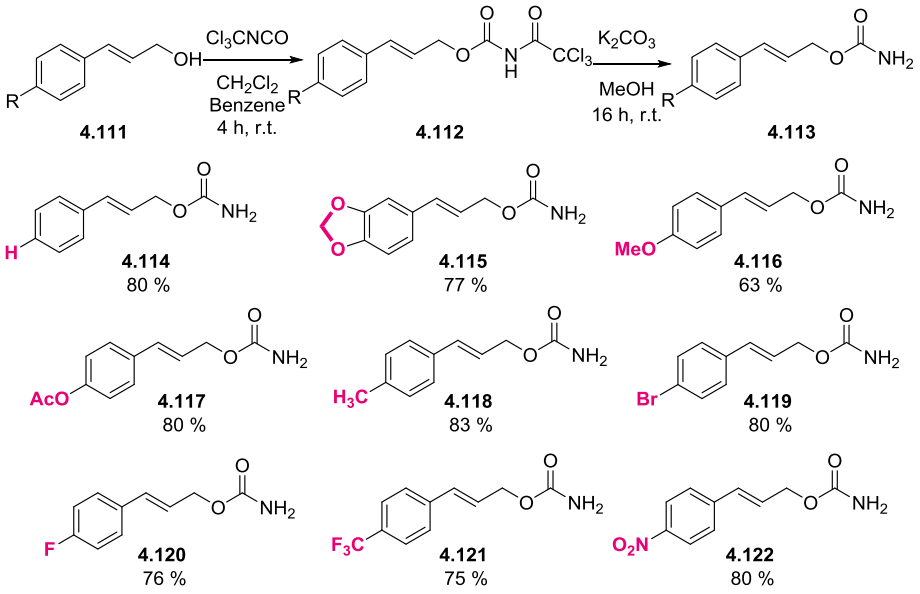


Figure 4.1. Scope of cinnamyl alcohols **4.103**-**4.108**.

4.3.1.2. Preparation of carbamates from cinnamyl alcohols.

With alcohols **4.101** and **4.103-4.108** in hand, we then performed the syntheses of their corresponding carbamates through a carbomoylation procedure using trichloroacetyl isocyanate (TAI) as nitrogen source and K_2CO_3 in methanol for the further hydrolysis of the imido intermediate.[45] In addition, these carbamates were crystallized in order to remove any trace of chloride contained in the sample. It is important to note that the removal of chlorides was required since in previous studies in our laboratory[46] chloride coming from the synthesis of carbamates were found to open aziridines obtained from reaction of dienyl carbamates with PhIO. On the other hand, the commercially available cinnamyl alcohol **4.109** and *p*-nitrocinnamyl **4.110** alcohol were also used in the carbomoylation reaction (Scheme 4.26).



Scheme 4.26. Syntheses of carbamates **4.114-4.122**.

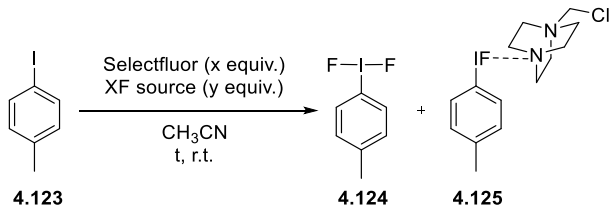
4.3.2. Synthesis of hypervalent iodoarene.

As commented in *Introduction section*, hypervalent iodoarenes are widely used in the syntheses of β-fluoroamines as a fluorine source. Thus, having this in mind, we focused our efforts on using 4-MePhIF_2 as both oxidant and fluorine source in the synthesis of aziridines and their corresponding ring-opening process.

Multiple methods have been described to prepare difluoroiodoarenes from iodoarenes. They involve the use of fluorinating reagent such as F_2, XeF_2, Cl_2/HF, HgO/HF, SF_4, BuNF or AgF or electrochemical fluorination.[47] Shreeve developed the synthesis of difluoroiodoarenes using Selectfluor as fluorine source and also afforded the difluorination of iodoarenes in two steps starting from elemental iodine and Selectfluor.[48] Very recently and following the strategy described by Shreeve, Gilmour and co-workers reported the synthesis of difluoroiodoarenes by adding some fluorine additives besides Selectfluor and controlled their formation by NMR studies.[49]

In this context and taking as a reference the study carried out by Gilmour, we measured the amount of difluoroiodoarene **4.124** generated from the reaction of 4-iodotoluene with Selectfluor and/or $Et_3N{\cdot}3HF$ and CsF employing 1-pentadecene as an internal standard (Table 4.2).

Table 4.2. Screening in the formation of hypervalent iodoarene 4-MePhIF$_2$.



4.123 4.124 4.125

Entry[a]	Selectfluor (equiv.)	XF source	XF$^-$ (equiv.)	time (h)	Yield 4.124 (%)[b]	Yield 4.125 (%)[b]
1	2.6	--	--	22	6	--
2	4	CsF	5	14	48	18
3	3.5	$Et_3N{\cdot}3HF$	3.6	22	83	3

[a] General conditions: 4-iodotoluene **4.123** (0.1 mmol), Selectfluor (x equiv.), XF source (y equiv.), CH_3CN (2.5 mL). [b] Measured by ^1H NMR using 1-pentadecene as an internal standard.

When we explored the reaction in the absence of additive, the compound **4.124** was obtained as unique product in 6 % yield despite 100 % of conversion was observed after 22 h of reaction (entry 1). The incorporation of CsF as an extra fluoride source improved the result and compound **4.124** was afforded in 48 %. Furthermore, the intermediate **4.125** described by Gilmour was also detected in 18 % yield (entry 2), which is involved in a dynamic fluoride exchange with difluoroiodoarene in solution.[49] To our delight, the replacement of CsF by $Et_3N{\cdot}3HF$ led to the formation of **4.124** in 86 % where **4.125** was only detected in 3 % (entry 3) (Figure 4.2).

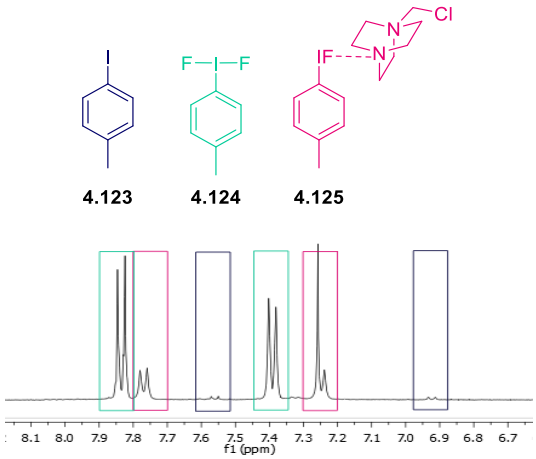


Figure 4.2. Species observed in the difluorination of 4-iodotoluene **4.123**.

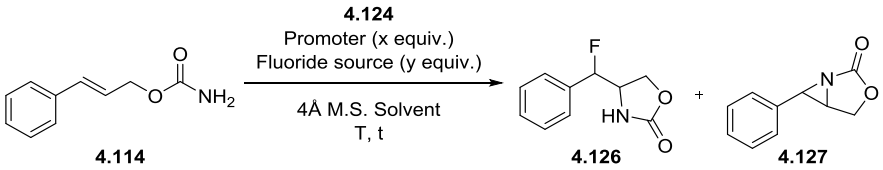
4.3.3. Synthesis of β-fluoroamines.

4.3.3.1. Solvent and fluoride source optimization.

β-Fluoroamines can be prepared following several procedures (see *section 4.1*). Nevertheless, we envisioned that they might be synthesized combining the allyl carbamates **4.114-4.122** and hypervalent difluoroiodoarene **4.124** through intramolecular alkene aziridination followed by *in situ* ring-opening of the aziridine intermediate.

In this context, we explored these reactions in a one-pot sequence where different solvents, promoters, extra fluoride sources and temperatures were screened (Table 4.3). Besides, the simplest cinnamyl carbamate **4.114** was selected as a benchmark substrate. It is worth mentioning that only chlorinated solvents were tested during the aziridination and ring-opening steps since previous studies in which this kind of reaction was explored showed formation of fluoroamines only when CH_2Cl_2, 1,2-DCE and chloroform were used. Furthermore, it should be mentioned that 4-MePhIF$_2$ was freshly prepared prior to every aziridination reaction due to problems derived from its storage.[48] Previous studies in our group[50] had concluded that it was necessary to use 2 equivalents of I(III)-compound related to the starting carbamate.

Table 4.3. Screening of solvents and fluoride source for the synthesis of β-fluoroamine **4.126**.



Entry[a]	F source (equiv.)	Solvent	T (°C)	t (h)	*d.r.* (*syn/anti*)	Yield 4.126 (%)[b]	Yield 4.127 (%)[b]
1	--	1,2-DCE	60	48	49:51	5	8
2[c]	KF (5)	1,2-DCE	Reflux	16	--	C.M.[d]	--
3[e]	--	$CHCl_3$	Reflux	40	43:57	22	--
4[c]	KF (5)	$CHCl_3$	Reflux	16	--	C.M.[d]	--
5	--	CH_2Cl_2	Reflux	16	75:25	41	--
6[f]	--	CH_2Cl_2	Reflux	16	38:62	21	--
7[g]	--	CH_2Cl_2	Reflux	48	--	--[h]	--
8	CsF (2)	CH_2Cl_2	Reflux	48	--	--[i]	--
9[j]	KF (2.5)	CH_2Cl_2	Reflux	48	--	--	>95
10	Xtal-F (1.4)	CH_2Cl_2	Reflux	16	--	--[i]	--
11	$Et_3N{\cdot}3HF$ (6)	CH_2Cl_2	Reflux	120	--	--[e]	54
12	$Et_3N{\cdot}3HF$ (10)	CH_2Cl_2	Reflux	120	--	N.R.[k]	--
13	py·9HF (10)	CH_2Cl_2	Reflux	20	--	C.M.[d]	--
14	py·9HF (20)	CH_2Cl_2	Reflux	20	--	C.M.[d]	--

[a] General *conditions*: 4-iodotoluene **4.123** (0.22 mmol), Selectfluor (0.77 mmol), $3HF{\cdot}Et_3N$ (0.79 mmol), CH_3CN (5.5 mL). Then, carbamate (0.09 equiv.), promoter (x equiv.), fluoride source (y equiv.), 4 Å M.S. (90 mg), solvent (2.3 mL). [b] Measured by ^{1}H-NMR. [c] Reaction performed in the presence of $BF_3{\cdot}Et_2O$ (2 equiv.) and 18-crown-6 (1 equiv.). [d] C.M. = Complex mixture. [e] Starting material no totally consumed. [f] Reaction performed without molecular sieves. [g] Reaction performed in the presence of *p*TsOH (1.5 equiv.). [h] Aziridine opened with *p*TsOH. [i] Decomposition. [j] Reaction performed in the presence of 18-crown-6 (1 equiv.). [k] N.R. = No reaction.

Based on the result from entry 3 Table 4.2, difluorination reaction of iodotoluene was assumed to yield 83 % in all cases and

consequently the carbamate was added in 0.5 equivalents with respect to the amount of difluoroarene formed.

When the reaction of carbamate **4.114** with Selectfluor was performed at 60°C in the absence of additive and using 1,2-DCE as solvent, **4.126** was obtained in very low yield (5%) as a mixture of *syn*/*anti* diastereoisomers (49:51). Furthermore, aziridine **4.127** was also obtained in 8 % (entry 1). An increase in temperature and the use of KF as extra fluoride source did not improve the results and a complex mixture was observed (entry 2). Likewise, the replacement of 1,2-DCE by $CHCl_3$ led to poor results and the compound **4.126** was obtained in moderate yield as a mixture of diastereoisomers in the best case (entries 3-4). Nevertheless, better yield and diastereoselectivity (*syn/anti* = 75:25) were obtained when the reaction took place in CH_2Cl_2 (entry 5). *Syn* product[21] was obtained as major diastereoisomer in spite of the fact that aziridines are commonly opened through a bimolecular process in an *anti* manner (see *Section 4.3.3.3* for comparison with reported data). Additionally, the absence of molecular sieves led to a decrease in yield with inversion of the diastereoselectivity, favoring the *anti* product (entry 6).

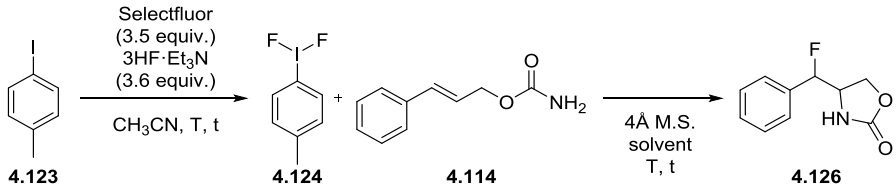
The use of a promoter or the addition of an extra fluoride source to open the aziridine resulted unsuccessful. When *p*TsOH was added as a promoter to activate the aziridine, this reagent acted as nucleophile instead opening the aziridine (entry 7). The use of fluoride salts led to erratic results: with KF, aziridine was obtained in 95 % (entry 9) whereas the use of CsF and Xtal-F led to decomposition of the product (entries 8 and 10). The replacement of these salts by HF stabilized in triethylamine or pyridine did not improve the results and unaltered starting material or complex mixtures were obtained even using different amounts of fluoride (entries 11-14). These results are consistent with the fact that the acidity of $Et_3N{\cdot}3HF$ is low due to the high basicity of triethylamine which, together with the poor nucleophilicity of HF, rendered the aziridine (entry 11) or no conversion (entry 12). In

contrast, the acidity of py·9HF is higher than $Et_3N·3HF$, thus it is not surprising that the reaction proceeded although a really complex mixture was observed in all cases.

4.3.3.2. Iodoarene loading and temperature screening.

Since the best result originally obtained for fluoroamination could not be reproduced after several attempts (Table 4.3, entry 5 and for comparison table 4.4, entry 1), we decided to explore whether the reproducibility problems could arise from the insufficient formation of 4-$MePhIF_2$ reagent from the starting 4-iodotoluene.

Table 4.4. Optimization of 4-MePhI loading and temperature.



Entry[a]	4-MePhI (mmol)	T (°C)	t (h)	*d.r.* (*syn/anti*)	Yield 4.126 (%)[b]
1	0.22	Reflux	16	75:25	41
2	0.45	Reflux	4	85:15	63
3	0.45	25	48	97:3	42

[a] *Conditions*: 4-iodotoluene **4.123** (x mmol), Selectfluor (3.5 equiv.), 3HF·Et_3N (3.6 equiv.), CH_3CN (x mL). Then, carbamate (0.09 equiv.), 4 Å M.S. (90 mg), CH_2Cl_2 (2.3 mL). [b] Measured by ^{1}H-NMR.

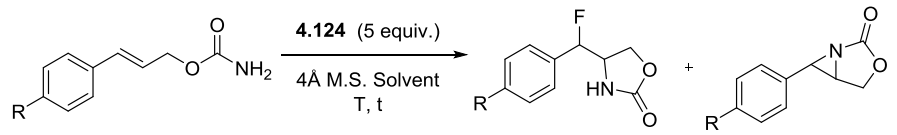
When we explored the reaction in the presence of 5 equivalents of 4-iodotoluene **4.123** and in refluxing CH_2Cl_2, β-fluoroamine was obtained in 60 % as a mixture of diastereoisomers (85:15) with *syn* product **4.126** as major one (entry 2). Furthermore, considerable shorter reaction time was required to complete the reaction. Importantly, this reaction could be easily reproduced, confirming that a big excess of iodoarene is not detrimental for the synthesis of the aziridine and its further ring-opening. The decrease of temperature up to

25 °C led to excellent diastereoselectivity although the reaction took place more slowly and moderate yield was obtained (entry 3).

4.3.3.3. Scope of substrates for fluoroamination.

To explore the scope and the limitations of this reaction, we applied the method to a variety of carbamates. A set of compounds bearing electron-withdrawing (EW) and electron-donor (ED) substituents were selected in order to know their influence in the reaction. The results obtained are shown in Table 4.5.

Table 4.5. Substrate scope for the syntheses of β-fluoroamines.



4.116, R = OMe
4.117, R = OAc
4.119, R = Br
4.121, R = CF_3
4.122, R = NO_2

4.128, R = OMe
4.130, R = OAc
4.132, R = Br
4.134, R = CF_3
4.136, R = NO_2

4.129, R = OMe
4.131, R = OAc
4.133, R = Br
4.135, R = CF_3
4.137, R = NO_2

Entry[a]	Subst.	T (°C)	t (h)	*d.r.* (*syn/anti*)[b]	Yield ring-opened (%)[b]	Yield Azir. (%)[b]
1	**4.116**	Reflux	5	--	-- [c]	--
2	**4.116**	25	20	66:34	64	--
3	**4.116**	0	48	64:38	55	--
4	**4.117**	Reflux	20	58:42	65	--
5	**4.117**	25	72	80:20	48	11
6	**4.119**	Reflux	20	91:9	48	--
7	**4.121**	Reflux	20	95:5	33	--
8	**4.122**	Reflux	72	99:1	32	--

[a] *General conditions*: 4-iodotoluene **4.123** (0.45 mmol), Selectfluor (1.58 mmol), 3HF·Et_3N (1.62 mmol), CH_3CN (11 mL). Then, carbamate (0.09 mmol), 4 Å M.S. (90 mg), CH_2Cl_2 (2.3 mL). [b] Measured by ^{1}H-NMR. [c] Decomposition.

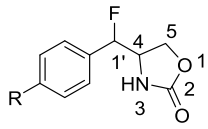
Decomposition of the product was observed when electron-donating group OMe was chosen as substituent and the reaction was performed using the optimal conditions (entry 1). However, a decrease in the temperature to 25 °C led to the formation of compound

4.128 in 64 % yield as a mixture *syn/anti* = 66:34 (entry 2). A similar diastereoselectivity outcome was obtained when the reaction was performed at 0 °C, although lower yield and longer reaction time was required to complete the reaction (entry 3). The use of carbamate **4.117** bearing a less electron-donating group afforded better results than **4.116** under refluxing conditions. Nevertheless, the diastereoselectivity was also moderate. This result improved decreasing the temperature, where diastereoselectivity reached an 80:20 value although aziridine intermediate **4.131** was also detected in 11 %. Interestingly, when electron-withdrawing groups were used, slightly lower yields although excellent diastereoselectivies were obtained (entries 6-8). For the case of the compound **4.122** bearing a NO_2 as substituent, the process was completely selective and only *syn* product was observed. The difference in reactivity according to the nature of substituents and its influence in the plausible mechanism are explained in *section 4.3.3.4*.

In order to confirm that the major product was the *syn* isomer in all cases, the shifts corresponding to protons of the oxazolidinone for both compounds observed (*syn* and *anti*) were compared with the reported data for compound *syn*- and *anti*-**4.126** (Table 4.6). The shift corresponding to the proton in α-position regarding to fluorine has been omitted since both compounds share the same value in $CDCl_3$ solution.

As seen in bibliography,[21] Xu described that compound ***syn*-4.126** showed chemical shifts at 4.54-4.50 and 4.19-4.11 ppm ranges for protons H5 and H4, respectively whereas the same protons displayed chemical shifts at 4.33-4.21 and 4.17-4.14 ppm in the case of the *anti* compound. Similar results were observed in our case, where our major compound exhibited the same shifts than reported for *syn* diastereoisomer and the minor isomer the same than *anti* product. We then extended these observations to the rest of β-fluoroamines confirming that they followed a similar trend than those previously described. Consequently, structure *syn/anti* can be attributed in each case (Table 4.6).

Table 4.6. Determination of diastereoselectivity for compounds **4.126**, **4.128, 4.130**,**4.132**, **4.134** and **4.136**.



Reported data for *syn* isomer[21]			
Nº	**δ (ppm)**	**m**	***J* (Hz)**
5	4.50	d	6.4
4	4.19-4.11	m	--

Reported data for *anti* isomer[21]			
Nº	**δ (ppm)**	**m**	***J* (Hz)**
5	4.33-4.21	m	--
4	4.17-4.14	m	--

R	**Major**			**Minor**		
	Nº	**δ (ppm)[a]**	**m[a]**	**Nº**	**δ (ppm)[a]**	**m**
H	5	4.54-4.50	m	5	4.30-4.20	m
	4	4.20-4.09	m	4	4.17-4.11	m
OMe	5	4.66-4.39	m	5	4.37-4.15	m
	4	4.24-4.06	m	4	4.11-3.98	m
OAc	5	4.54-4.46	m	5	4.29	td[b]
	4	4.22-4.06	m	4	4.25-4.15	m
Br	5	4.64-4.42	m	5	4.34-4.28	m
	4	4.20-4.05	m	4	4.24-4.16	m
CF_3	5	4.51-4.44	m	5	4.46-4.39	m
	4	4.22-4.10	m	4	4.30-4.22	m
NO_2	5	4.49-4.44	m	5	--	--
	4	4.25-4.15	m	4	--	--

[a] Determined by ^{1}H RNM. [b] J = 8.4 and 2.1 Hz.

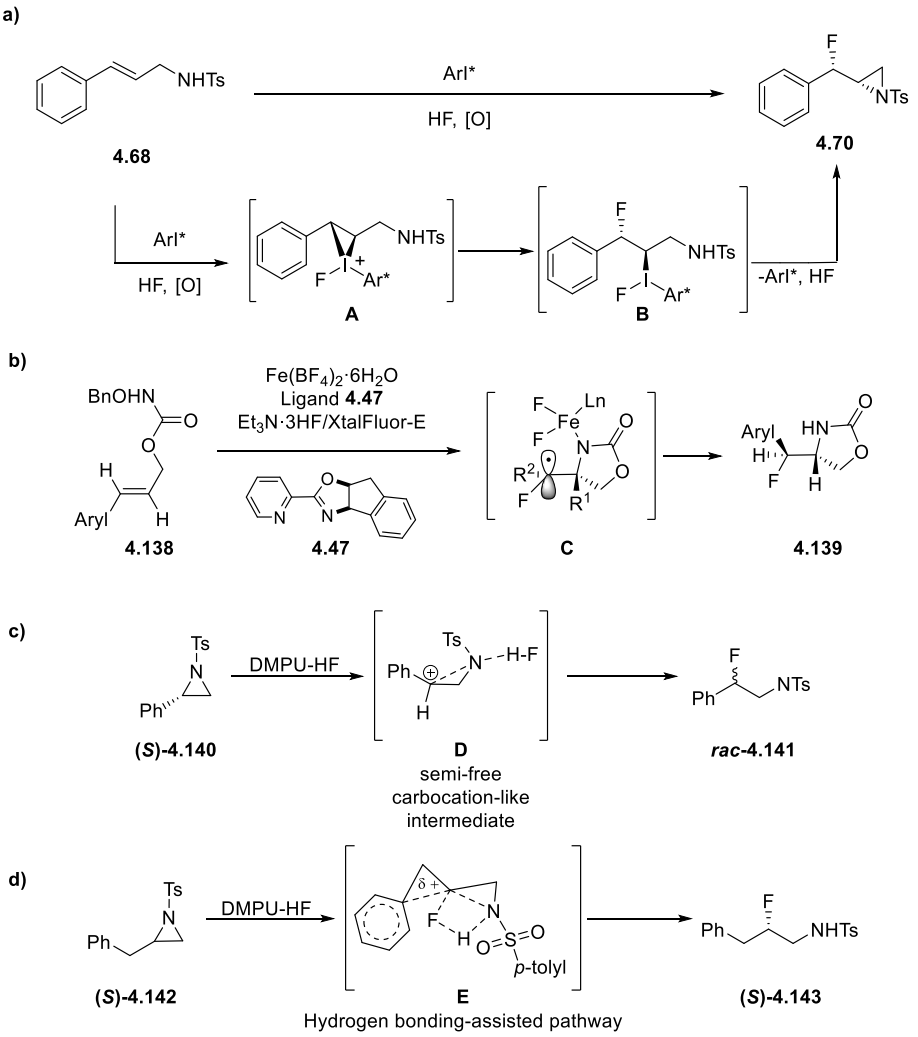
On the basis of these unexpected results, we might assume that the reaction did not proceed through a classical ring-opening of aziridines, characterized by providing *anti* products from *trans* aziridines, but also other alternatives should be also considered including the competition between two or more mechanisms.

4.3.3.4. Mechanistic studies.

As discussed in the *Introduction section*, several fluoroamines have been synthesized using cinnamyl derivatives as starting materials. For example, Jacobsen has reported the synthesis of *syn*-β-fluoroaziridines in an enantioselective manner.[31] He hypothesized that the reaction of tosylamide **4.68** with chiral $ArIF_2$, generated *in situ* from chiral ArI, py·HF and *m*CPBA as oxidant, evolved through an interaction of the double bond with the I(III) reagent to give intermediate **A**, which was then opened by fluoride in a *trans* manner affording **B**. An intramolecular displacement of the iodine derivative by the nitrogen of the tosylamide furnished the final product **4.70** with a *syn* disposition of fluorine and amino groups (Scheme 4.27a).

Xu demonstrated that the reaction of carbamoyl cinnamyl derivatives with Fe catalyst and Et_3N·HF afforded fluorooxazolidinones as a mixture *syn/anti* of isomers.[21] He proposed the formation of a radical intermediate and a transfer of fluorine from intermediate **C** (see Scheme 4.11 and Scheme 4.27b). The *syn* isomer was mainly afforded when the EW groups (Scheme 11, R^3= *p*-EtOOCPh, $R^1 = R^2 = H$) were used as substituents of the aromatic ring.

Additionally, a study performed by Hammond[41] about the opening of 2-phenyl-1-tosyl-aziridine with DMPU·HF led to racemic fluroamines, which was explained on the basis of a S_N1 mechanism (Scheme 4.24 and Scheme 27c). However, the use of 2-benzyl-1-tosylaziridine gave access to the *syn* isomer under similar reaction conditions (Scheme 27d). In this case, the retention of the configuration resulted from the participation of the phenyl group, which contributed to form a highly delocalized phenonium ion-like. Then, the delivery of HF assisted by and F-H-N bond provided the addition of the fluoride by the same face of the nitrogen.



Scheme 4.27. Different mechanisms proposed for the synthesis of β-fluoroamines starting from cinnamyl derivatives.

In our case, important mechanistic information can be extracted from the synthetic results collected in Tables 4.3-4.5:

a) The reaction was in general not stereoselective and mixtures *syn/anti* are obtained.

b) Activity and stereoselectivity were highly influenced by substituents present at aromatic ring. Thus, compounds with

ED groups reacted at room temperature while heating was required when EW groups were bound to the aromatic ring. Concerning the stereoselectivity, the presence of EW groups led to mainly *syn* products while mixtures *syn/anti* were obtained when ED were used.

c) Only aziridine was detected in excellent yield when the reaction was driven in the presence of KF whereas CsF and Xtal-F favored the decomposition of the starting material.

d) No conversion or aziridine was detected after the addition of $Et_3N{\cdot}HF$. However, the use of py·HF led to a complex mixture.

e) The absence of molecular sieves dramatically decreased the amount of fluoroamines formed and favored the formation of the opposite isomer *anti*.

f) Aziridines were detected in all cases.

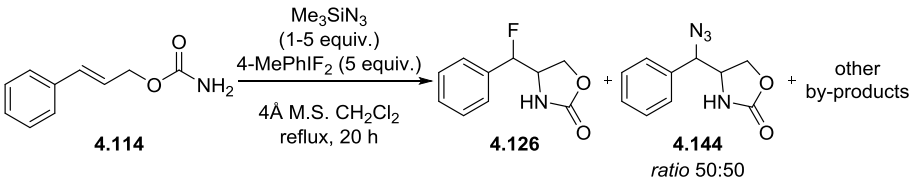
These results are more in agreement with the proposals of Xu[21] and Hammond,[41] who suggested that the reaction evolved through S_N1 mechanism with the formation of a radical or a pseudo-carbocation intermediates.

The formation of a carbocation may be consistent with the fact that ED groups stabilize it at the benzylic position with the consequent formation of a mixture of isomers. However, this mechanism would not justify the *syn* selectivity observed for EW groups.

In order to gain insight on the formation a carbocation-like intermediate, we attempted the reaction under standard conditions in the presence of Me_3SiN_3. The hypothesis was that if fluoride ion was generated in the reaction medium, it could react with the silyl reagent

releasing azide anion, a good nucleophile. This azide species, in turn, would be able to open the aziridine following an S_N2 mechanism.

Initially we performed a competitive reaction by reacting carbamate **4.114** with 4-MePhIF$_2$ (**4.124**), and Me_3SiN_3 under optimal conditions (Scheme 4.28).

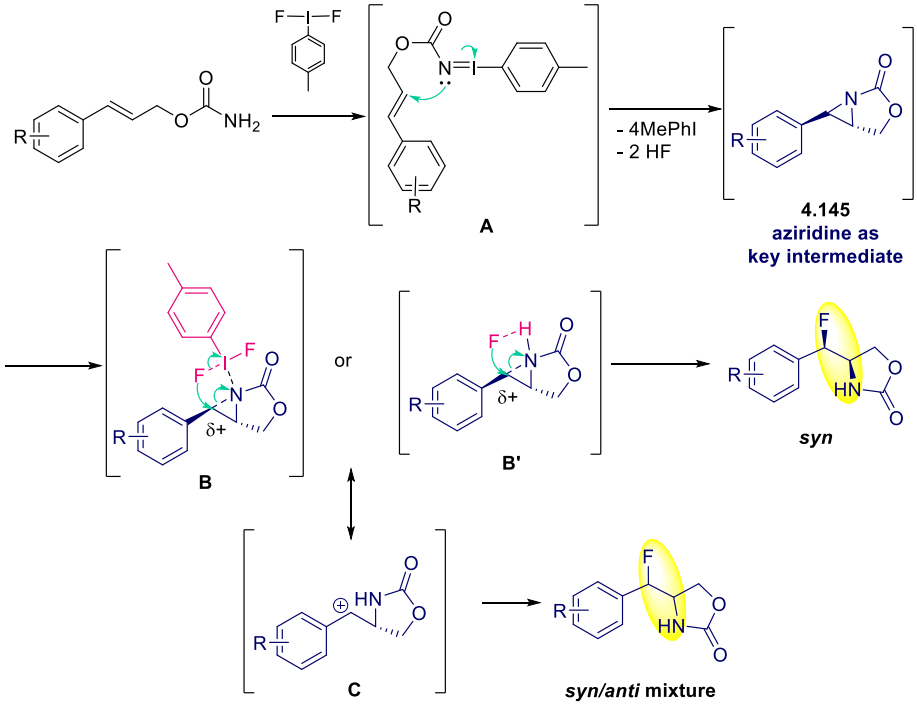


Scheme 4.28. Competitive ring-opening between 4-MePhIF$_2$ and Me_3SiN_3.

When carbamate **4.114** was treated under the standard reaction conditions in the presence of 1 equivalent of Me_3SiN_3, the ring-opened product **4.126** was afforded as major product, being the *syn* diastereoisomer the major one. Nevertheless, when the reaction was conducted using 2 equivalents of Me_3SiN_3, products resulting from opening with azide, as a mixture 50:50 of two diastereoisomers, were mainly obtained. Besides, other non-identified by-products containing azide and ***anti*-4.126** were also detected. Additionally, the treatment of the carbamate **4.114** and PhIF$_2$ with 5 equivalents of Me_3SiN_3 led to the formation of azido derivatives **4.144** also as a 50:50 mixture of *syn/anti* isomers, together with additional by products.

In view of these results, it can be deduced that anion N_3^- is generated under the reaction conditions, which allows concluding that the anion F^- is present in the medium. These results also suggest that both products **4.126** and **4.144** might be formed by different mechanisms. Particularly, the formation of the azido derivatives **4.144** can be justified through the formation of a carbocation since two diastereoisomers were afforded in 50:50 *ratio*. This ratio is of similar order than that obtained when **4.116** was treated with 4-MePhIF$_2$ under the standard conditions.

Taking into account these results, it can be proposed that the reaction proceeds through an S_N1 type reaction by the formation of a carbocation. When electron-withdrawing groups are attached to the aromatic ring, the interaction of the iodo-nitrene with double bond is slowed down and, hence, the formation of carbocation is less favorable. In this case, the *syn* selectivity might be explained by a carbocation-like intermediate with interaction of HF or 4-MePhIF$_2$ with the aziridinic nitrogen, which would activate the aziridine opening and would assist the delivery of F by the same face of the nitrogen. The latest tests revealed that the addition of an extra equivalent of 4-MePhIF$_2$ to the reaction mixture after 2 days of reaction was able to open the aziridine intermediate which had been formed. Thus, this finding might suggest that the formation of **B'** intermediate may be more plausible than **B** although any posibility should be discarded.



Scheme 4.29. Proposed mechanism for the formation of *syn*/*anti* diastereoisomers in the reaction of carbamates **4.114-4.122** with 4-MePhI$_2$.

On the other hand, the formation of the carbocation is more favored for the presence of electron-donating groups. In this case, the previous mechanism would compete with the attack to the carbocation affording mixtures of compounds where the *syn* isomer would be still the major one. However, a mixture 50:50 of *syn/anti* isomers was obtained for the synthesis of azido derivatives since the interaction with the nitrogen would not be possible in this case (Scheme 4.29).

This mechanism is also compatible with the fact that the addition of fluoride sources do not increase the yield, and may be detrimental limiting the interaction of 4-MePhIF_2 with the carbamate.

The mechanistic proposal would be completed with the reaction of carbamate with 4-MePhIF_2 to give the imidoiodinane **A**, which would undergo an intramolecular cyclization to furnish the aziridine **4.145** in a similar manner to previous studies carried out in our group.[50]

Despite proposing a mechanism to explain the observed products, further investigations should be carried out in order clarify it. DTF calculations might contribute enormously in elucidating these results and, therefore should be considered in the future investigations.

4.4. CONCLUSIONS.

In summary, the syntheses of β-fluoroamines starting from carbamates and mediated by hypervalent iodine (III) have been studied. To reach that purpose, cinnamyl carbamates were prepared from the corresponding cinnamyl alcohols which, in turn, were synthesized from the corresponding commercially available cinnamic acids. Fluoroamination reaction was then performed under different conditions and in the presence of several fluoride sources. In this case, 4-MePhIF_2 was selected as fluoride and oxidant reagent and it was prepared through fluorination reaction of the corresponding

4-iodotoluene in the presence of Selectfluor and $Et_3N{\cdot}3HF$. Thus, from that study, the following conclusions were extracted:

i) This last reaction only works in chlorinated solvents.

ii) The amount of hypervalent iodine (III) is key to reproduce the results.

iii) The presence of an extra fluoride source such as CsF, KF, py·9HF, $Et_3N{\cdot}3HF$ or Xtal-F did not improved the results, but was detrimental for the formation of β-fluoroamines.

iv) Unexpected diastereoselectivity was observed from the ring-opening process, the *syn* diastereomeric product being obtained in preference and in moderate yields.

v) The installation of electron-donating groups in the aryl ring led to the formation of a mixture of products in moderate diastereoselectivity. However, the presence of electron-withdrawing ones increased the selectivity towards the formation of *syn* product. The more electron-withdrawing group resulted in better syn stereoselectivity.

vi) Two different reaction paths have been proposed to explain these results in which aziridine would be a key intermediate generated *via* an intramolecular nitrene transfer. The first reaction path might proceed through the formation of a carbocation. The second plausible reaction path compiting with the former would involve a pseudo-carbocation where the nitrogen atom would have a directing role assisting fluoride nucleophilic attack on the same face via hydrogen bonding or via interaction of N with I(III)-F species.

vii) DFT calculations and further studies are required to elucidate the mechanism.

4.5. EXPERIMENTAL SECTION

4.5.1. General methods.

All reagents were purchased from Sigma Aldrich, CYMIT or Fluorochem chemical companies. Dichloromethane (CH_2Cl_2) was distilled from CaH_2, tetrahydrofurane (THF) was distilled from sodium and acetonitrile (CH_3CN) and triethylamine (Et_3N) were stored with activated 4Å M.S. Anhydrous chloroform ($CHCl_3$) and 1,2-dichloroethane (DCE) were purchased from Sigma Aldrich. 4Å M.S. were activated by heating under high vacuum at 260 °C for 10 h and then were stored at 165 °C. Methanol (MeOH) was used without any distillation. ^{1}H, ^{13}C NMR and ^{19}F spectra were recorded on a Varian® Mercury VX 400 or on a Bruker® Avance Ultrashield (400 MHz, 100.6 and 177 MHz respectively) spectrometer. NMR signals were fully assigned by COSY, HSQC, NOESY and HMBC experiments. All chemical shifts are quoted on the δ scale in ppm using the residual solvent as internal standard (^{1}H NMR: $CDCl_3$ = 7.26; CD_2Cl_2 = 5.32 ^{13}C NMR: $CDCl_3$ = 77.2; CD_2Cl_2 = 54.0). Coupling constants (J) are reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Infrared (IR) spectra were recorded on a JASCO FTIR-600 plus Fourier Transform Infrared Spectrophotometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Melting points (m.p.) were recorded with Reichert apparatus. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck® aluminium backed sheets coated with 60 F_{254} silica gel. Visualization of the silica plates was achieved using a UV lamp (λmax = 254 nm) and/or by heating plates previously dipped in an anisaldehyde solution. Flash chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh).

4.5.2. General procedures.

4.5.2.1. General procedure for reductions of cinnamyl acids.[44b]

Triethylamine (2.00 mmol) was added to a solution of cinnamic acid (2.00 mmol) in dry THF (3.3 mL) at -5 °C. The reaction mixture was stirred for 1 h and then ethylchloroformate (2.00 mmol) was slowly added over 10 min. After stirring 1h, $NaBH_4$ (7.60 mmol) was introduced in one portion and the mixture was allowed to stir for 30 min. Then, methanol (2.3 mL) was added dropwise for 15 min and the mixture was stirred for 2.5 h at room temperature. Saturated NH_4Cl solution (3.6 mL) was added to quench the reaction and the aqueous phase was extracted with dichloromethane (3x10 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by flash chromatography using hexane/AcOEt mixtures.

4.5.2.2. General protocol for carbomoylation of cinnamyl alcohols.[45]

A solution of trichloroacetyl isocyanate (TAI) (1.05 mmol) in dry benzene (1.0 mL) was added to a solution of cinnamyl alcohol (1.00 mmol) in dry dichloromethane (2.0 mL) at room temperature. The mixture was stirred until TLC showed complete consumption of the starting alcohol. Then, a solution of K_2CO_3 (20 mol%) in methanol (3.0 mL) was added and the mixture was stirred at room temperature until methanolysis was complete. After solvent evaporation, the residue was dissolved in a mixture 1:1 diethylether and water. The aqueous phase was extracted with diethylether (3x10 mL) and washed with brine. The combined organic phases was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The product was purified by flash chromatography using hexane/AcOEt mixtures and then it was recrystallised by slow diffusion of pentane into a solution of the carbamate in THF.

4.5.2.3. General procedure for the difluorination of p-iodotoluene*.*

To a flamed Schlenk containing a solution of 4-iodotoluene (0.45 mmol) and Selectfluor (1.58 mmol) in dry CH_3CN (11 mL),

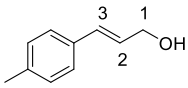
$Et_3N{\cdot}3HF$ (1.62 mmol) was added at room temperature. The reaction mixture was protected from the light and stirred for 22 h. Solvent was removed under inert conditions and reduced pressure and the residue was redissolved in a mixture 3:1 hexane/$CHCl_3$. The residue was extracted (3x1.5 mL) using this mixture under inert atmosphere and the organic phases were concentrated under vacuum. The resulting residue was used in the next step without purification.

4.5.2.4. General method for the aminofluorination of carbamates.

To a flamed Schlenk charged with carbamate (0.09 mmol) and 4 Å M.S. (90 mg), a solution of 4-$MePhIF_2$ (0.37 mmol) in dry CH_2Cl_2 (2.3 mL) was added. The reaction mixture was warmed to reflux or stirred at room temperature until complete consumption of starting material. The mixture was filtered through a pad of celite, washed with CH_2Cl_2 and the solvent was removed under reduced pressure. The resulting crude was purified by flash chromatography using hexane/AcOEt mixtures.

4.5.3. Characterization data.

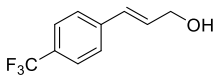
(*E*)-3-(*p*-tolyl)prop)-2-en-1-ol (4.101):



The title compound was synthesized following the procedure described for reductions of cinnamic acids starting from the *p*-methylcinnamic acid (600 mg, 3.70 mmol), ethyl chloroformate (354 µL, 3.70 mmol) and Et_3N (516 µL, 3.70 mmol) in THF (5.4 mL). Then, $NaBH_4$ (531.9 mg, 14.06 mmol) and methanol (4.3 mL) were introduced to the mixture at it was allowed to stir to complete consumption of starting material. A mixture of products in 88:12 ratio was obtained arose from the partial and complete reduction. Purification of this mixture using hexane/ethyl acetate (80:20) yield compound **4.101** (292.6 mg, 1.97 mmol, 53 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.1 Hz, 2H, H_{ar}), 7.18 – 7.09 (d, *J* = 8.1 Hz, 2H, H_{ar}), 6.56 (d, *J* = 15.9 Hz, 1H, H_3), 6.30 (dt, *J* = 15.9, 5.8 Hz, 1H, H_2), 4.28 (d, *J* = 5.8 Hz, 2H, H_1), 2.33 (s, 3H, $C\underline{H_3}$), 1.95 (bs, 1H, H_{OH}). ^{13}C NMR

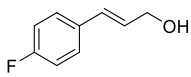
(100 MHz, $CDCl_3$) δ 137.6 (C_{ar}), 134.0 (C_{ar}), 131.2 (C_3), 129.4 (C_{ar}), 127.6 (C_2), 126.5 (C_{ar}), 63.8 (C_1), 21.3 ($\underline{C}H_3$). HR ESI-TOF MS for [M^+] $C_{10}H_{12}O^+$ (m/z): 148.0888; found: 148.0886. Analytical data were identical to that previously reported.[51]

(*E*)-3-(4-(trifluoromethyl)phenyl)prop)-2-en-1-ol (4.103):



The title compound was synthesized following the procedure described for reductions of cinnamic acids starting from *p*-trifluoromethylcinnamic acid (550 mg, 2.55 mmol), ethyl chloroformate (244 µL, 2.55 mmol) and Et_3N (355 µL, 2.55 mmol) in THF (4.2 mL). Then, $NaBH_4$ (366.6 mg, 9.69 mmol) and methanol (2.9 mL) were added to the mixture which was stirred until complete consumption of starting material. A mixture of products in 88:12 ratio was obtained arose from the partial and complete reduction. The crude was then purified by flash chromatography with hexane/ethyl acetate (70:30) to give alcohol **4.103** (214.1 mg, 1.06 mmol, 41 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2H, H_{ar}), 7.45 (d, *J* = 8.3 Hz, 2H, H_{ar}), 6.65 (d, *J* = 16.0 Hz, 1H, H_3), 6.44 (dt, *J* = 16.0, 5.3 Hz, 1H, H_2), 4.36 (dd, *J* = 5.3, 1.3 Hz, 2H, H_1), 1.94 (bs, 1H, H_{OH}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3 (d, *J* = 1.2 Hz, C_{ar}), 131.4 (C_3) 129.6 (d, *J* = 32.7 Hz, C_{ar}), 129.1 (C_2), 126.7 (C_{ar}), 125.7 (q, *J* = 3.8 Hz, C_{ar}), 124.9 (q, *J* = 270.5 Hz, $\underline{C}F_3$), 63.4 (C_1). ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.5. HR ESI-TOF MS for [M-H^-] $C_{10}H_8F_3O^-$ (m/z): 201.0527; found: 201.0537. Analytical data were identical to that previously reported.[52]

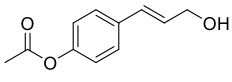
(*E*)-3-(4-fluorophenyl)prop)-2-en-1-ol (4.104):



The title compound was synthesized following the procedure described for reductions of cinnamic acids starting from *p*-fluorocinammic acid (692.8 mg, 4.17 mmol), ethyl chloroformate (400 µL, 4.17 mmol) and Et_3N (580 µL, 4.17 mmol) in THF (6.9 mL). Then, $NaBH_4$ (600 mg, 15.8 mmol) and methanol (4.8 mL) were added to the mixture which was stirred to complete consumption of starting material. A mixture of products in 93:7 ratio was obtained arose from the partial and complete reduction. The crude was purified by flash

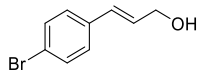
chromatography with hexane/ethyl acetate (60:40) to achieve the cinnamyl alcohol **4.104** (385.6 mg, 2.53 mmol, 61 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.7, 5.5 Hz, 2H, H_{ar}), 7.00 (t, *J* = 8.7 Hz, 2H, H_{ar}), 6.57 (d, *J* = 15.9 Hz, 1H, H_3), 6.41 – 6.21 (dt, *J* = 15.9, 5.7, 1H, H_2), 4.30 (d, *J* = 5.7 Hz, 2H, H_1), 1.92 (bs, 1H, H_{OH}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, *J* = 246.8 Hz, C_{ar}), 133.0 (d, *J* = 3.1 Hz, C_{ar}), 130.0 (C_2), 128.4 (d, *J* = 2.2 Hz, C_3), 128.1 (d, *J* = 8.0 Hz, C_{ar}), 115.6 (d, *J* = 21.7 Hz, C_{ar}), 63.64 (C_1). ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.4. HR ESI-TOF MS for [M^+] $C_9H_9FO^+$ (m/z): 152.0637 found: 152.0635. Analytical data were identical to that previously reported.[53]

(*E*)-3-(4-acetoxyphenyl)prop)-2-en-1-ol (4.105):



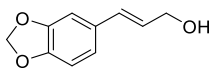
The title compound was synthesized following the procedure described for reductions of cinnamic acids starting from *p*-acetoxycinnamic acid (1600 mg, 7.76 mmol), ethyl chloroformate (742 µL, 7.76 mmol) and Et_3N (1080 µL, 7.76 mmol) in THF (12.8 mL). Then, $NaBH_4$ (1115.5 mg, 29.49 mmol) and methanol (8.9 mL) were added to the mixture which was stirred until complete consumption of starting material. A mixture of products in 90:10 ratio was obtained arose from the partial and complete reduction. The crude was purified by flash chromatography with dichloromethane/ethyl acetate (60:40) to give the cinnamyl alcohol **4.105** (618.8 mg, 3.21 mmol, 42 %) as a yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.6 Hz, 2H, H_{ar}), 7.03 (d, *J* = 8.6 Hz, 2H, H_{ar}), 6.57 (d, *J* = 15.9 Hz, 1H, H_3), 6.29 (dt, *J* = 15.9, 5.4 Hz, 1H, H_2), 4.28 (d, *J* = 5.4 Hz, 2H, H_1), 2.29 (s, 3H, $C\underline{H}_3CO$), 2.00 (bs, 1H, H_{OH}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7 ($CH_3\underline{C}O$), 150.1 (C_{ar}), 134.6 (C_{ar}), 130.0 (C_3), 128.9 (C_2), 127.5 (C_{ar}), 121.8 (C_{ar}), 63.6 (C_1), 21.2 ($\underline{C}H_3CO$). HR ESI-TOF MS for [M+Na^+] $C_{11}H_{12}NaO_3^+$ (m/z): 215.0679; found: 215.0680. Analytical data were similar to that previously reported.[54]

(*E*)-3-(4-bromophenyl)prop)-2-en-1-ol (4.106):



The title compound was synthesized following the procedure described for reductions of cinnamic acids starting from *p*-bromocinnamic acid (454.1 mg, 2.00 mmol), ethyl chloroformate (191 µL, 2.00 mmol) and Et_3N (279 µL, 2.00 mmol) in THF (3.3 mL). Then, $NaBH_4$ (287.5 mg, 7.60 mmol) and methanol (2.3 mL) were added to the reaction mixture at it stirred until complete consumption of starting material. A mixture of products in 82:18 ratio was obtained arose from the partial and complete reduction. The crude was then purified by flash chromatography with hexane/ethyl acetate (70:30) to render the cinnamyl alcohol **4.106** (340.1 mg, 1.60 mmol, 80 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 2H, H_{ar}), 7.22 (d, *J* = 8.5 Hz, 2H, H_{ar}), 6.54 (d, *J* = 15.9 Hz, 1H, H_3), 6.33 (dt, *J* = 15.9, 5.1 Hz, 1H, H_2), 4.22 (d, *J* = 5.1Hz, 2H, H_1), 1.96 (bs, 1H, H_{OH}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (C_{ar}), 131.8 (C_3), 129.8 (C_{ar}), 129.4 (C_{ar}), 128.1 (C_2), 121.5 (C_{ar}), 63.5 (C_1). HR ESI-TOF MS for [M-H$^-$] $C_9H_9BrO^-$ (m/z): 211.9837 found: 211.9838. Analytical data were identical to that previously reported.[51]

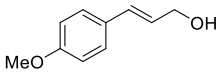
(*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)prop-2-en-1-ol (4.107):



The title compound was synthesized following the procedure described for reductions of cinnamic acids starting from (*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)acrylic acid (700 mg, 3.64 mmol), ethyl chloroformate (348 µL, 3.64 mmol) and Et_3N (507 µL, 3.64 mmol) in THF (6.0 mL). Then, $NaBH_4$ (523.2 mg, 13.84 mmol) and methanol (4.2 mL) were added to the mixture at it was stirred until complete consumption of starting material. A mixture of products in 85:15 ratio was obtained arose from the partial and complete reduction. The crude was purified by flash chromatography with hexane/ethyl acetate (70:30) to give the cinnamyl alcohol **4.107** (350.7 mg, 1.97 mmol, 54 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, *J* = 1.5 Hz, 1H, H_{ar}), 6.82 (d, 8.0 Hz, 1H, H_{ar}), 6.75 (d, 8.0 Hz, 1H, H_{ar}), 6.51 (d, *J* = 15.8 Hz, 1H, H_3), 6.19 (dt, *J* = 15.8, 5.9 Hz, 1H, H_2), 5.95 (s, 2H, O-CH_2-O), 4.28 (d, *J* = 5.9 Hz, 2H, H_1), 1.60 (s, 1H, H_{OH}). ^{13}C NMR

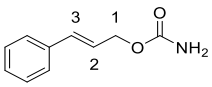
(100 MHz, $CDCl_3$) δ 148.1 (C_{ar}), 147.4 (C_{ar}), 131.2 (C_{ar}), 131.1 (C_3), 126.8 (C_2), 121.3 (C_{ar}), 108.4 (C_{ar}), 105.9 (C_{ar}), 101.2 (O-CH_2-O), 63.9 (C_1). HR ESI-TOF MS for [M^+] $C_{10}H_{10}O_3^+$ (m/z): 178.0630 found: 178.0626. Analytical data were identical to that previously reported.[55]

(*E*)-3-(4-methoxyphenyl)prop)-2-en-1-ol (4.108):



The title compound was synthesized following the procedure described for reductions of cinnamic acids starting from *p*-methoxycinnamic acid (712.8 mg, 4.00 mmol), ethyl chloroformate (182.4 µL, 4.00 mmol) and Et_3N (558 µL, 4.00 mmol) in THF (6.6 mL). Then, $NaBH_4$ (575 mg, 15.20 mmol) and methanol (4.6 mL) were added to the mixture that was stirred until complete consumption of starting material. A mixture of products in 85:15 ratio was obtained arose from the partial and complete reduction. The crude was purified by flash chromatography with hexane/ethyl acetate (70:30) to afford the cinnamyl alcohol **4.108** (342.2 mg, 2.08 mmol, 52 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.7 Hz, 2H, H_{ar}), 6.85 (d, *J* = 8.7 Hz, 2H, H_{ar}), 6.54 (d, *J* = 15.9 Hz, 1H, H_3), 6.23 (dt, *J* = 15.9, 5.9 Hz, 1H, H_2), 4.28 (dd, *J* = 5.9, 1.2 Hz, 2H, H_1), 3.80 (s, 3H, $C\underline{H_3}O$), 1.82 (bs, 1H, H_{OH}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (C_{ar}), 131.0 (C_3), 129.5 (C_{ar}), 127.8 (C_{ar}), 126.4 (C_2), 114.1 (C_{ar}), 64.0 (C_1), 55.4 ($\underline{C}H_3O$). HR ESI-TOF MS for [M^+] $C_{10}H_{12}O_2^+$ (m/z): 168.0837 found: 164.0837. Analytical data was identical to that previously reported.[56]

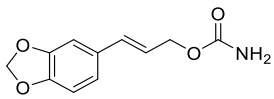
(*E*)-3-(phenyl)allyl carbamate (4.114):



The title compound was prepared following the general protocol described for the synthesis of carbamates starting from a solution of commercially available (*E*)-3-phenyl-2-propen-1-ol (**4.109**) (1055 mg, 7.9 mmol) and TAI (0.6 mL, 8.3 mmol) in CH_2Cl_2 (16.0 mL) and benzene (8.0 mL). Then, K_2CO_3 (217.4 mg, 1.6 mmol) and MeOH (24.0 mL) were added to the mixture and the reaction was stirred until complete consumption of starting material. The residue was purified by flash chromatography using hexane/ethyl acetate (80:20), and then it was recrystallized to give

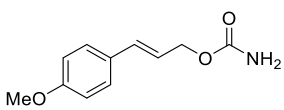
the compound **4.114** (1200 mg, 6.78 mmol, 83 %) as a white powder. m.p. 120-126 °C. IR (neat): 3409, 3328, 3264, 3055, 1679, 1626, 1602, 1409, 1341, 1115, 1048, 969 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$: δ 7.40-7.37 (m, 2H, H_{ar}), 7.34-7.30 (m, 2H, H_{ar}), 7.28-7.24 (m, 1H, H_{ar}), 6.65 (d, *J* = 15.9 Hz, 1H, H_3), 6.29 (dt, *J* = 15.9, 6.4 Hz, 1H, H_2), 4.99 (bs, 2H, H_{NH}), 4.73 (dd, *J* = 6.4, 1.3 Hz, 2H, H_1). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0 (O<u>C</u>(O)NH2), 136.3 (C_{ar}), 133.9 (C_3), 128.7 (C_{ar}), 128.1 (C_{ar}), 126.7 (C_{ar}), 123.6 (C_2), 65.7 (C_1). HR ESI-TOF MS for $[M+Na]^+$ $C_{10}H_{11}NNaO_2$ (m/z): 200.0682, found: 200.0680.

(*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)allyl carbamate (4.115):



The title compound was prepared following the general protocol described for the synthesis of carbamates starting from a solution of **4.107** (506.8 mg, 2.84 mmol) and TAI (214 µL, 3 mmol) in CH_2Cl_2 (5.7 mL) and benzene (2.8 mL). Then, K_2CO_3 (78.5 mg, 0.57 mmol) and MeOH (8.6 mL) were added to the mixture and the reaction was stirred until complete consumption of starting material. The residue was purified by flash chromatography using hexane/ethyl acetate (60:40) and then, it was recrystallized to give the compound **4.115** (485.5 mg, 2.19 mmol, 77 %) as a colorless solid. m.p. 96-100 °C. IR (neat): 3420, 3328, 3257, 2885, 2785, 1683, 1615, 1417, 1348, 1246, 1035, 966 cm^{-1}. ^1H NMR (400 MHz, CD_2Cl_2) δ 6.96 (d, *J* = 1.0 Hz, 1H, H_{ar}), 6.85 (d, *J* = 8.0 Hz, 1H, H_{ar}), 6.78 (d, *J* = 8.0 Hz, 1H, H_{ar}), 6.57 (d, *J* = 15.9 Hz, 1H,H_2), 6.15 (dt, *J* = 15.9, 6.4 Hz, 1H, H_3), 5.97 (s, 2H, O-CH_2-O), 4.89 (bs, 2H, H_{NH}), 4.67 (dd, *J* = 6.4, 0.6 Hz, 2H, H_2). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 157.2 (O<u>C</u>(O)NH_2), 148.7 (C_{ar}), 148.1 (C_{ar}), 133.7 (C_2), 131.3 (C_{ar}), 122.6 (C_3), 121.9 (C_{ar}), 108.7 (C_{ar}), 106.1 (C_{ar}), 101.9 (O-CH_2-O), 66.0 (C_1). HR ESI-TOF MS for $[M+Na^+]$ $C_{11}H_{11}NNaO_4^+$ (m/z): 244.0580; found: 244.0579.

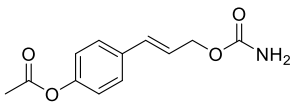
(*E*)-3-(4-methoxyphenyl)allyl) carbamate (4.116):



The title compound was prepared following the general protocol described for the synthesis of carbamates starting from a solution of **4.108**

(445.7 mg, 2.71 mmol) and TAI (203 µL, 2.84 mmol) in CH_2Cl_2 (5.4 mL) and benzene (2.7 mL). Then, K_2CO_3 (74.9 mg, 0.54 mmol) and MeOH (8.2 mL) were added to the mixture and the reaction was stirred until complete consumption of starting material. The residue was purified by flash chromatography using hexane/ethyl acetate (60:40) and then, it was recrystallized to yield the compound **4.116** (356.2 mg, 1.72 mmol, 63 %) as a colorless solid. m.p. 110-118 °C. IR (neat): 3429, 3332, 3270, 3205, 2954, 2832, 2359, 1683, 1511, 1352, 1251 cm^{-1}. ^1H NMR (400 MHz, CD_2Cl_2) δ 7.34 (d, *J* = 8.7 Hz, 2H, H_{ar}), 6.86 (d, *J* = 8.7 Hz, 2H, H_{ar}), 6.59 (d, *J* = 15.9 Hz, 1H, H_3), 6.16 (dt, *J* = 15.9, 6.4 Hz, 1H, H_2), 4.79 (bs, 2H, H_{NH}), 4.66 (dd, *J* = 6.4, 1.1 Hz, 2H, H_2), 3.79 (s, 3H, $C\underline{H_3}O$). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 160.1 ($O\underline{C}(O)NH_2$), 157.1 (C_{ar}), 133.7 (C_3), 129.5 (C_{ar}), 128.3 (C_{ar}), 122.1 (C_2), 114.5 (C_{ar}), 66.2 (C_1), 55.8 ($\underline{C}H_3O$). HR ESI-TOF MS for [M+Na^+] $C_{11}H_{13}NNaO_3^+$ (m/z): 230.0788; found: 230.0791.

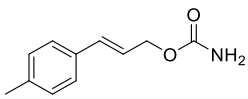
(*E*)-3-(4-acetylphenyl)allyl carbamate (4.117):



The title compound was prepared following the general protocol described for the synthesis of carbamates starting from a solution of **4.105** (460.7 mg, 2.40 mmol) and TAI (180 µL, 2.52 mmol) in CH_2Cl_2 (4.8 mL) and benzene (2.4 mL). Then, K_2CO_3 (66.3 mg, 0.48 mmol) and MeOH (7.3 mL) were added to the mixture and the reaction was stirred until complete consumption of starting material. The residue was purified by flash chromatography using hexane/ethyl acetate (60:40) and then, it was recrystallized to render the compound **4.117** (218.9 mg, 0.93 mmol, 39 %) as a yellowish powder. m.p. 138-139 °C. IR (neat): 3419, 3335, 3255, 3210, 2966, 2364, 1754, 1683, 1617, 1508, 1350, 1214, 1062 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.8 Hz, 2H, H_{ar}), 7.05 (d, *J* = 8.8 Hz, 2H, H_{ar}), 6.63 (d, *J* = 15.9 Hz, 1H, H_3), 6.25 (dt, *J* = 15.9, 6.4 Hz, 1H, H_2), 4.71 (m, 4H, H_1, H_{NH}), 2.29 (s, 3H, $C\underline{H_3}CO$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 ($CH_3\underline{C}O$), 156.6 ($O\underline{C}ONH_2$)150.5 (C_{ar}), 134.2 (C_{ar}), 133.0 (C_3), 127.7 (C_2), 124.0 (C_{ar}), 121.9 (C_{ar}), 65.7 (C_1), 21.3 ($\underline{C}H_3CO$).

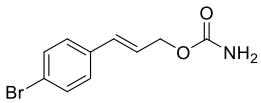
HR ESI-TOF MS for [M+Na$^+$] $C_{12}H_{13}NNaO_3^+$ (m/z): 242.0788; found: 242.0735.

(*E*)-3-(*p*-tolyl)allyl carbamate (4.118):



The title compound was prepared following the general protocol described for the synthesis of carbamates starting from a solution of **4.101** (432.5 mg, 2.90 mmol) and TAI (218 μL, 3.04 mmol) in CH_2Cl_2 (5.9 mL) and benzene (2.9 mL). Then, K_2CO_3 (80.2 mg, 0.58 mmol) and MeOH (8.8 mL) were added to the mixture and the reaction was stirred until complete consumption of starting material. The residue was purified by flash chromatography using hexane/ethyl acetate (60:40) and then, it was recrystallized to give the compound **4.118** (462.3 mg, 2.42 mmol, 83 %) as a colorless solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.29 (d, *J* = 8.1 Hz, 2H, H_{ar}), 7.16 (d, *J* = 8.1 Hz, 2H, H_{ar}), 6.61 (d, *J* = 15.9 Hz, 1H, H_3), 6.25 (dt, *J* = 15.9, 6.3 Hz, 1H, H_2), 4.86 – 4.58 (m, 4H, H_1, H_{NH}), 2.33 (s, 3H, C$\underline{H}_3$). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 157.0 (O$\underline{C}$(O)NH_2), 138.5 (C_{ar}), 134.0 (C_{ar}), 133.8 (C_3), 129.7 (C_{ar}), 126.9 (C_{ar}), 123.2 (C_2), 66.0 (C_1), 21.4 ($\underline{C}H_3$). HR ESI-TOF MS for [M+Na$^+$] $C_{11}H_{13}NNaO_2^+$ (m/z): 214.0838; found: 214.0839. Analytical data was identical to that previously reported.[57]

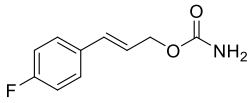
(*E*)-3-(4-bromophenyl)allyl carbamate (4.119):



The title compound was prepared following the general protocol described for the synthesis of carbamates starting from a solution of **4.106** (560.7 mg, 2.63 mmol) and TAI (197 μL, 2.76 mmol) in CH_2Cl_2 (5.3 mL) and benzene (2.6 mL). Then, K_2CO_3 (72.7 mg, 0.53 mmol) and MeOH (8.0 mL) were added to the mixture and the reaction was stirred until complete consumption of starting material. The residue was purified by flash chromatography using hexane/ethyl acetate (60:40) and then, it was recrystallized to achieve the compound **4.119** (538.4 mg, 2.10 mmol, 80 %) as a colorless solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.46 (d, *J* = 8.5 Hz, 2H, H_{ar}), 7.28 (d, *J* = 8.5 Hz, 2H, H_{ar}), 6.59 (d, *J* = 16.0 Hz, 1H,

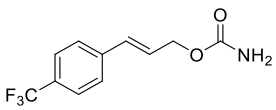
H_3), 6.30 (dt, *J* = 16.0, 6.1 Hz, 1H, H_2), 4.88 – 4.54 (m, 4H, H_1, H_{NH}). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 156.9 (O<u>C</u>(O)NH_2), 134.0 (C_{ar}), 132.3 (C_{ar}), 132.2 (C_3), 128.6 (C_{ar}), 125.4 (C_2), 122.2 (C_{ar}), 65.7 (C_1). HR ESI-TOF MS for [M+Na$^+$] $C_{10}H_{10}BrNNaO_2^+$ (m/z): 277.9787; found: 277.9789. Analytical data correspond which was reported in bibliography.[57]

(*E*)-3-(4-fluorophenyl)allyl carbamate (4.120):



The title compound was prepared following the general protocol described for the synthesis of carbamates starting from a solution of alcohol **4.104** (511.0 mg, 3.36 mmol) and TAI (252 µL, 3.53 mmol) in CH_2Cl_2 (6.8 mL) and benzene (3.4 mL). Then, K_2CO_3 (92.9 mg, 0.67 mmol) and MeOH (10.2 mL) were added to the mixture and the reaction was stirred until complete consumption of starting material. The residue was purified by flash chromatography using hexane/ethyl acetate (60:40) and then, it was recrystallized to afford the compound **4.120** (497.0 mg, 2.55 mmol, 76 %) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.31 (m, 2H, H_{ar}), 7.12 – 6.94 (m, 2H, H_{ar}), 6.62 (d, *J* = 15.9 Hz, 1H, H_3), 6.23 (dtd, *J* = 15.9, 6.2, 0.5 Hz, 1H, H_2), 4.68 (dd, *J* = 6.2, 1.4 Hz, 2H, H_1). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 163.1 (d, *J* = 246.4 Hz, C_{ar}), 157.3 (O<u>C</u>(O)NH_2), 133.3 (d, *J* = 3.2 Hz, C_{ar}), 132.7 (C_3) 128.8 (d, *J* = 8.0 Hz, C_{ar}), 124.4 (d, *J* = 2.1 Hz, C_2), 116.02 (d, *J* = 21.7 Hz, C_{ar}), 65.9 (C_2). ^{19}F NMR (377 MHz, CD_2Cl_2) δ -112.9. HR ESI-TOF MS for [M+Na$^+$] $C_{10}H_{10}FNNaO_2^+$ (m/z): 218.0588; found: 218.0587. Analytical data was identical to that previously reported.[57]

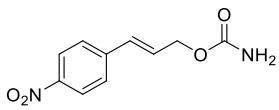
(*E*)-3-(4-(trifluoromethyl)phenyl)allyl carbamate (4.121):



The title compound was prepared following the general protocol described for the synthesis of carbamates starting from a solution of **4.103** (293.8 mg, 1.45 mmol) and TAI (109 µL, 1.52 mmol) in CH_2Cl_2 (2.9 mL) and benzene (1.5 mL). Then, K_2CO_3 (40.0 mg, 0.29 mmol) and MeOH (4.4 mL) were added to the mixture and the reaction was stirred until complete consumption of starting material. The residue was purified by

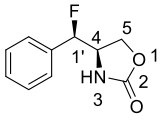
flash chromatography using hexane/ethyl acetate (60:40) and then, it was recrystallized to render the compound **4.121** (266.9 mg, 1.09 mmol, 75 %) as a colorless solid. m.p. 118-120 °C. IR (neat): 3443, 3327, 3268, 3197, 3038, 2966, 2359, 2327, 1740, 1686, 1321, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.2 Hz, 2H, H_{ar}), 7.48 (d, *J* = 8.2 Hz, 2H, H_{ar}), 6.68 (d, *J* = 16.0 Hz, 1H, H_3), 6.38 (dt, *J* = 16.0, 6.1 Hz, 1H, H_2), 4.90 – 4.61 (m, 4H, H_1, H_{NH}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5 (O<u>C</u>(O)NH_2), 139.9 (C_{ar}), 132.1 (C_3), 129.9 (q, *J* = 32.2 Hz, C_{ar}), 127.0 (apparent d, *J* = 271.9 Hz, <u>C</u>F_3) 126.9 (C_{ar}), 126.6 (C_2), 125.73 (q, *J* = 4.5 Hz, C_{ar}), 65.3 (C_1). ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.6. HR ESI-TOF MS for [M-H^-] $C_{11}H_9F_3NO_2^-$ (m/z): 244.0585; found: 244.0590.

(*E*)-3-(4-nitrophenyl)allyl carbamate (4.122):



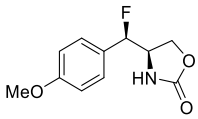
The title compound was prepared following the general protocol described for the synthesis of carbamates starting from a solution of alcohol **4.110** (300 mg, 1.67 mmol) and TAI (125 µL, 1.75 mmol) in CH_2Cl_2 (3.4 mL) and benzene (1.7 mL). Then, K_2CO_3 (46.2 mg, 0.33 mmol) and MeOH (5.1 mL) were added to the mixture and the reaction was stirred until complete consumption of starting material. The residue was purified by flash chromatography using hexane/ethyl acetate (60:40) and then, it was recrystallized to yield the compound **4.122** (295.4mg, 1.32 mmol, 80 %) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H, H_{ar}), 7.52 (d, *J* = 8.8 Hz, 2H, H_{ar}), 6.71 (d, *J* = 16.0 Hz, 1H, H_3), 6.46 (dt, *J* = 16.0, 5.8 Hz, 1H, H_2), 4.77 (dd, *J* = 5.8, 1.3 Hz, 2H, H_2), 4.70 (bs, 2H, H_{NH}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3 (O<u>C</u>(O)NH_2), 147.3 (C_{ar}), 142.8 (C_{ar}), 131.0 (C_3), 128.8 (C_2), 127.3 (C_{ar}), 124.2 (C_{ar}), 65.0 (C_1). HR ESI-TOF MS for [M-H^-] $C_{10}H_9N_2O_4^-$ (m/z): 221.0562; found: 221.0537. Analytical data were identical to that previously reported.[57]

***Syn*-4-(fluoro(phenyl)methyl)oxazolidin-2-one (4.126):**



The title compound was synthesized following the general procedures for the difluorination of 4-toluene and the subsequent aminofluorination of carbamates. First, 4-MePhIF$_2$ was prepared starting from 4-iodotoluene **4.123** (59.5 µL, 0.45 mmol), Selectfluor (558 mg, 1.58 mmol) and Et$_3$N·HF (270 µL, 1.62 mmol) in CH$_3$CN (11 mL). After the work-up, difluorinated compound was dissolved in CH$_2$Cl$_2$ (2.3 mL) and introduced into a flamed Schlenk together with carbamate **4.114** (16.2 mg, 0.09 mmol) and 4Å M.S (90 mg), affording **4.126** as a mixture *syn/anti* of two diastereoisomers in a ratio 90:10. This mixture was purified by flash chromatography using hexane/ethyl acetate (50:50) to yield **4.126** (10.2 mg, 0.05 mmol, 56 %) as an inseparable mixture of compounds *syn/anti*. An aliquot of this mixture was purified several times by flash chromatography using hexane/ethyl acetate (60:40) to get a sample of **4.126** as a white solid, pure enough to get the analytical data. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 – 7.41 (m, 3H, H$_{ar}$), 7.35 (m, 2H, H$_{ar}$), 5.35 (dd, *J* = 46.3, 7.0 Hz, 1H, H$_{1'}$), 5.15 (bs, 1H, H$_{NH}$), 4.54 – 4.50 (m, 2H, H$_5$), 4.20 – 4.09 (m, 1H, H$_4$). ^{13}C NMR (100 MHz, CDCl$_3$) δ 158.8 (C$_2$), 135.1 (d, *J* =19.7 Hz, C$_{ar}$), 129.9 (d, *J* = 1.8 Hz, C$_{ar}$), 129.3 (C$_{ar}$), 126.3 (d, *J* = 6.7 Hz, C$_{ar}$), 93.6 (d, *J* = 178.6 Hz, C$_{1'}$), 66.9 (d, *J* = 2.8 Hz, C$_5$), 56.3 (d, *J* = 31.5 Hz, C$_4$). ^{19}F NMR (377 MHz, CDCl$_3$) δ -186.3 (dd, *J* = 46.3, 10.5 Hz). HR ESI-TOF MS for [M+Na$^+$] C$_{10}$H$_{10}$FNNaO$_2^+$ (m/z): 218.0588; found: 218.0593. Analytical data correspond with those reported in bibliography.[21]

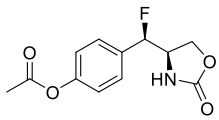
***Syn*-4-(fluoro(4-methoxyphenyl)methyl)oxazolidin-2-one (4.128):**



The title compound was synthesized following the general procedure described for the difluorination of 4-toluene and the subsequent aminofluorination of carbamates. First, 4-MePhIF$_2$ was prepared starting from 4-iodotoluene **4.123** (59.5 µL, 0.45 mmol), Selectfluor (558 mg, 1.58 mmol) and Et$_3$N·HF (270 µL, 1.62 mmol) in CH$_3$CN (11 mL). After the work-up, difluorinated compound was dissolved in CH$_2$Cl$_2$ (2.3 mL) and introduced

into a flamed Schlenk together with carbamate **4.116** (18.2 mg, 0.09 mmol) and 4Å M.S. (90 mg), affording **4.128** as a mixture *syn/anti* of two diastereoisomers in a ratio 66:34. After the work-up the reaction mixture was purified by flash chromatography using hexane/ethyl acetate (50:50) to yield **4.128** (13.1 mg, 0.06 mmol, 63 %) as an inseparable mixture of compounds *syn/anti*. An aliquot of this mixture was purified several times by flash chromatography using hexane/ethyl acetate (60:40) to get a sample of **4.128** as a white solid, pure enough to get the analytical data. m.p. 94-96 °C. IR (neat): 3288, 2920, 2850, 1743, 1614, 1515, 1246, 1178, 1025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 2H, H_{ar}), 6.95 (d, *J* = 8.5 Hz, 2H, H_{ar}), 5.27 (dd, *J* = 45.9, 7.4 Hz, 1H, $H_{1'}$), 4.97 (bs, 1H, H_{NH}), 4.66 – 4.39 (m, 2H, H_5), 4.26 – 4.04 (m, 1H, H_4), 3.83 (s, 3H, $C\underline{H_3}O$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8 (C_{ar}), 158.8 (d, *J* = 198.7 Hz, C_2), 128.0 (d, *J* = 6.0 Hz, C_{ar}), 127.0 (d, *J* = 20.4 Hz, C_{ar}), 114.6 (C_{ar}), 93.6 (d, *J* = 177.4 Hz, $C_{1'}$), 67.2 (d, *J* = 2.6 Hz, C_5), 56.1 (d, *J* = 33.2 Hz, C_4), 55.5 (CH_3O). ^{19}F NMR (377 MHz, $CDCl_3$) δ -180.9 (dd, *J* = 45.4, 9.1 Hz). HR ESI-TOF MS for [2M+Na^+]: $C_{22}H_{24}F_2N_2NaO_6^+$ (m/z): 473.1495; found: 473.1498.

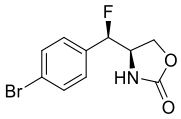
***Syn*-4-(fluoro(4-acetoxyphenyl)methyl)oxazolidin-2-one (4.130):**



The title compound was synthesized following the general procedures for the difluorination of 4-toluene and the subsequent aminofluorination of carbamates. First, 4-$MePhIF_2$ was prepared starting from 4-iodotoluene **4.123** (59.5 µL, 0.45 mmol), Selectfluor (558 mg, 1.58 mmol) and $Et_3N{\cdot}HF$ (270 µL, 1.62 mmol) in CH_3CN (11 mL). After the work-up, difluorinated compound was dissolved in CH_2Cl_2 (2.3 mL) and introduced into a flamed Schlenk together with carbamate **4.117** (21.2 mg, 0.09 mmol) and 4Å M.S (90 mg), affording **4.130** as a mixture *syn/anti* of two diastereoisomers in a ratio 58:42. After the work-up the reaction mixture was purified by flash chromatography using hexane/ethyl acetate (50:50) to yield **4.130** (13.3 mg, 0.05 mmol, 56 %) as an inseparable mixture of compounds *syn/anti*. An aliquot of this mixture was purified several times by flash chromatography using hexane/ethyl

acetate (60:40) to get a sample of **4.130** as a white solid, pure enough to get the analytical data. m.p. 108-110 °C. IR (neat): 3290, 2923, 2851, 2349, 1742, 1509, 1408, 1370, 1192, 911 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.5 Hz, 2H, H_{ar}), 7.17 (d, *J* = 8.5 Hz, 2H, H_{ar}), 5.52 (bs, 1H, H_{NH}), 5.36 (dd, *J* = 46.1, 6.8 Hz, 1H, $H_{1'}$), 4.54 – 4.46 (m, 2H, H_5), 4.22 – 4.06 (m, 1H, H_4), 2.32 (s, 3H, CH_3CO). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4 (CH_3CO), 158.9 (C_2), 151.7 (d, *J* = 2.0 Hz, C_{ar}) 132.8 (d, *J* = 20.2 Hz, C_{ar}), 127.5 (d, *J* = 6.7 Hz, C_{ar}), 122.5 (C_{ar}), 93.1 (d, *J* = 179.2 Hz, $C_{1'}$), 66.8 (d, *J* = 2.9 Hz, C_5), 56.3 (d, *J* = 31.5 Hz, C_4), 21.3 (CH_3CO).^{19}F NMR (377 MHz, $CDCl_3$) δ -186.9 (dd, *J* = 46.1, 6.8 Hz). HR ESI-TOF MS for [M+Na^+]: $C_{12}H_{12}FNNaO_4^+$ (m/z): 276.0643; found: 276.0643.

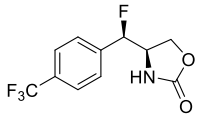
***Syn*-4-(fluoro(4-bromophenyl)methyl)oxazolidin-2-one (4.132):**



The title compound was synthesized following the general procedure described for the difluorination of 4-toluene and the subsequent aminofluorination of carbamates. First, 4-$MePhIF_2$ was prepared starting from 4-iodotoluene **4.123** (59.5 µL, 0.45 mmol), Selectfluor (558 mg, 1.58 mmol) and $Et_3N{\cdot}HF$ (270 µL, 1.62 mmol) in CH_3CN (11 mL). After the work-up, difluorinated compound was dissolved in CH_2Cl_2 (2.3 mL) and introduced into a flamed Schlenk together with carbamate **4.119** (23.0 mg, 0.09 mmol) and 4Å M.S. (90 mg), affording **4.132** as a mixture *syn/anti* of two diastereoisomers in a ratio 91:9. After the work-up the reaction mixture was purified by flash chromatography using hexane/ethyl acetate (50:50) to yield **4.130** (11.2 mg, 0.04 mmol, 45 %) as an inseparable mixture of compounds *syn/anti*. An aliquot of this mixture was purified several times by flash chromatography using hexane/ethyl acetate (60:40) to get a sample of **4.132** as a white solid, pure enough to get the analytical data. m.p. 118-120 °C. IR (neat): 3242, 3142, 2958, 2924, 2359, 1750, 1489, 1402, 1234, 1010, 802 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2H, H_{ar}), 7.23 (d, *J* = 8.4 Hz, 2H, H_{ar}), 5.32 (dd, *J* = 46.1, 7.1 Hz, 1H, $H_{1'}$), 4.81 (bs, 1H, H_{NH}), 4.64 – 4.42 (m, 2H, H_5), 4.20 – 4.05 (m, 1H, H_4). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0 (C_2), 134.1 (d, *J* = 20.2 Hz, C_{ar}), 132.4 (C_{ar}), 127.8 (d, *J* = 6.8 Hz, C_{ar}), 124.1 (d, *J* = 2.1 Hz,

C_{ar}), 92.97 (d, *J* = 179.6 Hz, $C_{1'}$), 66.63 (d, *J* = 3.3 Hz, C_5), 56.14 (d, *J* = 30.8 Hz, C_4). ^{19}F NMR (377 MHz, $CDCl_3$) δ -186.3 (dd, *J* = 46.1, 11.5 Hz). HR ESI-TOF MS for [M+Na$^+$] $C_{10}H_9BrFNNaO_2^+$ (m/z): 295.9693; found: 295.9702.

Syn-4-(fluoro(4-(trifluoromethyl)phenyl)methyl)oxazolidin-2-one (4.134):



The title compound was synthesized following the general procedure described for the difluorination of 4-toluene and the subsequent aminofluorination of carbamates. First, 4-MePhIF$_2$ was prepared starting from 4-iodotoluene **4.123** (59.5 µL, 0.45 mmol), Selectfluor (558 mg, 1.58 mmol) and $Et_3N{\cdot}HF$ (270 µL, 1.62 mmol) in CH_3CN (11 mL). After the work-up, difluorinated compound was dissolved in CH_2Cl_2 (2.3 mL) and introduced into a flamed Schlenk together with carbamate **4.121** (22.1 mg, 0.09 mmol) and 4Å M.S (90 mg), affording **4.132** as a mixture *syn/anti* of two diastereoisomers in a ratio 91:9. After the work-up the reaction mixture was purified by flash chromatography using hexane/ethyl acetate (50:50) to yield **4.134** (8.5 mg, 0.03 mmol, 34 %) as an inseparable mixture of compounds *syn/anti*. An aliquot of this mixture was purified several times by flash chromatography using hexane/ethyl acetate (60:40) to get a sample of **4.134** as a white solid, pure enough to get the analytical data. IR (neat): 3292, 2922, 2852, 2359, 1748, 1417, 1324, 1253, 1067, 1017 cm^{-1}.1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2H, H_{ar}), 7.49 (d, *J* = 81 Hz, 2H, H_{ar}), 5.44 (dd, *J* = 46.2, 6.6 Hz, 1H, $H_{1'}$), 5.16 (bs, 1H, H_{NH}), 4.59 – 4.44 (m, 2H, H_5), 4.25 – 4.05 (m, 1H, H_4). ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.91 (s, CF_3), -189.44 (dd, *J* = 46.1, 10.5 Hz, CF). HR ESI-TOF MS for [M+Na$^+$] $C_{11}H_9F_4NNaO_2^+$ (m/z): 286.0462; found: 286.0453.

4.6. REFERENCES

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UNIVERSITAT ROVIRA I VIRGILI
NOVEL STRATEGIES FOR THE SYNTHESES OF SPHINGOSINE KINASE INHIBITORS, B-FLUOROAMINES AND ENANTIOENRICHED ALLENES
Macarena Corro Morón

CHAPTER 5

Copper-mediated enantioselective synthesis of allenes

This work have been carried out in the laboratory of Prof. Alois Fürstner at Max-Panck-Institute für Kohlenforschung.

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5.1. INTRODUCTION

5.1.1. Stereochemistry of allenes.

Allenes are a class of compounds which are characterized by having two cumulated carbon-carbon double bonds[1,2] and are important building blocks in organic synthesis.[3,4] The terminal carbon atoms possess sp^2 hybridation whereas the central carbon is sp hybridized (Figure 5.1). The terminal carbons are bonded to central one by π-bonds which are perpendicular to each other. In the same way, the four substituents in the allenic moiety are also at right angles. Therefore, allenes can become asymmetric if $R^1 \neq R^2$ and $R^3 \neq R^4$ despite not having any chiral carbon. This kind of chirality is called axial chirality.

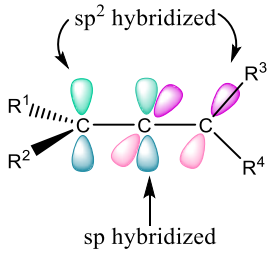
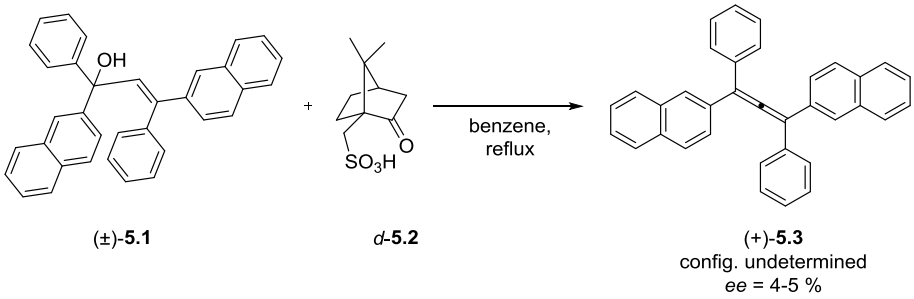


Figure 5.1. Stereochemistry of allenes.

5.1.2. Enantioselective syntheses of allenes.

The existence of allenes was predicted by van't Hoff in 1875[5] although the first allene was not synthesized until 1887 by Burton and von Pechmann who incorrectly described it as an alkyne instead of an allene.[6] Confirmation of the correct achiral structure was established by Whiting in 1954 by spectroscopic methods.[7]

In 1935, Maitland and Mills published the first enantioselective synthesis of an allene *via* dehydration of racemic allylic alcohol **5.1** in the presence of camphorsulfonic acid (**5.2**).[8] Both enantiomers could be obtained by changing the chiral acid although low enantioselectivities were afforded in both cases (Scheme 5.1).

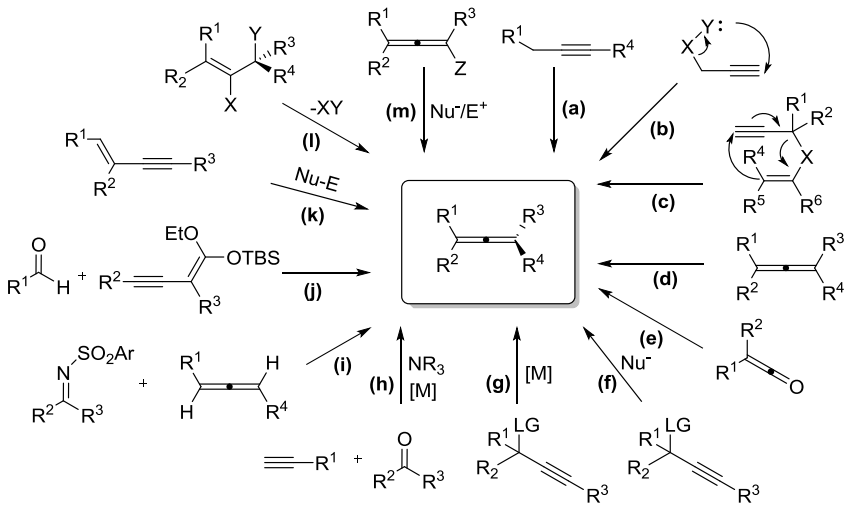


(±)-**5.1** *d*-**5.2** (+)-**5.3**
config. undetermined
ee = 4-5 %

Scheme 5.1. Synthesis of the first enantioenriched allene.

5.1.2.1. General methods for the enantioselective synthesis of allenes.

As aforementioned, the first allene was prepared by enantioselective dehydration of an achiral alcohol.[8] However, this is not the unique method which has been described to enantioselectively synthesize allenes. These compounds can be also generated by isomerization from the corresponding alkynes,[3g,9] via [2,3][3g,9b,c,e,10] or [3,3]-sigmatropic rearrangements,[3g,9,b,11,12] kinetic[3g,9c,13] or dynamic kinetic resolutions,[14] olefination of ketenes,[9c,15] S_N2' substitutions,[3g,4,9b,12,16,17] metal-catalyzed cross-coupling,[9c,e,17] allenylation of terminal alkynes (ATA),[9b,c,18] alleno-Mannich[19] and Mukaiyama aldol reactions;[20] addition to enynes or diynes,[3g,9b,c,e,13,21] elimination[22] and by nucleophilic or electrophilic allenylation from racemic allenes[9b,c,e,17,23] (Scheme 5.2).



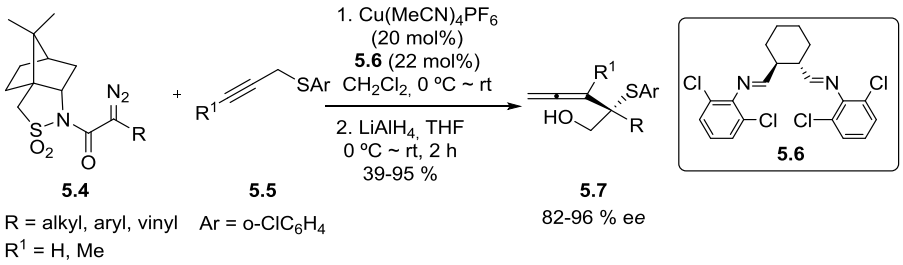
Scheme 5.2. General methods for the enantioselective synthesis of allenes. (a) isomerization of alkynes, (b) [2,3]-sigmatropic rearrangement, (c) [3,3]-sigmatropic rearrangement, (d) kinetic or dynamic kinetic resolution, (e) olefination of ketenes, (f) *S*$_N$*2'* substitutions, (g) metal-catalyzed cross-coupling, (h) ATA reaction, (i) alleno-Mannich reaction, (j) Mukaiyma aldol reaction, (k) addition to enynes or diynes, (l) elimination, (m) nucleophilic or electrophilic allenylation from racemic allenes.

Some of these reactions are promoted by copper catalysts or some copper reagents are involved in them. Since our work has been developed using mesityl copper as a reagent, this introduction will be focused on the enantioselective preparation of allenes where copper has been used either as a catalyst or a reagent.

5.1.3. Copper-mediated enantioselective synthesis of allenes.

5.1.3.1. [2,3]-sigmatropic rearrangement.

Synthesis of substituted allenic compounds bearing phosphates, phosphinites, sulfones and sulfoxides are often carried out through [2,3]-sigmatropic rearrangement.[9b] However, only one example involving Cu(I) catalyst has been reported to date.[24] In 2005, Wang and co-workers found that highly enantioenriched 3,4-allenols could be afforded *via* [2,3]-Wittig rearrangement of propargyl sulfonium ylides in the presence of a Cu(I) salt and chiral ligand **5.6** (Scheme 5.3).

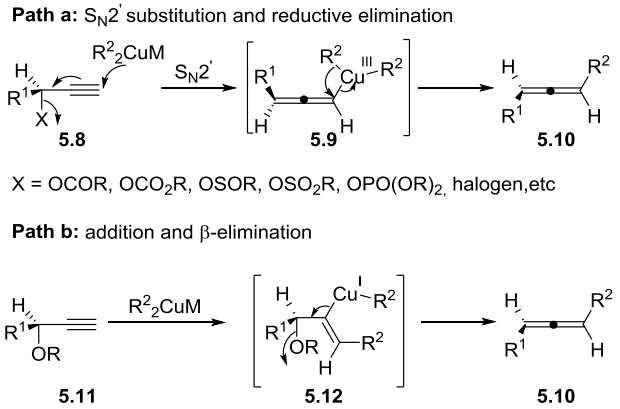


Scheme 5.3. Asymmetric synthesis of 3,4-allenols *via* [2,3]-Wittig rearrangement.

5.1.3.2. S_N2' substitutions of propargylic compounds.

One of the most commonly used methods in the synthesis of allenes is *S_N2'* substitution. α-Alkyl- or α-haloallenes, α-allenols, α-allenylamines or allenylboronates are some allene derivatives which can be synthesized from propargylic compounds containing phosphates, halides, sulfonates, sulfinates, acetates, carbonates, mesylates, tosylates, alcohols, ethers, epoxides, β-lactones or aziridines as leaving groups.[4,9b,17,25]

Taking into account the kind of leaving group, two different pathways with *anti* displacement have been described to explain this reaction:[16a,b,26] (a) when propargylic compounds contain a good leaving group such as acetates, carbonates, phosphates, halides, sulfonates and sulfinates, the reaction may proceed *via S_N2'* substitution followed by reductive elimination from Cu(III) intermediate (path a, Scheme 2.4). However, (b) a *syn*-addition followed by *anti*-β-elimination might come along if weak leaving groups are present at propargylic position (path b, Scheme 5.4).



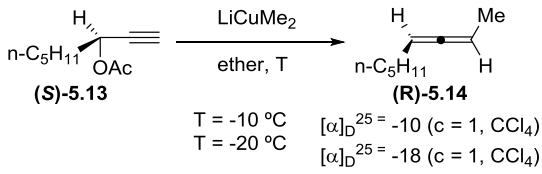
Scheme 5.4. Possible pathways for *S_N2'* substitutions.

a) S_N2' substitution from chiral substrates.

As commented above, several kinds of allenes can be formed *via* nucleophilic addition to propargyl derivatives. In this sense, different allenes formed from enantioenriched substrates will be grouped regarding the kind of obtained product.

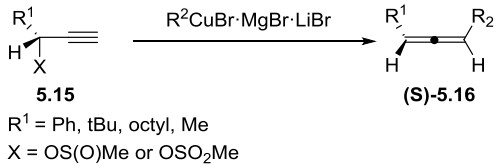
i) Syntheses of α-alkylallenes.

Alkylation of allenes starting from propargylic compounds was firstly carried out by Crabbé who achieved to transfer the central chirality of an enantioenriched propargylic acetate to the axial chirality of an allene by using an organolithium cuprate reagent. Unfortunately, the efficiency of this process could not be clarified since the enantioselectivity was not determined (Scheme 5.5).[27]



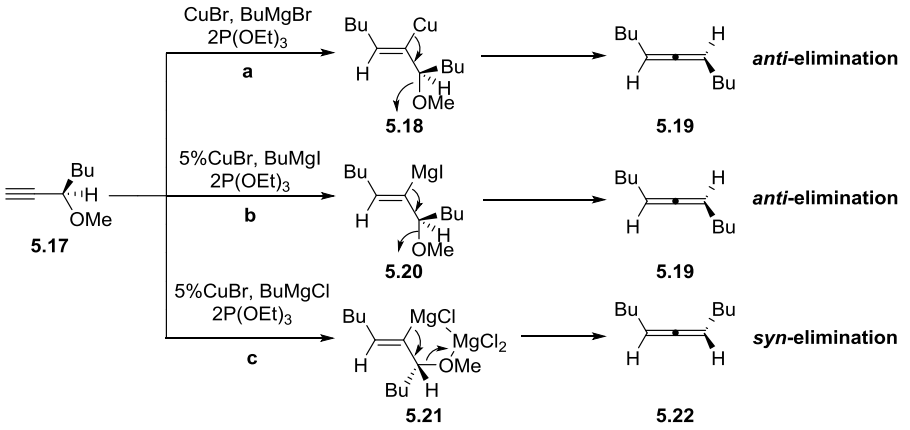
Scheme 5.5. First asymmetric synthesis of allene via *S_N2'* substitutions of propargyl acetate **(*S*)-5.13**.

Following the pioneering work reported by Crabbé, many efforts have been made to improve his results in alkylation of propargylic compounds. In this context, Elsevier and co-workers described an *anti*-stereospecific substitution of propargyl mesylates or sulfinates in the presence of organocopper (I) reagents affording high enantioselectivities (Scheme 5.6).[28]



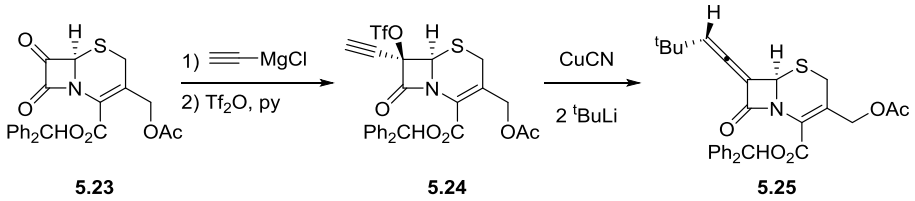
Scheme 5.6. Organocopper-mediated stereospecific S_N2' substitution of propargyl alcohol derivatives.

Later on, Alexakis et *al.* developed a new asymmetric synthesis of allenes by using propargyl ethers.[16b] They found that the addition of phosphites such as $P(OEt)_3$ interestingly increased the enantiomeric excess (a, Scheme 5.7). Furthermore, they also figured out that the reaction proceeded *via anti*-elimination with stoichiometric amounts of an organocopper reagent or in the presence of catalytic Cu (I) salts and Grignard reagents type RMgI (b, Scheme 5.7). On the other hand, a *syn*-elimination took place when a Grignard reagent type RMgCl was used (c, Scheme 5.7). This outcome was explained by the formation of a cyclic transition state enhanced by the small size and the electronegativity of chlorine where the Lewis acidity of $MgCl_2$ favors the *syn*-elimination. The big size of iodine does not allow the same kind of transition state and the elimination occurs predominantly in *anti* manner.



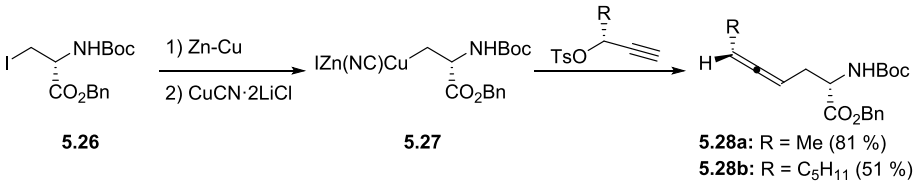
Scheme 5.7. Halogen effect in the allene elimination for copper-catalyzed reactions.

In 1994, the synthesis of vinylidenecephem derivative **5.25** was reported by Buynak, who accomplished the chiral allene by reacting copper cyanide with the propargyl triflate **5.24** (Scheme 5.8).[29]



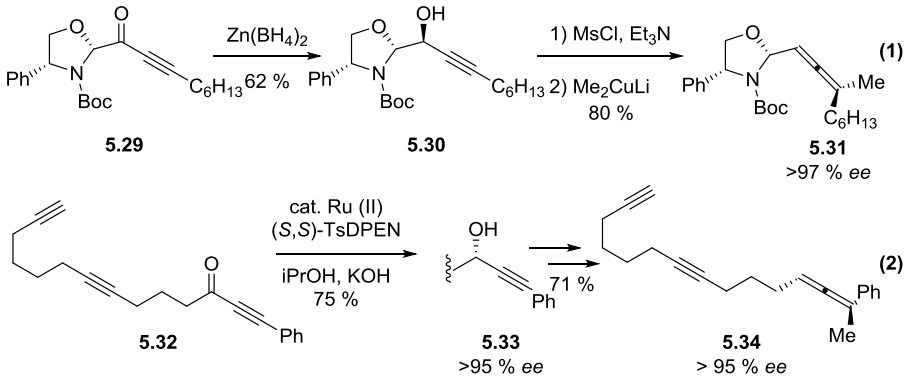
Scheme 5.8. Synthesis of enantioenriched vinylidenecephem derivative **5.25**.

One year later, β-aminoalcohols were generated by employing serine-derived zinc-copper reagents, which were then submitted to substitution in the presence of chiral propargyl tosylates (Scheme 5.9).[30]



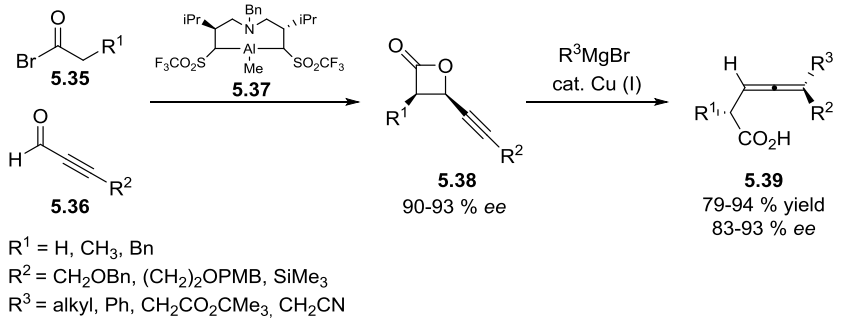
Scheme 5.9. Asymmetric synthesis of chiral β-aminoalcohols.

Allenylation of propargyl mesylates was the strategy chosen by Mathieu[31] and Malacria[32] to synthesize enantioenriched α-alkylallenes. In both cases, firstly propargylic alcohols were selectively reduced by using zinc boronhydride (1, Scheme 5.10) or by utilizing a chiral ruthenium (II) catalyst (2, Scheme 5.10). Further treatment of the corresponding mesylates with copper reagents provided the desired allenes in excellent enantioselectivity.



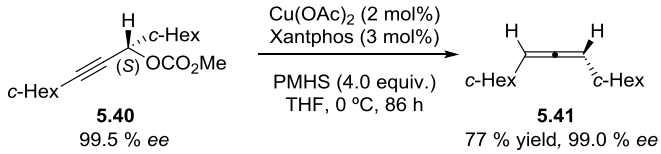
Scheme 5.10. Synthesis of chiral allenes from propargylic alcohols by Mathieu and Malacria. 32

In the same year, Nelson published the Cu (I)-catalyzed ring-opening of optically active alkynyl β-lactones with Grignard reagents.[33] Lactones were prepared using a chiral catalyst **5.37** and the opening step took place with good chirality transfer (Scheme 5.11).



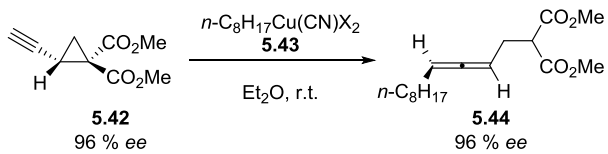
Scheme 5.11. Synthesis of enantioenriched β-allenic acids from β-lactones.

Cu(I)/Xantphos was the system selected by Sawamura to synthesize highly enantioenriched disubstituted allenes (Scheme 5.12).[34] To carry out the reaction, non-racemic propargyl carbonates were submitted to substitution and Xantphos was used to stabilize the copper complexes.



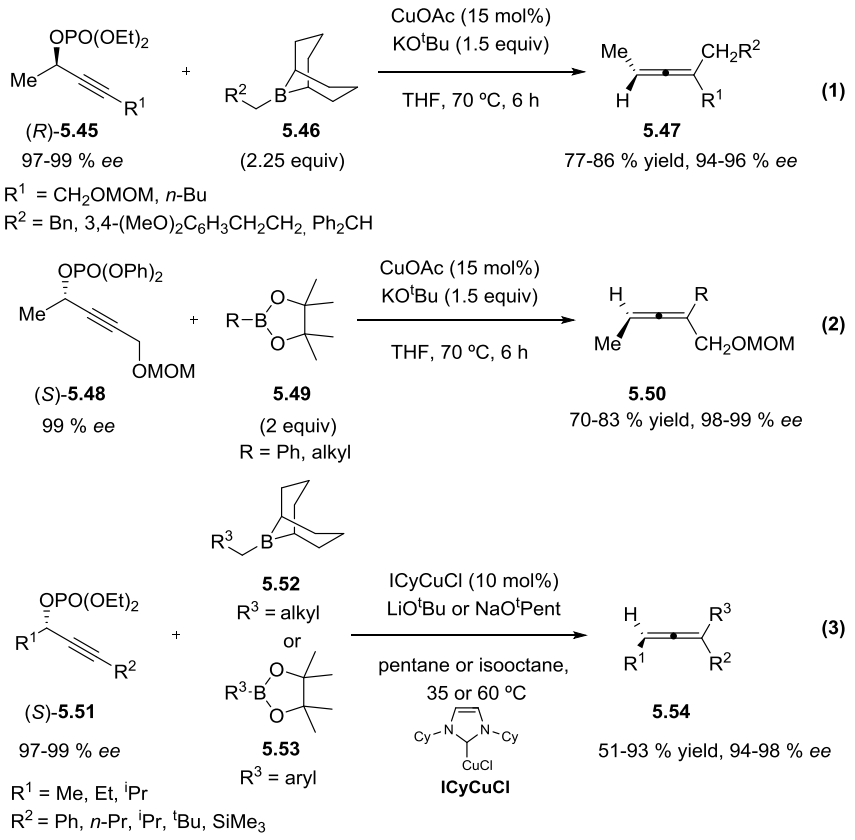
Scheme 5.12. Sawamura system for the enantioselective synthesis of alkylallenes.

Interestingly, ethynylcyclopropanes are versatile building blocks which can be modified thank to their enhanced reactivity.[35] Treatment of propargylcyclopropane **5.42** with organocuprate reagent **5.43** provided the enantioenriched allene **5.44** in a regioselective way and with total chirality transfer (Scheme 5.13).[36]



Scheme 5.13. Enantioselective synthesis of allene **5.44** from ethynylcyclopropane **5.42**.

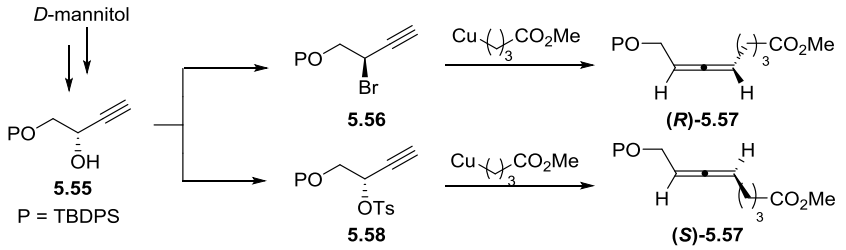
Almost at the same time, Sawamura[37] and Lalic[38] independently demonstrated that alkylallenes could be furnished by treating propargyl phosphonates with alkyl-, alkenyl- or arylboronates. In the first case, CuOAc or $CuCl_2$ catalyzed the reaction (1 and 2, Scheme 5.14) whereas in the second one the reaction took place in the presence of copper complexes with NHC-ligands (3, Scheme 5.14).



Scheme 5.14. Synthesis of enantioenriched allenylboronates from propargyl phosphates.

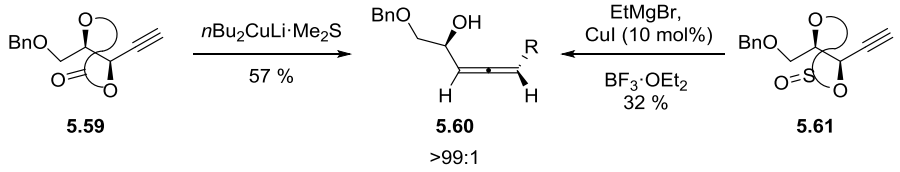
ii) Preparation of α-allenols.

Enantiopure α-allenols were firstly introduced by Copper in 1991 when successfully reported the synthesis of both enantiomers of α-allenol **5.57** starting from the derivative of *D*-mannitol **5.55**.[39] This compound was submitted to tosylation or bromination followed by S_N2' substitution mediated by a copper reagent affording enantioselectivies higher than 94 % (Scheme 5.15).



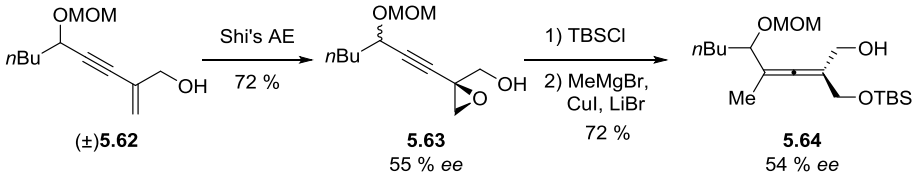
Scheme 5.15. Enantioselective synthesis of the two enantiomers of **5.57** from **5.55.**

One year later, the enantioselective synthesis of disubstituted allenol **5.60** was developed by Cho.[40] Cyclic carbonates and sulfites were nucleophilically ring-opened through reaction promoted by copper affording poor to moderated yields (Scheme 5.16).



Scheme 5.16. Enantioselective synthesis of α-allenols from cyclic compounds.

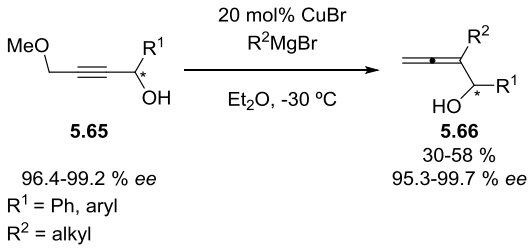
Epoxides are another kind of cyclic compounds liable to be opened by nucleophilic addition. In 2000, Spino and Fréchette published the asymmetric synthesis of α-allenols by a combination of Shi's epoxidation followed by a copper-mediated ring-opening reaction (Scheme 5.17).[41]



Scheme 5.17. Shi's epoxidation followed by allene synthesis of **5.64**.

Ma and co-workers also prepared optically active α-allenols. They afforded enantioenriched allenes by reacting chiral propargyl ether **5.65** and primary alkyl Grignard in the presence of CuBr as a catalyst.[42]

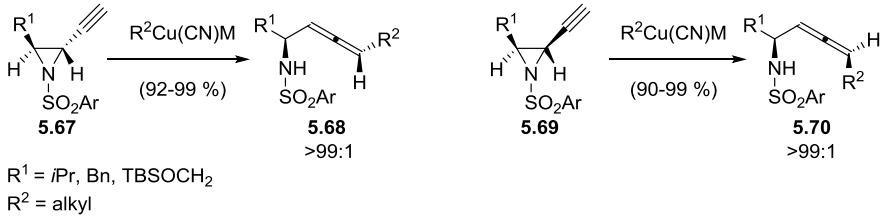
Allenes were obtained in high enantioselectivity although yields were somewhat low (Scheme 5.18). Only aryl groups were tolerated in the synthesis of chiral tetrasubstituted allenes.



Scheme 5.18. Copper-catalyzed asymmetric synthesis of α-allenols.

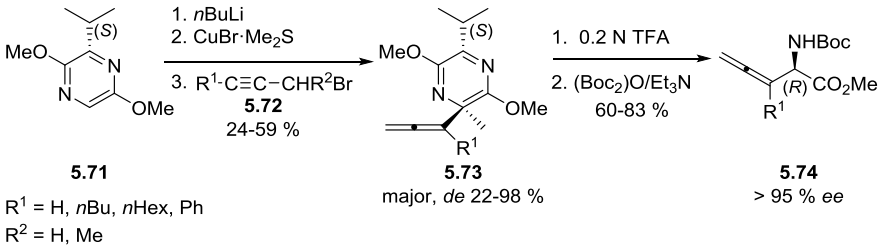
iii) Enantioselective synthesis of α-aminoallenes.

Similarly to epoxides to generate α-allenols, aziridines can be nucleophilically opened to provide α-aminoallenes. In this sense, synthesis of enantiomerically enriched α-aminoallenes coming from 2-ethynylaziridines was developed by Ohno and co-workers.[43] Both *cis* and *trans* aziridines were reacted with cyanocuprate reagents affording *anti*-allenes in both high yields and excellent enantioselectivities (Scheme 5.19).



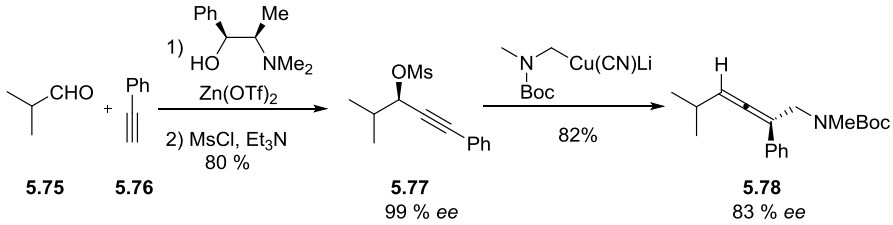
Scheme 5.19. Synthesis of α-aminoallenes by ring-opening of 2-ethynylaziridines.

Copper-catalyzed S_N2' substitution was also used by Klinge to prepare enantiomerically enriched α-allenylglycines **5.74** after hydrolysis of allenyl-substituted bislactim ether product **5.73** generated during the reaction between the corresponding bislactim **5.71** and propargyl halides **5.72** (Scheme 5.20).[44]



Scheme 5.20. Synthesis of enantioenriched α-allenylglycine **5.74.**

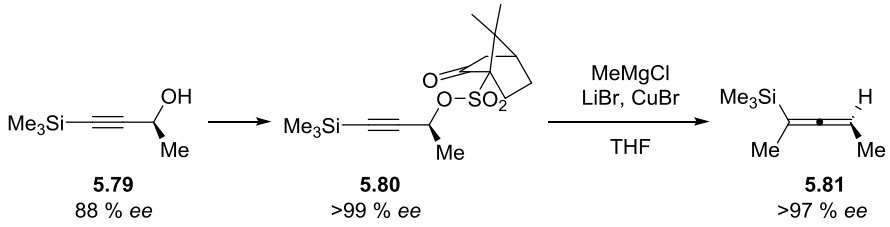
Analogously to the strategy used by Mathieu[31] and Malacria,[32] Yu and co-workers synthesized optically active α-aminoallenes by treating chiral propargyl mesylates with copper reagents providing the desired allenes in high enantioselectivity (Scheme 5.21).[45] Enantiopure substrates were produced by asymmetric addition of a terminal alkyne to aldehyde described by Carreira.[46]



Scheme 5.21. Synthesis of chiral allenes from propargylic mesylates by Yu.

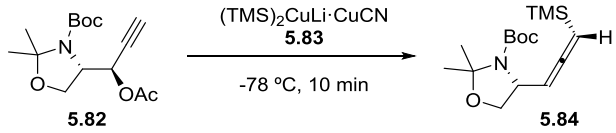
iv) Chiral synthesis of allenylsilanes and allenylboronates.

Camphorsulfonates are interesting protecting groups of alcohols which are not commonly used in the enantioselective synthesis of allenes. Nevertheless, Fleming proved that optically active allenylsilanes could be achieved by using chiral propargyl camphorsulfonates as starting materials.[47] Satisfactorily, he found that central to axial chirality transfers took place almost without loss of enantioselectivity furnishing enantioenriched allenes above 97 % (Scheme 5.22).



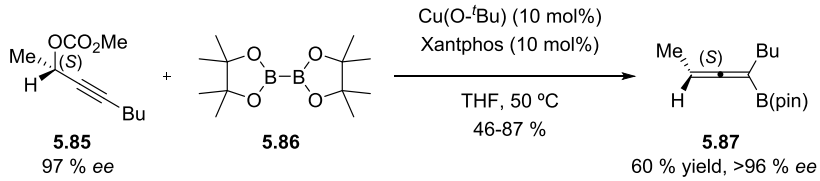
Scheme 5.22. Copper salt-mediated chiral synthesis of allene **5.81** from propargyl camphorsulfonate **5.80**.

In 2008, Broguiere described the non-racemic synthesis of allenylsilane **5.84** by reacting chiral oxazolidine propargyl acetate **5.82** with (trimethylsilyl)cyanocuprate **5.83** through S_N2' substitution (Scheme 5.23).[48]



Scheme 5.23. Enantioselective synthesis of allylsilane **5.84**.

As already commented for the enantioleselective synthesis of alkylallenes, Sawamura used Cu(I)/Xantphos to obtain highly enantioenriched disubstituted allenylboronates **5.87** from chiral propargyl carbonates **5.85** in excellent enantioselectivity (Scheme 5.24).[49]

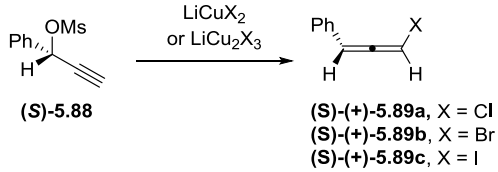


Scheme 5.24. Sawamura system for the enantioselective synthesis of alkylallenes and allenylboronates.

v) Enantioselective synthesis of α-haloallenes.

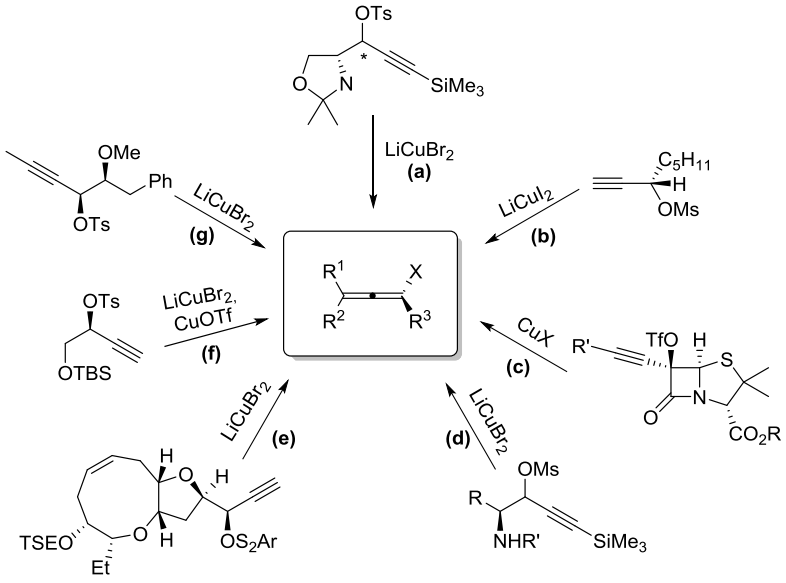
In 1982, Elsevier reported the first enantioselective synthesis of α-haloallenes[50] following the procedure described by Montury and

Goré[51] for the preparation of achiral ones. In this sense, propargyl mesylates **5.88** were reacted with halocuprates type $LiCuX_2$ or $LiCu_2X_3$ accomplishing high enantiomeric excesses (Scheme 5.25).[52]



Scheme 5.25. Synthesis of α-haloallenes mediated by lithiumcuprates reagents from propargyl mesylates.

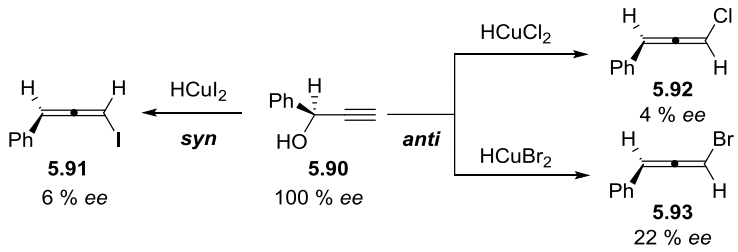
The use of this methodology to prepare haloallenes was extended to other syntheses in which silylated bromoallenes starting from *syn*- and *anti*-propargyl tosylates (a, Scheme 5.26)[53], α-iodoallenes (b, Scheme 2.26),[54] 6-vinyllidenepenams (c, Scheme 5.26)[55], α-bromoallenes coming from α-amino acids (d, Scheme 5.26)[56] and other α-bromoallenes (e, f and g, Scheme 5.26) [57,58,59] were formed (Scheme 5.26).



Scheme 5.26. Synthesis of α-haloallenes by using Montury-Goré method.

Although halocuprates are extendedly employed in the enantioselective synthesis of allenes, other compounds can be also used

to this purpose. In 1984, Elservier found that 1,3-substitution in propargyl alcohols could be modulated by different Landor reagents.[60] According to this study, *syn* allenes were obtained by reaction with $HCuI_2$, whereas the use of $HCuCl_2$ or $HCuBr_2$ enhanced the formation of *anti*-products. Presumably, the substituents at propargylic center are involved in the course of the reaction where all products were afforded in very low enantioselectivities (Scheme 5.27).

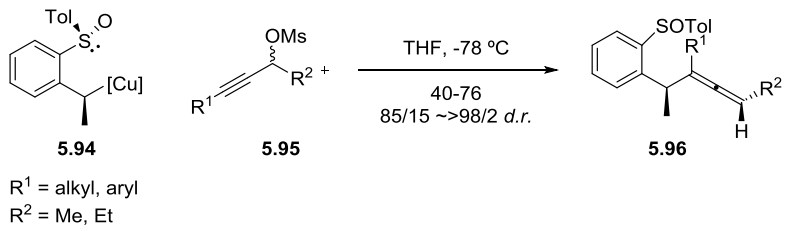


Scheme 5.27. *Syn*- and *anti*-stereoselective synthesis of haloallenes.

b) Chiral-nucleophile-mediated enantioselective synthesis of allenes.

Enantioselective allenylation of achiral substrates can be successfully accomplished through the use of chiral nucleophiles. Despite being an interesting system to achieve non-racemic allenes, only one example has been reported to date.

The asymmetric synthesis of allene **5.96** was described by Alemán research group, who achieved to transfer the chirality from the organocopper reagent **5.94** to the product by reaction with propargyl mesylates **5.95** (Scheme 5.28).[61] The reaction proceeds in an *anti*-stereoselective manner providing the first example in which an enantiopure allene attached to a chiral center.

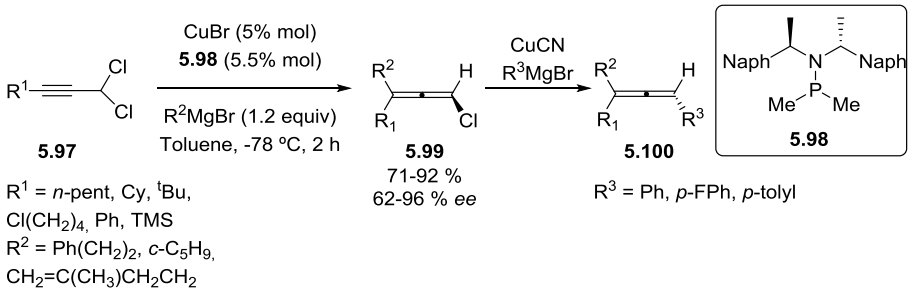


Scheme 5.28. Transfer chirality from sulfonyl group to allene **5.96.**

c) Synthesis of allenes mediated by chiral catalysts.

Another way to synthesize chiral allenes is by employing chiral catalysts. The design of attractive ligands which might be able to modulate the selectivity in allenylation reaction is an approach which has not been much explored yet. Actually, only one method has been developed to perform enantioselective allenes.

Alexakis and co-workers developed a new ligand **5.98** which in combination with a catalytic amount of CuBr generated chloroallenes **5.99** when 1,1-dichloropropargyl compounds were reacted with Grignard reagents.[62] Curiously, this reaction proceeds with exclusive regioselectivity and moderate to good enantioselectivity. In addition, chloroallenes can be readily transformed into trisubstituted allenes in the presence of aryl Grignard reagents without appreciable loss of enantioselectivity (Scheme 5.29).



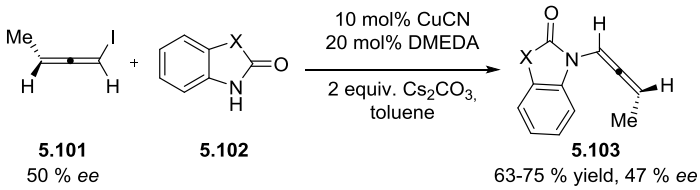
Scheme 5.29. Catalytic asymmetric reaction for the synthesis of chloroallenes.

5.1.3.3. Copper-catalyzed cross-coupling reactions.

Palladium-catalyzed cross-coupling reactions are widely used to furnish allenes in a straightforward manner. Other metals including copper are also employed in this kind of reaction. Still, there are not many examples where enantioenriched allenes are catalytically prepared through this methodology and using copper as catalyst.

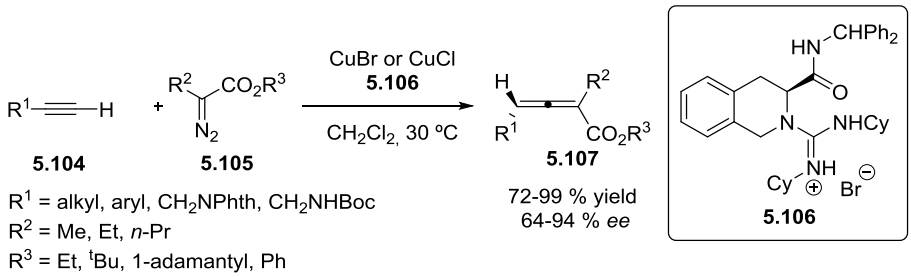
In 2005, Hsung et *al*. examined the cross-coupling reaction between amides and iodoallenes to produce optically active

alleneamides. The reaction was catalyzed by copper (I) salts and the chirality was successfully transferred from iodoallenes to the new compounds (Scheme 5.30).[63]



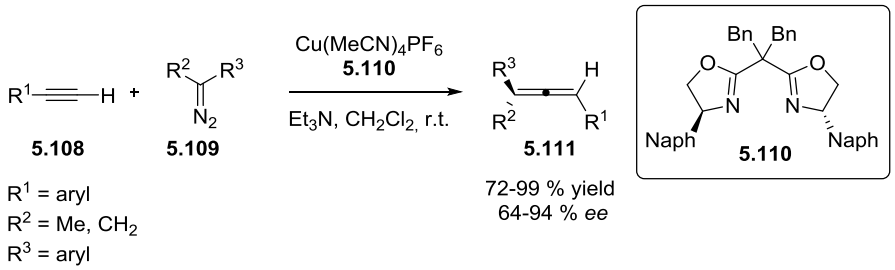
Scheme 5.30. Cross-coupling of chiral iodoallenes and amides.

In 2015, Liu reported the first asymmetric coupling of α-diazoesters and terminal alkynes in the presence of a guanidinium salt/Cu (I) complex.[64] Trisubstituted allenes were formed in high both yields and enantioselectivity (Scheme 5.31).



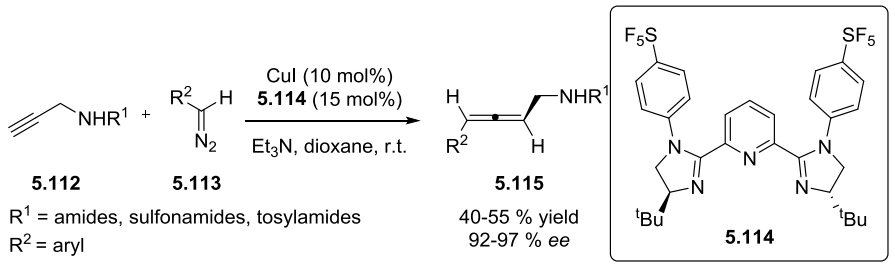
Scheme 5.31. Copper-catalyzed cross-coupling of terminal alkynes and α-diazoesters.

Similarly, non-stabilized aryldiazoalkanes **5.109** were used by Wang and co-workers to carry out the coupling with terminal alkynes **5.108** and generate trisubstituted allenes with excellent enantiomeric excesses.[65] A new bisoxazoline ligand **5.110** was designed to accomplish the coupling reaction where $Cu(MeCN)PF_6$ was selected as catalyst (Scheme 5.32).



Scheme 5.32. Synthesis of chiral allenes by cross-coupling of terminal alkynes and non-stabilized aryldiazoalkanes.

Recently, the group of Ley utilized flow-generated aldehyde-derived diazo compounds to synthesize disubstituted allenes.[66] Treatment of these diazo compounds with terminal alkynes in the presence of CuI and a new ligand **5.114** provided chiral allenes with moderate yields but excellent enantioselectivity (Scheme 5.33).



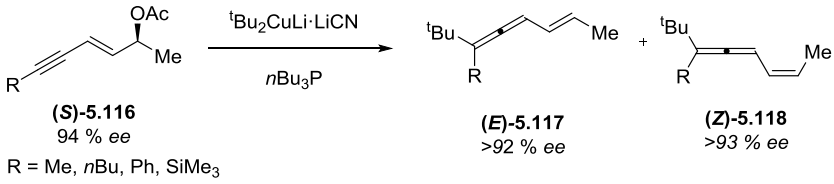
Scheme 5.33. Preparation of allenes *via* cross-coupling between flow-generated aldehyde-derived diazo compounds and terminal alkynes.

5.1.3.4. Copper-mediated addition to enynes.

The nucleophilic addition to enynes represents a versatile strategy to afford multi-substituted allenes in a direct manner. However, few examples employing copper have been reported until the date for the asymmetric synthesis of allenes.

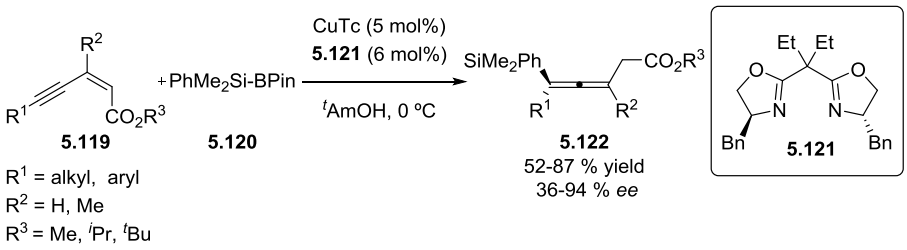
In 2000, a remote 1,5-stereocontrolled synthesis of vinylallenes was developed by Krause.[67] Chiral enynes were prepared by lipase-catalyzed kinetic resolution of the corresponding racemic enynes which were then nucleophilically attacked by cyano-Gilman reagent

^{t}Bu$_2$CuLi·LiCN affording poor enantioselectivity. Interestingly, it dramatically improved after the addition of nBu$_3$P or (EtO)$_3$P (Scheme 5.34).



Scheme 5.34. Remote stereocontrolled synthesis of vinylallenes.

Synthesis of enantioenriched silylallenes by 1,6-addition to enynes was reported by Loh and co-workers in 2015.[68] This reaction was promoted by combination of Cu(I) thiophene-2-carboxylate (CuTc) and bisoxazoline **5.121**, accomplishing moderated and excellent enantioselectivity although it decreased when R^1 = alkyl or R^2 ≠ H (Scheme 5.35).



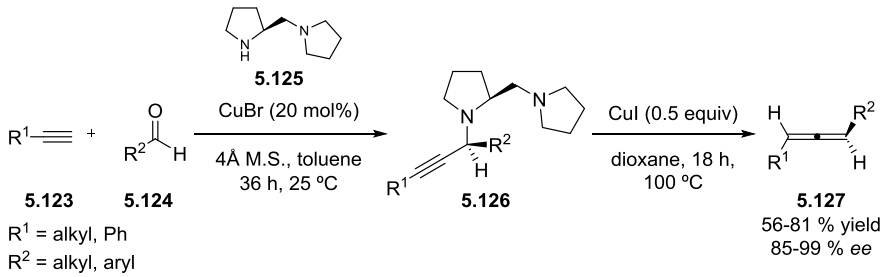
Scheme 5.35. Copper (I)-catalyzed 1,6-addition to enynes.

5.1.3.5. ATA reactions promoted by copper catalyst.

Allenylation of terminal alkyne (ATA) reaction was firstly introduced by Crabbé who demonstrated that allenes could be formed by treating terminal alkynes with paraformaldehyde and isopropylamine in the presence of copper bromide.[69] This kind of reaction, now commonly called Crabbé homologation, has been modified by other authors and chiral allenes can be obtained just adding asymmetric amines.

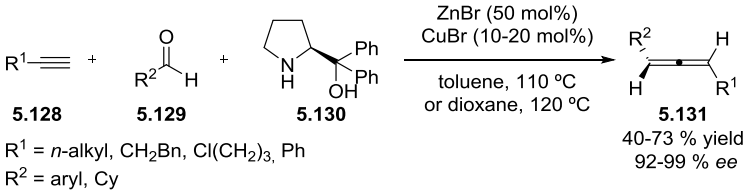
In 2013, Periasamy reported a useful synthesis of disubstituted allenes starting from chiral propargylamines which were prepared by

using chiral dialkylaminopyrrolidine, terminal alkynes and aldehydes.[18d] Further treatment of the corresponding propargylamine with CuI provided non-racemic allenes in remarkable yields and enantiomeric excess (Scheme 5.36).



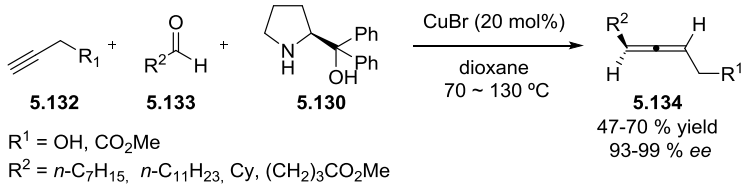
Scheme 5.36. ATA reaction starting from terminal alkynes, aldehydes and dialkylaminopyrrolidine.

The same year, Ma and co-workers developed a Cu^{+}/Zn^{2+} bimetallic system which is able to produce chiral allenes by using prolinol **5.130** as chirality source.[18e] They found that CuBr is involved in the formation of propargylic amine while both CuBr and $ZnBr_2$ are responsible for allenylation (Scheme 5.37).



Scheme 5.37. Synthesis of chiral allenes *via* Crabbé homolagation reaction using prolinol **5.130.**

Highly enantioenriched allenols or other allenes bearing a range of interesting functionalities were synthesized by Ma et *al*. in 2015.[70] The use of terminal substituted alkynes in combination with aldehydes in presence of $CuBr_2$ led to the desired allenyl compounds in moderate yields but striking enantioselectivity (Scheme 5.38).



Scheme 5.38. Chiral allenylation of terminal alkynes catalyzed by copper bromide.

Considering this background and that in recent studies about C-methylation of alkoxysilanes the Fürstner group observed small amount of allenes,[71] they decided to investigate how allenes were produced in some cases. In this sense, a new study was developing when the pre-doctoral student was incorporated to the project. The main goal of this work was the enantioselective synthesis of allenes starting from both *cis* and *trans* hydroxysilanes using copper sources as well as the determination of the absolute configuration of the products obtained. In addition, hydroxysilanes were synthesized from the corresponding enantioenchired propargylic alcohols, in turn, prepared from racemic propargylic ketones by employing chiral catalysts.

5.2. OBJECTIVES

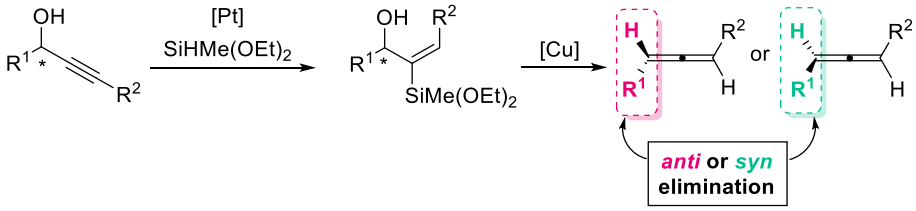
Taking into account the aforementioned and just considering the work carried out by the student, the aims of this chapter are the following:

i) Platinum-catalyzed synthesis of *cis* chiral hydroxysilanes starting from enantioenriched propargyl alcohols.

ii) Copper-mediated enantioselective synthesis of allenes by using hydroxysilanes as starting materials.

iii) Racemization control test in order to confirm the stability of chiral allenes in the presence of copper sources at longer reaction times.

iv) Mechanistic study trying to elucidate the plausible mechanism of the reaction.



This project has been carried out in collaboration with Felix Anderl and Karin Radkowski. It has been supervised by Prof. Alois Fürstner during a stay at Max-Planck-Institut für Kohlenforschung in Mülheim an der Rurh, Germany.

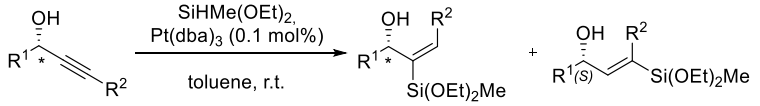
5.3. RESULTS AND DISCUSION

5.3.1. Hydrosilylation.

As commented before, we envisioned the preparation of chiral allenes *via* the formation of *cis* hydroxylsilanes as synthetic intermediates. Thus, hydrosilylation of enantioenriched propargyl alcohols[72] were first explored.

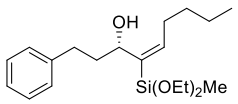
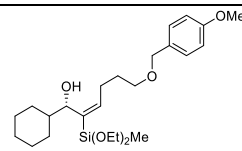
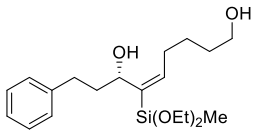
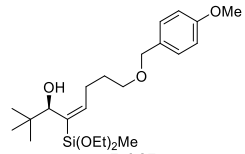
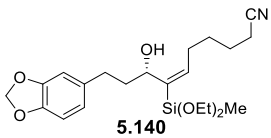
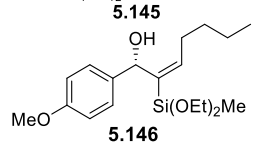
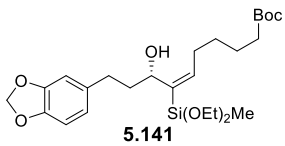
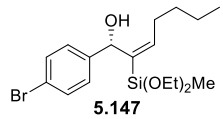
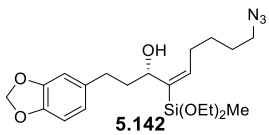
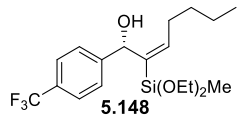
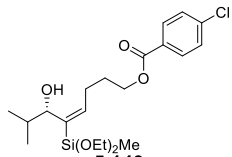
In 2014, Ferreira described that *cys* hydroxysilanes could be afforded by hydrosilylation of propargylic alcohols.[73] Reactions were performed in the presence of platinum catalyst providing good selectivities. Based on this work, an exhaustive study performed in Furnster group[72] of catalysts, catalyst loadings and solvents led to optimal conditions for the reaction as 0.1 mol% of $Pt(dba)_3$ as catalyst and toluene as solvent. Taking into account this study, different propargyl alcohols were subjected to hydrosilylation. Results are summarized in Table 5.1 where *distal* products have been omitted.

Table 5.1. Hydrosilylation of propargylic alcohols.



5.135 **5.136** **5.137**

Pro*ximal/distal*

Entry	Major Product	*Prox/ Distal ratio*[b]	Entry	Major Product	*Prox/ Distal ratio*[b]
1	 **5.138**	11:1	7	 **5.144**	3.2:1
2	 **5.139**	3.2:1	8	 **5.145**	2.2:1
3	 **5.140**	4.3:1	9	 **5.146**	24:1
4	 **5.141**	3:1	10	 **5.147**	10:1
5	 **5.142**	3.3:1	11	 **5.148**	24:1
6	 **5.143**	4:1			

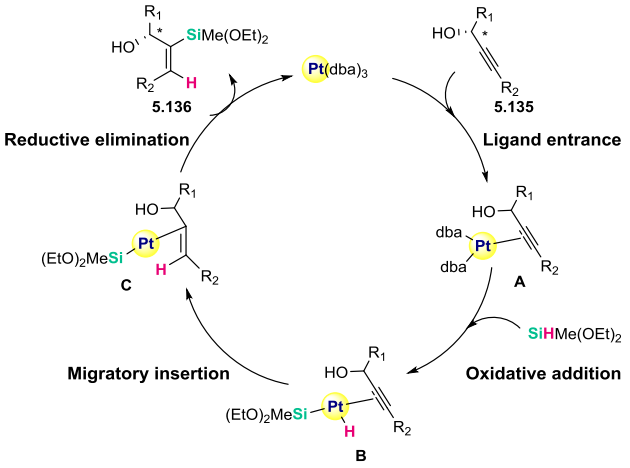
[a] General conditions: alkyne (1 equiv.), $SiHMe(OEt)_2$ (1.1 equiv), $Pd(dba)_3$ (0.1 mol%) , toluene (x mL). [b] Determined by ^{1}H-NMR based on olefinic protons.

Poor to moderate regioselectivities were observed for propargylic alcohols bearing aliphatic chains bonded to the propargylic carbon regardless the substitution pattern of the alkyl chain

(entries 1-8). However, the presence of aromatic rings bearing either electron withdrawing or electron donating groups directly attached to the propargylic carbon considerably increased the regioselectivity (entries 9-10). This fact might be explained by electronic effects of the aryl group during the hydrosilylation process whereby the aryl ring polarizes the alkyne and directs the hydride to the more electropositive carbon.[74] Interestingly, product **5.139** does not follow the trend observed for products **5.141-5.147** and excellent regioselectivity was obtained. It cannot be discarded that the other functional groups present in the molecules interact with the catalyst decreasing the regioselectivity.

The mechanism for *syn*-hydrosilylation of alkynes catalyzed by platinum was studied by Chalk and Harrod.[75] They concluded that this kind of reaction was characterized by the initial coordination of alkyne followed by the oxidative addition of silane, migration of hydride to triple bond and final reductive elimination. However, their study was only based on catalysts that involved Pt(II) and Pt(IV) species. For that reason, Roy and Taylor focused their efforts on trying to demonstrate that that mechanism might be also applied to catalysts involving Pt(0) and Pt(II) species.[76] Indeed, they studied the induction period, which some precatalysts like $Pt(cod)Cl_2$ must undergo before being catalytically active species, concluding that the mechanism involving Pt(0)/Pt(II) was similar to that involving Pt(II)/Pt(IV) species.

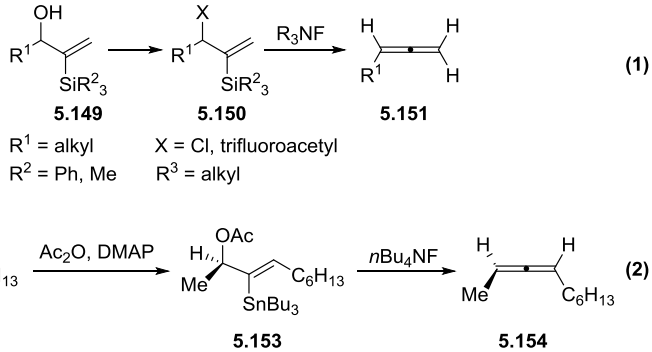
Analogously to the Chalk-Harrod mechanism, in our case the catalytic cycle would start with the coordination of alkyne to platinum to give π-complex **A**, followed by oxidative addition of silane to afford **B**. It is worth mentioning that the order of these two events could be inverted, taking place the oxidative addition of silane prior to coordination of the alkyne substrate. Next, a migratory insertion of hydride from platinum to triple bond would provide **3**. In this case, the polarization of the alkyne would enhance the hydride insertion at the distal carbon affording aforementioned complex **C**. Finally, a reductive elimination would provide the *cis* alkene **5.136** (Scheme 5.39).



Scheme 5.39. Proposed catalytic cycle for hydrosilylation with $Pt(dba)_3$.[75]

5.3.2. Elimination and formation of allene.

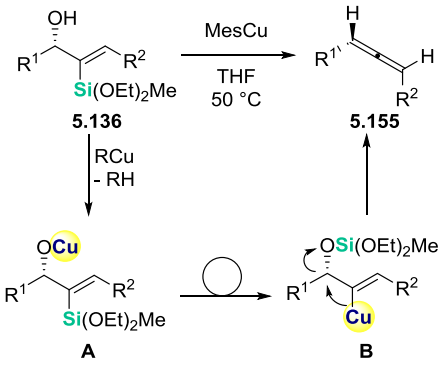
As commented in *Section 5.1.3.6,* recently, Fürstner group observed small amount of allenes during his study about C-methylation of alkoxysilanes.[71] Previously, Harpp (1, Scheme 5.40)[77] and Araki (2, Scheme 5.40)[78] had independently described the formation of allenes by *anti*-specific β-elimination of α-vinylsilanes or stannyl allylic alcohols, respectively.



Scheme 5.40. Synthesis of allenes by β-elimination of α-vinylsilanes and α-vinylstannylane **5.152**.

Based on these studies, we might envision that the formation of our allenes may take place by β-siloxide elimination of an intermediate

organocopper species **B** in *anti* manner. In turn, this intermediate might come from deprotonation of hydroxyl group by mesityl copper (intermediate **A**) (Scheme 5.41). However, further investigations are required to demonstrate this hypothesis.



Scheme 5.41. Plausible mechanism for the copper-mediated enantioselective synthesis of allenes

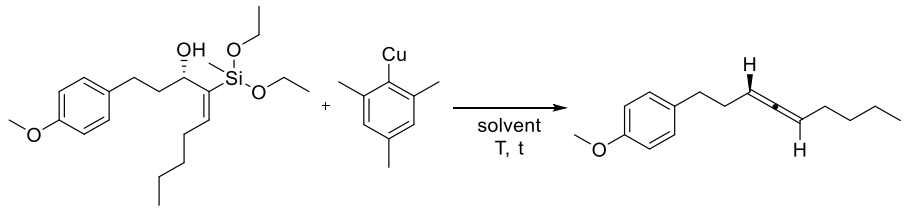
In this context, we focused our efforts on the stereoselective synthesis of allenes using *cis* hydroxysilanes as starting materials and mesityl copper as organometallic source. It is important to note that a previous screening of copper reagents was carried out before starting this work.[79] That screening included LiO^{t}Bu + CuI, Me_2CuLi*LiI, MeCu*LiI, MesCu and $[CuHPPh_3]_6$ as copper sources, with mesityl copper achieving the best results of enantioselectivity. These experiments were carried out in the presence of the analogous *trans* hydroxysilane **5.139**.

5.3.2.1. Solvent optimization.

After selection of copper reagent, we continued with the study of the different reaction parameters in order to obtain the best results in enantioselectivity. For that reason, an optimization to choose the most suitable solvent was carried out. As it can be seen in Table 5.2, enantioselectivity was not affected much by changes in ether solvents (Table, 5.2, entries 1-4). Note that the reaction proceeded in dichloromethane even at room temperature (Table 5.2, entry 5). The use of more polar solvents such as acetonitrile or DMF resulted in lower

yields and/or enantioselectivities (Table 5.2, entries 6-7). It is also interesting to note the fact that when the reaction was carried out in benzene the enantioselectivity increased 20 % with regard to that conducted in toluene (Table 5.2, entries 8-9) albeit the yield improved only slightly. Along these lines, the best results for both yield and enantioselectivity were achieved by using hexane as solvent despite the reaction mixture was not completely homogeneous (Table 5.2, entry 10).

Table 5.2. Solvent screening for elimination reaction.



5.138 **5.156** **5.157**

Entry	Solvent	T (°C)	t (h)	ee (%)[c] (+)[d]	Yield (%)[b]
1	THF	r.t.→50	5.0	73	67
2	dioxane	r.t.→50	3.5	78	66
3	Et_2O	r.t.	4.5	74	35
4	DME	r.t.→50	3.5	76	63
5	CH_2Cl_2	r.t.	4.5	77	51
6	MeCN	r.t.→50	4.5	64	56
7	DMF	r.t.→50	4.5	17	13
8	benzene	r.t.→50	3.5	77	63
9	toluene	r.t.→50	3.5	57	57
10	hexane	r.t.→50	3.5	81	72

[a] General conditions: vinylsilane (1 equiv.), mesityl copper (3.3 equiv.), solvent (0.5 mL), room temperature. [b] Determined by HPLC. [c] Determined by optical rotation. [d] Isolated yield.

2.3.2.2. Ligand screening.

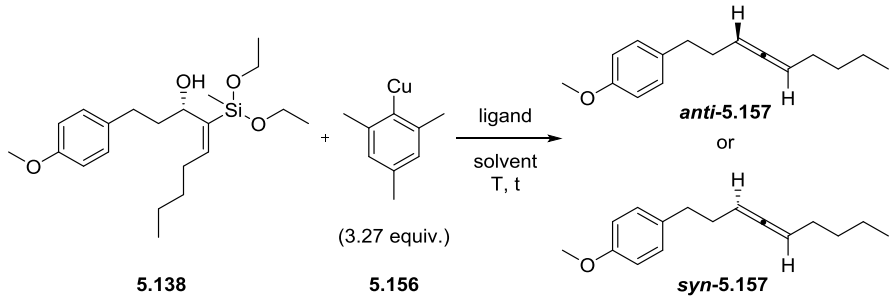
In 1990, Alexakis and co-workers reported that the enantioselectivity in the synthesis of allenes could be increased by adding phosphines or phosphites to the reaction mixture.[16b] Therefore, we decided to explore how the enantioselectivity was affected by the presence of different ligands. In this sense, phosphines and phosphites with different steric and electronic properties were screened. Lower enantioselectivities were observed when $P(OEt)_3$ or $P(NEt_2)_3$ were employed as ligands (Table 5.3, entries 1-2). These poor results could likely be caused by the low solubility of the reagents in hexane. To solve this drawback, dioxane, which had given only slightly lower enantioselectivity compared with hexane, was used instead of hexane as solvent. Fortunately, better results of enantioselectivity were afforded when the reaction was performed in dioxane and using an excess of phosphine (Table 5.3, entries 3-6). The use of other P donors with different electronic properties but with similar steric characteristics such as $P(OPh)_3$ or PBu_3 in dioxane, did not increase selectivity compared to entries 4 and 6 (Table 5.3, entries 7-9). Nevertheless, the replacement of dioxane by THF led to enantioselectivities up to almost 90 % when $P(OEt)_3$ was selected as ligand (Table 5.3, entry 10). The use of a much more electron-donating and bulkier ligand did not increase the selectivity (Table 5.3, entry 11). Unexpectedly, *syn* allenes were obtained when ligands with similar electronic properties but bulkier than $P(OEt)_3$ were used. When $P(O^iPr)_3$ and $P(O^tBu)_3$ were used, poor and moderate results of enantioselectivity were achieved (Table 5.3, entries 12-13). In the case of $P(O^tBu)_3$ it was even necessary to heat to 50 °C to assure reaction completion. Analogously, the use of PPh_3 also required to heating the reaction mixture to reach reaction completion although the enantioselectivity was quite poor and no better results were obtained (Table 5.3, entry 14). Interestingly, a moderately less electron-donating ligand like $P[p(PhCl)]_3$ compared to PPh_3 provided the best enantioselectivity for *syn* elimination (Table 5.3, entry 15). However, no product was formed when $P(Ph_2C_6F_5)$ was used as ligand despite having similar electronic properties than $P[p(PhCl)]_3$ (Table 5.3, entry 16).

Steric effects of this ligand might be the reason for this behaviour. On the other hand, change of solvent did not improve the enantioselectivity either (Table 5.3, entries 17-18). As a curiosity, the use of PBu_3 in hexane promoted the *syn* elimination instead of the *anti* one.

In spite of having a lot of experimental pieces of evidence with respect to enantioselectivity, further investigations are necessary. Based on the type of ligand used and according to the literature, the *anti* elimination product has been assumed to be obtained.[16b,77,78] Nonetheless, further experiments are required to determine the absolute configuration of allenes.

Taking into account all these results, the rest of the optimization process was carried out based on the best result obtained towards *anti* elimination, that is, 6.54 equiv. of $P(OEt)_3$ and 3.27 equiv. of mesityl copper were used.

Table 5.3. Effect of the ligand in *anti* elimination.



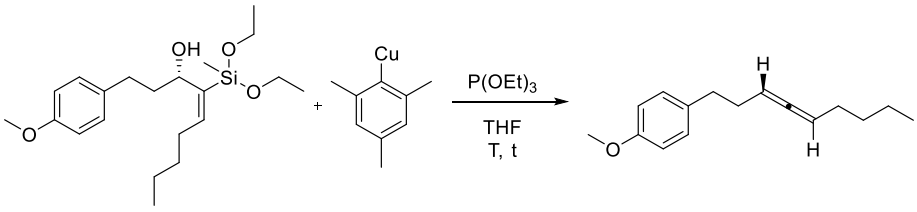
Entry	Ligand	Equiv. Ligand	Solvent	T (°C)	t (h)	Product	*ee* (%)[b]
1	$P(OEt)_3$	6.54	hexane	r.t.	1.5	***anti***	65 (+)[c]
2	$P(NEt_2)_3$	6.54	hexane	r.t.	1.5	***anti***	55 (+)[c]
3	$P(NEt_2)_3$	3.27	dioxane	r.t.	2.0	***anti***	67 (+)[c]
4	$P(NEt_2)_3$	6.54	dioxane	r.t.	2.0	***anti***	83 (+)[c]
5	$P(OEt)_3$	3.27	dioxane	r.t.	2.0	***anti***	72 (+)[c]
6	$P(OEt)_3$	6.54	dioxane	r.t.	2.0	***anti***	86 (+)[c]
7	$P(OPh)_3$	6.54	dioxane	r.t. → 50	5.0	***anti***	82 (+)[c]
8	PBu_3	3.27	dioxane	r.t.	2.0	***anti***	80 (+)[c]
9	PBu_3	6.54	dioxane	r.t.	2.0	***anti***	80 (+)[c]
10	$P(OEt)_3$	6.54	THF	r.t.	1.0	***anti***	89 (+)[c]
11	PCy_3	6.54	THF	0 →r.t.	3.0	***anti***	86 (+)[c]
12	$P(OiPr)_3$	6.54	dioxane	r.t.	1.0	***syn***	49
13	$P(O^tBu)_3$	6.54	dioxane	r.t.→50	4.0	***syn***	53
14	PPh_3	6.54	dioxane	r.t.→50	4.0	***syn***	30
15	$P(p\text{ClPh})_3$	6.54	dioxane	r.t.	4.0	***syn***	82
16	PPh_2PhF_5	6.54	dioxane	r.t.	3.0	***syn***	--[d]
17	PBu_3	6.54	hexane	r.t.	1.5	***syn***	23
18	$P(OiPr)_3$	6.54	THF	r.t.	1.0	***syn***	39

[a] General conditions: vinylsilane (1 equiv.), mesityl copper (3.27 equiv.), phosphine/phosphite (x equiv.), solvent (0.5 mL). [b] Determined by HPLC. [c] Determined by optical rotation. [d] Allene is not formed.

5.3.2.3. Effect of temperature and copper loading.

It is well-known that enantioselectivity is influenced by factors such as temperature and stoichiometry of reagents used in the reaction. In this sense, a series of tests were carried out decreasing both temperature and copper loading. In all cases, the *ratio* 2:1 between the ligand and mesityl copper were kept since the best result was reached under these conditions. Results obtained in this study are summarized in Table 5.4.

Table 5.4. Effect of temperature and amount of mesityl copper in allene formation.



5.138 **5.156** ***anti*-5.157**

Entry	Equiv. Copper	Equiv. Ligand	T (°C)	t (h)	*ee* (%)[b](+)[c]	Yield (%)[d]
1	3.27	6.54	r.t.	1.0	89	N.D.[e]
2	3.27	6.54	-20	1.0	92	N.D.[e]
3	3.27	6.54	0	1.0	91	90
4	2.00	4.00	0	1.0	86	N.D.[e]
5	1.20	2.40	0	1.0	90	N.D.[e]
6	1.00	2.00	0	1.0	92	N.D.[e]

[a] General conditions: vinylsilane (1 equiv.), mesityl copper (3.27 equiv.), $P(OEt_3)$ (x equiv.), THF (0.5 mL). [b] Determined by HPLC. [c] Determined by optical rotation. [d] Isolated yield. [e] N.D. = No determined.

As discussed in the previous section, an excellent selectivity for *anti* elimination was achieved when the reaction took place in THF at room temperature employing 3.27 equiv. of mesityl copper and 6.54

equiv. of $P(OEt)_3$ (entry 1). Fortunately, better results of enantioselectivity were achieved when the reaction was conducted at -20 and 0 °C although no remarkable differences were found for both conditions (entries 2-3). Furthemore, exceptional yields were obtained when the reaction was driven at 0 °C in low and moderate scale (entry 3). It is worth mentioning that in all cases only allene and mesytol (by-product formed during the reaction) were detected. It was also found that the amount of copper is vital in this elimination reaction since other by-products such as protodesilylated compound were obtained when 2 or less equivalents of copper was used (entries 4-6).

5.3.2.4. Substrate scope.

Encouraged by outcomes obtained for *anti* elimination we also explored the substrate scope of the reaction with different types of hydroxysilanes. In this scope functional group tolerance, steric hindrance and electronic influence of some substituents were studied.

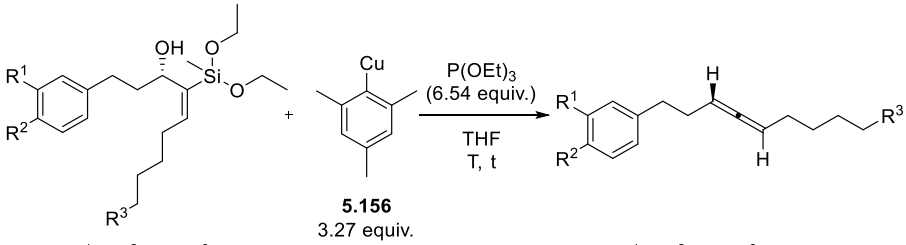
a) Study of functional group tolerance.

Four compounds with similar structure but with different groups at the end of the aliphatic chain were submitted to allenylation under the optimized reaction conditions in order to test their stability. Results are summarized in Table 5.5.

The presence of an extra hydroxyl group in **5.139** was expected to be a problem since the copper reagent presumably acts as base and it had to distinguish between two hydroxyl groups. Unexpectedly, no reaction was detected in the absence of ligands, although excellent enantioselectivity was obtained in its presence (Table 5.5, entries 1-2). The low yield might be explained by the competition between both hydroxyl groups. Substrate **5.140** containing a nitrile group was also tested in elimination reaction providing good enantioselectivity and moderate yield. No significant improvements were detected even decreasing the temperature (Table 5.5, entries 3-4). Interestingly, the

use of a batch of freshly prepared mesityl copper improved the results of enantioselectivity for both **5.140** and **5.141** substrates (Table 5.5, entries 5 and 7). However, a decrease in yield was obtained when **5.141** was reacted under optimized conditions and further investigations need to be made to clarify this fact. Unfortunately, the reaction with **5.142** did not take place by decomposition of the starting material (Table 5.5, entry 8).

Table 5.5. Screening for substrates bearing different functional groups at the terminal carbon.



5.156
3.27 equiv.

5.139: $R^1 = R^2 = H$, $R^3 = OH$
5.140: $R^1 = R^2 = CH_2O$, $R^3 = CN$
5.141: $R^1 = R^2 = CH_2O$, $R^3 = NHBoc$
5.142: $R^1 = R^2 = CH_2O$, $R^3 = N_3$

5.158: $R^1 = R^2 = H$, $R^3 = OH$
5.159: $R^1 = R^2 = CH_2O$, $R^3 = CN$
5.160: $R^1 = R^2 = CH_2O$, $R^3 = NHBoc$
5.161: $R^1 = R^2 = CH_2O$, $R^3 = N_3$

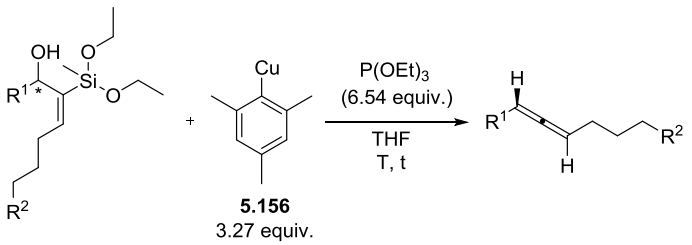
Entry	Substrate	T (°C)	t (h)	*ee* (%)[b]	Yield (%)[c]
1[d]	**5.139**	r.t.	3.00	--	N.R.[e]
2	**5.139**	0	2.00	89	29
3	**5.140**	0	2.00	88 (-)[f]	65
4	**5.140**	-20	2.00	89 (-)$_f$	65
5	**5.140**	0	0.75	91 (-)[f]	72[g]
6	**5.141**	0	2.00	89 (+)[f]	72
7	**5.141**	0	0.75	90 (+)[f]	44[g]
8	**5.142**	0	2.00	--	--[h]

[a] General conditions: vinylsilane (1 equiv.), mesityl copper (3.27 equiv.), $P(OEt_3)$ (6.54 equiv.), THF (0.5 mL). [b] Determined by HPLC. [c] Isolated yield. [d] Reaction in the absence of ligand. [e] N.R. = No reaction. [f] Determined by optical rotation. [g] Freshly prepared mesityl copper. [h] Decomposition of starting material.

b) Effect of steric hindrance.

After testing different substrates with similar structure at the vicinity of the reactive centers, we centered our attention on studying the influence of bulky susbstituents attached to the carbinol center in the reaction outcome (Table 5.6).

Table 5.6. Screening for substrates with different steric hindrance.



(***S***)-**5.143**: R^1 = ^{i}Pr, R^2 = *p*ClPhC(O)O
(***S***)-**5.144**: R^1 = cy, R^2 = *p*OMePhCH$_2$O
(***R***)-**5.145**: R^1 = ^{t}Bu, R^2 = *p*OMePhCH$_2$O

5.162: R^1 = ^{i}Pr, R^2 = *p*ClPhC(O)O
5.163: R^1 = cy, R^2 = *p*OMePhCH$_2$O
5.164: R^1 = ^{t}Bu, R^2 = *p*OMePhCH$_2$O

Entry	Substrate	T (°C)	t (h)	ee (%)[b]	Yield (%)[c]
1	**(*S*)-5.143**	0	1.0	>90[d] (+)[e]	10[f]
2	**(*S*)-5.144**	0	1.5	93 (+)[e]	82[g]
3	**(*R*)-5.145**	0	2.0	80 (-)[e]	42
4	**(*R*)-5.145**	-20 to 0	4.0	76 (-)[e]	N.D.[h]

[a] General conditions: vinylsilane (1 equiv.), mesityl copper (3.27 equiv.), P(OEt$_3$) (6.54 equiv.), THF (0.5 mL). [b] Determined by HPLC. [c] Isolated yield. [d] Difficult separation and sample freshly measured. [e] Determined by optical rotation. [f] Measured by ^{1}H NMR the product was afforded in 70 %. [g] The reaction was performed in 50 mg of starting material instead of 20 mg as usual. [h] N.D. = Not determined.

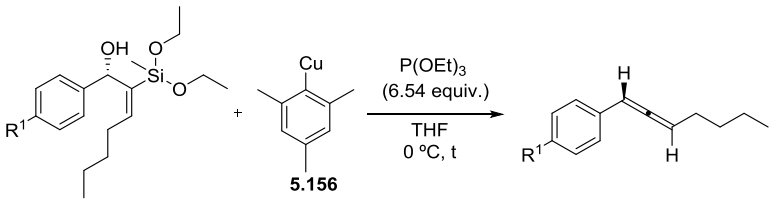
Isopropyl group, initially selected as a bulky group, gave very poor yield presumably by decomposition of the product on column although the enantioselectivity was very good (Table 5.6, entry 1). To our delight, excellent enantioselectivity and yield were achieved when compound **(*S*)-5.144**, with similar steric hindrance to **(*S*)-5.143**, was treated under the optimized reaction conditions (Table 5.6, entry 3). In contrast, slightly worse results were found when a *tert*-butyl group was

introduced at α-carbon bearing the hydroxyl group (Table 5.6, entry 4). When the reaction was conducted at lower temperature and for longer reaction times, the enantioselectivity slightly decreased. This fact might be due to racemization of the product in contact with copper species (Table 5.6, entry 5).[80]

c) Electronic influence in allene formation.

In parallel to the study of steric effects in elimination, we were also interested in investigating how elimination was affected by electronic effects. For that reason, three substrates bearing different substituents at the *para* position of the aryl group were submitted to allenylation reaction under the optimal conditions (Table 5.7). When compound **5.146** bearing an electron-donating group was treated with mesityl copper and $P(OEt)_3$, poor enantioselectivity was achieved even measuring it after the reaction was completed (Table 5.7, entries 1-2). Nevertheless, using bromine as electron-withdrawing group considerably increased both the enantioselectivity and the reaction rate completing the reaction just in 5 min (Table 5.7, entries 3, 4). Again, the difference of enantiomeric excess at different reaction times, entries 3 and 4, might be due to racemization of allene in solution. Allene **5.148** bearing a trifluoromethyl group was especially difficult to handle and extensive decomposition was observed during the chromatographic purification process. At this point, this result can be considered as provisional since it must be improved in further investigations.

Table 5.7. Influence of electronic effects in allenylation.



5.156
3.27 equiv.

5.146: R^1 = OMe
5.147: R^1 = Br
5.148: R^1 = CF_3

5.165: R^1 = OMe
5.166: R^1 = Br
5.167: R^1 = CF_3

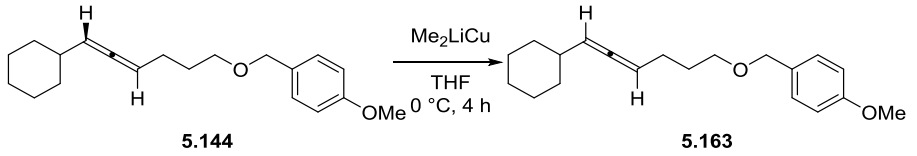
Entry	Substrate	time (h)	ee (%)[b]	Yield (%)[c]
1	**5.146**	1.50	23 (+)[f]	73
2	**5.146**	1.50	20[d] (+)[f]	N.D.[e]
3	**5.147**	0.50	80 (+)[f]	74
4	**5.147**	0.08	88[d] (+)[f]	N.D.[e]
5	**5.148**	1.00	3	N.D.[e]

[a] General conditions: vinylsilane (1 equiv.), mesityl copper (3.27 equiv.), $P(OEt_3)$ (6.54 equiv.), THF (0.5 mL). [b] Determined by HPLC. [c] Isolated yield. [d] Sample was measured after reaction. [e] Not determined. [f] Determined by optical rotation.

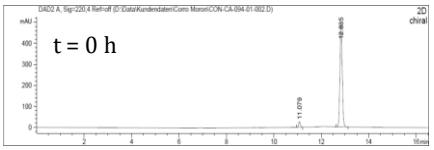
5.3.2.5. Racemization control.

Racemization in allenes is characterized by not being a too fast process and it can be promoted by organocopper or cuprate reagents,[80a] or even by Cu^0 species.[80b] Thus, considering that some of our results might be affected by this problem, allene **5.144** carrying a cyclohexyl moiety was submitted to a racemization test in the presence of dimethyllithium cuprate (Scheme 5.43).

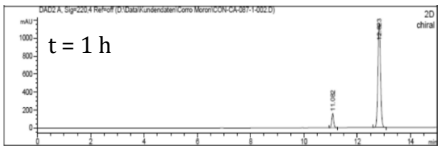
The reaction was monitored by HPLC and different aliquots from the reaction mixture were taken every hour and filtered through a short silica pad. From these data it can be clearly concluded that enantioselectivity decreased with the time from the initial 93 % to 55 % after 4 hours of reaction. Therefore, this study allows us to confirm that our compounds racemize under the standard conditions. However, no test about racemization employing mesityl copper was made and further investigations should be undertaken to confirm this fact in our system.



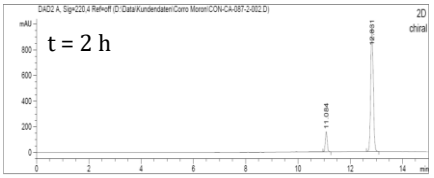
5.144 **5.163**



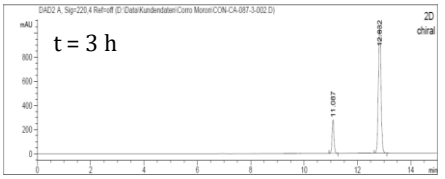
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral	
1	11.079	BB	0.0770	131.37808	26.44735	3.7503	1. enantiomer	ee = 92.5%
2	12.835	BB	0.1056	3371.77026	497.28555	96.2497	2. enantiomer	
Totals :				3503.14835	523.73290			



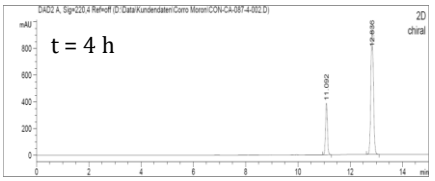
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral	
1	11.082	BB	0.0771	783.63171	187.98866	8.9639	1. enantiomer	ee = 82.1%
2	12.823	BB	0.1070	7958.48947	1189.98459	91.0361	2. enantiomer	
Totals :				8742.09119	1317.94326			



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral	
1	11.084	BB	0.0774	778.87390	156.87816	10.3526	1. enantiomer	ee = 79.3%
2	12.831	BB	0.1067	6744.56152	984.41980	89.6474	2. enantiomer	
Totals :				7523.43542	1141.29796			



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral	
1	11.087	BB	0.0773	1365.96643	275.49719	15.9363	1. enantiomer	ee = 68.1%
2	12.832	BB	0.1067	7205.46143	1051.50574	84.0637	2. enantiomer	
Totals :				8571.42786	1327.00293			



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	chiral	
1	11.092	BB	0.0776	1920.47949	385.64624	22.6544	1. enantiomer	ee = 54.7%
2	12.836	BB	0.1068	6556.80273	958.88275	77.3456	2. enantiomer	
Totals :				8477.28223	1344.52899			

Scheme 5.42. Racemization process for **5.143**.

5.3.2.6. Mechanistic study by ^{1}H NMR.

As discussed at the beginning of this section, the formation of allenes from hydroxysilanes might be explained through elimination of β-siloxide intermediate according to studies carried out by Harpp[77] and Araki.[78] In order to support this hypothesis, we sought to detect or isolate some of reaction intermediates postulated.

If the reaction takes place through the proposed mechanism, the corresponding β-siloxide intermediate should be observed at some point of the reaction. Thus, we decided to perform a reaction using the best conditions found by *syn* elimination since reaction times are longer. Then, aliquots were taken from the reaction mixture, quenched with a mixture of NH_3/NH_4Cl (1:9) and analyzed by ^1H NMR. The samples were taken at 10, 20, 40, 80, 160 and 240 minutes, respectively. Data extracted from spectra are summarized in Figure 5.2, where the most informative region from the spectrum, 3 to 6 ppm, was selected. This section has been chosen since changes at double bonds can be observed in this range of ppm.

Control experiment for allenylation of **5.138** started 10 minutes after the reaction was begun. At that point, the allene product **5.158** starts to form, as judged by the presence of signals at 5.16 ppm of the spectrum (Figure 5.2). At the same time, protodesilylated sub-product **5.168** is also detected (signals at 4.45 ppm), which means that part of the starting material will not be able to transform into allene since silylated moiety has been lost. In the rest of aliquots, the amount of protodesilylated compound seems to be constant while the starting material is progressively consumed and the allene produced. On the other hand, other changes are observed in additional regions of the spectrum but the complexity of the crude avoids elucidating any clear structure which can help to predict a plausible mechanism. Therefore, further investigations should be done before purposing or confirming any mechanism.

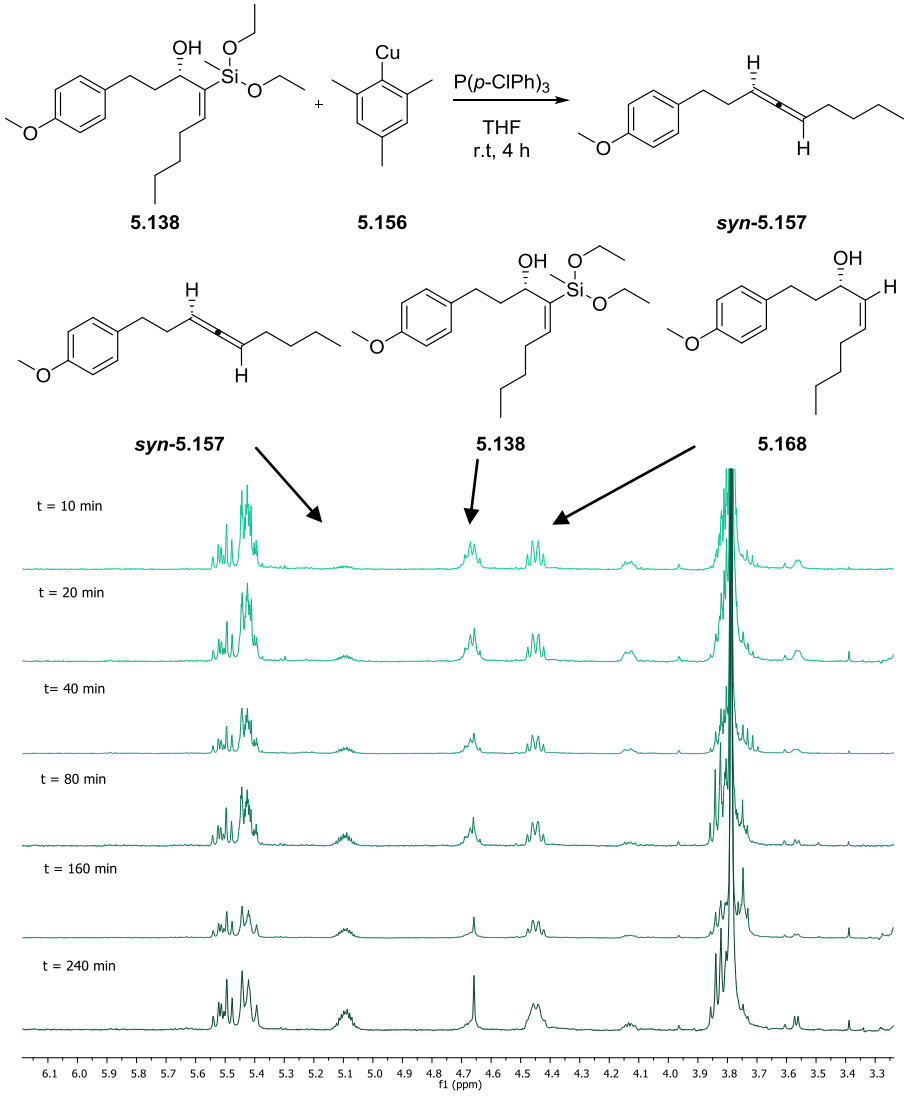


Figure 5.2. Control by ^{1}H NMR of the allenylation for **5.138**.

5.4. CONCLUSIONS.

The enantioselective synthesis of allenes starting from allyl alcohols bearing silanes in α-position with regard to hydroxyl group has been accomplished. The following conclusions have been extracted from this process:

i) The corresponding silanes were successfully prepared by hydrosilylation of chiral propargylic alcohols where $Pt(dba)_3$ acted as catalyst.

ii) The subsequent enantioenriched allenes were afforded by copper-mediated allenylation.

iii) It was found that enantioselectivity increased by the presence of phosphites or phosphines in the reaction mixture enhancing *anti*-elimination. Nonetheless, the use of less electron donating phosphines or bulkier phosphites with similar electronic properties changed this trend leading to the formation of *syn* allenes.

iv) Allenylation is influenced by either steric or electronic properties and presents moderate tolerance towards different functional groups.

v) Chiral allenes racemize in the presence of copper species at long reaction times.

vi) Attemps to try to elucidate the mechanism by detecting or isolating some reaction intermediate resulted unsuccessful.

5.5. EXPERIMENTAL PART.

5.5.1. General considerations.

All reactions were carried out under Ar atmosphere in flame-dried glassware using anhydrous solvents. Solvents were purified by distillation over the indicated drying agents and were transferred under Ar: toluene and hexane (Na/K), Et_2O, THF and DME (Mg, antracene), benzene (molecular sieves), acetonitrile and CH_2Cl_2 (CaH_2), dioxane and DMF were dried by an absorption solvent purification system based on molecular sieves. Flash chromatography: Merck Geduran® Si 60 (40–63 μm). NMR: Spectra were recorded at room

temperature on Bruker AV 400s in $CDCl_3$ and they were fully assigned using COSY, HSQC and HMBC. All chemical shifts are quoted on the δ scale in ppm using the residual solvent as internal standard (^{1}H NMR: $CDCl_3$ = 7.26; ^{13}C NMR: $CDCl_3$ = 77.16). Coupling constants (*J*) are reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, *p*d = pseudo doblet. IR: Perkin-Elmer Spectrum One spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS: ESI: Thermo Scientific LTQ-FT or Thermo Scientific Exactive; accurate mass determinations: Finnigan MAT 95, Thermo Scientific LTQ FT, or Thermo Scientific Exactive. Optical rotations $[\alpha]^{D}_{20}$ were measured with a PerkinElmer Model 343 polarimeter. LC-MS analyses were conducted on a Shimadzu LCMS2020 instrument. Silylated compounds were prepared according to the cited literature procedures. Commercially available compounds (Alfa Aesar, Acros, SigmaAldrich) were used as received.

5.5.2. General methods.

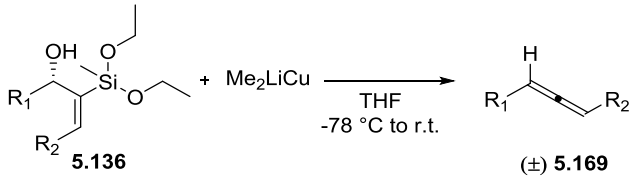
5.5.2.1. Representative procedure for hydrosilylation.

To a flamed Schlenk containing a solution of $Pt(dba)_3$ (0.005 mmol) in toluene (2.5 mL) was added the corresponding alkyne (0.5 mmol). The reaction mixture was stirred at room temperature for 3 min and then methyldiethoxysilane (0.525 mmol) was added dropwise. The mixture was stirred at this temperature until TLC analysis showed complete consumption of the starting material. The solvent was then removed under reduced pressure and the crude was purified by flash chromatography.

5.5.2.2. Representative procedure for synthesis of achiral allenes.

A flamed Schlenk containing a solution of silane (0.055 mmol) in THF (0.1 mL) was cooled at -78 °C and stirred for 5 min. Dimethyl lithium copper (0.06 mmol) was then slowly added and the solution was stirred for 20 min at this temperature before warming at room temperature. Once the reaction was completed, the solvent was removed

under vacuum and the residue was purified by flash chromatography (Scheme 5.43).



Scheme 5.43. General method to synthesize achiral allenes.

5.5.2.3. Representative procedure for synthesis of chiral allenes.

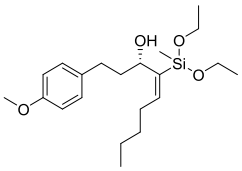
A flamed Schlenk containing a solution of mesityl copper (0.18 mmol) and $P(OEt)_3$ (0.36 mmol) in 0.5 mL of THF was cooled at 0 °C and stirred for 5 min. The corresponding silane (0.055 mmol) was then added and the solution was stirred at 0 °C until TLC analysis showed complete consumption of the starting material. The solvent was then removed under reduced pressure and the crude was purified by flash chromatography.

5.5.3. NMR study in the mechanistic elucidation.

A flamed Schlenk containing a solution of mesityl copper (0.26 mmol) and $P(p\text{PhCl})_3$ (0.52 mmol) in THF (3.7 mL) was stirred at room temperature for 5 min before silane **5.139** (0.079 mmol) was added. Different aliquots (0.1 mL) were taken from the reaction media at 10, 20, 40, 80, 160 and 240 minutes, respectively. Subsequently they were quenched with a mixture of NH_3/NH_4Cl (1:9) and extracted with ethyl acetate. The solvent of the combined organic phases was removed under reduced pressure and they were then measured by ^1H NMR.

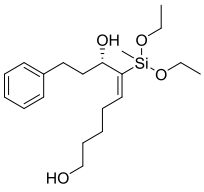
5.5.4. Characterization of compounds.

(*S,E*)-4-(diethoxy(methyl)silyl)-1-(4-methoxyphenyl)non-4-en-3-ol (5.138):



The residue was purified by flash chromatography using hexane/EtOAc (90:10) to afford the product **5.138** (859 mg, 55 %) as brownish liquid. $[\alpha]_D^{20}$ = —41.3°. (*c* 1.16, $CHCl_3$). IR (film, $CHCl_3$) 3499, 2957, 2926, 2862, 1612, 1584, 1512, 1456, 1390, 1299, 1246, 1165, 1073, 948, 762 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.88 (ddd, *J* = 7.7, 6.5,1.3 Hz, 1H), 4.46 (td, *J* = 8.9, 5.1 Hz, 1H), 3.87 – 3.67 (m, 7H), 3.31 (d, *J* = 8.9 Hz, 1H), 2.73 (ddd, *J* = 14.2, 10.0, 5.0 Hz, 1H), 2.58 (ddd, *J* = 14.2, 10.0, 6.9 Hz, 1H), 2.16 – 1.99 (m, 1H), 1.99 – 1.82 (m, 2H), 1.76-1.61 (dddd, *J* = 13.7, 10.0, 6.9, 5.0 Hz, 1H), 1.43 – 1.15 (m, 10H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 143.9, 140.4, 134.5, 129.5, 113.9, 71.1, 58.6, 55.4, 40.8, 31.5, 28.6, 22.5, 18.4, 14.1, -2.9. HRMS (ESI): m/z calculated for $C_{21}H_{36}O_4SiNa^+$ [M+Na^+]: 403.2278, found: 403.2275. The enantiomeric excess was determined to be 96% by HLPC analysis (150 mm Chiralpack AS-3R, 4.6 mm i.D., Acetonitrile/water = 70:30, 1 mL/min, 15.5 MPa, 298 K, UV 220 nm).

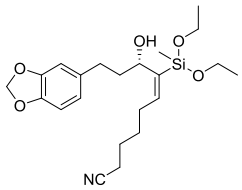
(*S,E*)-6-(diethoxy(methyl)silyl)-9-phenylnon-5-ene-1,7-diol (5.139):



Flash chromatographic purification of the crude (hexane/EtOAc = 70:30) yielded the product **5.139** (104.4 mg, 53 %) as brown syrup. $[\alpha]_D^{20}$ = —40.2° (*c* 1.03, $CHCl_3$). IR (film, $CHCl_3$) 3420, 2971, 2926, 1605, 1496, 1454, 1390, 1257, 1102, 947, 761 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.23 – 7.17 (m, 3H), 5.96 – 5.80 (ddd, *J* = 7.6, 6.5, 1.1, 1H), 4.46 (ddd, *J* = 8.7, 4.9, 1.0 Hz, 1H), 3.80 (q, *J* = 7.0 Hz, 2H), 3.79 (q, *J* = 7.0 Hz, 2H), 3.60 (t, *J* = 6.4 Hz, 2H), 2.79 (ddd, *J* = 14.2, 9.9, 5.0 Hz, 1H), 2.65 (ddd, *J* = 14.2, 9.9, 7.0 Hz, 1H), 2.14 – 2.03 (m, 1H), 2.03 – 1.88 (m, 2H), 1.71 (dddd, *J* = 13.8, 9.9, 7.0, 5.0 Hz, 1H), 1.58 – 1.46 (m, 2H), 1.46 – 1.37 (m, 2H),

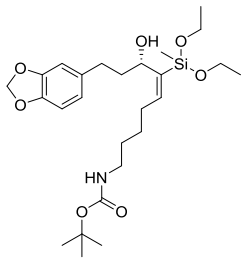
1.24 (t, *J* = 7.0 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 3H), 0.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 142.4, 141.0, 128.7, 128.5, 125.9, 71.0, 62.8, 58.6, 40.5, 32.4, 28.5, 25.5, 18.6, 18.4, -2.9. HRMS (ESI): m/z calculated for $C_{20}H_{34}O_4SiNa^+$ [M+Na$^+$]: 389.2120, found: 389.2119.

(*S,E*)-10-(benzo[*d*][1,3]dioxol-5-yl)-7-(diethoxy(methyl)silyl)-8-hydroxydec-6-enenitrile (5.140):



The residue was purified by flash chromatography using hexane/EtOAc (80:20) to afford the product **5.140** (131.8 mg, 44 %) as colorless oil. $[\alpha]_D^{20}$ = —41.3° (*c* 1.05, $CHCl_3$). IR (film, $CHCl_3$) 3486, 2972, 2928, 2884, 2250, 1609, 1489, 1441, 1390, 1364, 1245, 1164, 1101, 1072, 1038, 937 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 1.7 Hz, 1H), 6.65 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.92 (m, 2H), 5.83 (ddd, *J* = 7.6, 6.4, 1.1 Hz, 1H), 4.40 (dd, *J* = 9.1, 4.7 Hz, 1H), 3.80 (q, *J* = 7.0 Hz, 2H), 3.78 (q, *J* = 7.0 Hz, 2H), 3.26 (bs, 1H), 2.70 (ddd, *J* = 14.0, 9.2, 5.1 Hz, 1H), 2.58 (ddd, *J* = 14.0, 9.2, 7.6 Hz, 1H), 2.31 (t, *J* = 7.0 Hz, 2H), 2.12 (dq, *J* = 15.0, 7.6 Hz, 1H), 2.01 – 1.86 (m, 2H), 1.75 – 1.59 (m, 3H), 1.58-1.50 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 0.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 145.7, 141.9, 141.8, 136.0, 121.4, 119.6, 109.1, 108.2, 100.9, 70.6, 58.7, 40.6, 32.0, 28.2, 27.9, 25.1, 18.4, 17.1, -3.0. HRMS (ESI): m/z calculated for $C_{22}H_{23}NO_5SiNa^+$ [M+Na$^+$]: 442.2020, found: 442.2020.

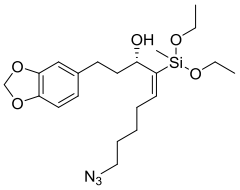
***Tert*-butyl (*S,E*)-[9-(benzo[*d*][1,3]dioxol-5-yl)-6-(diethoxy(methyl)silyl)-7-hydroxynon-5-ene-1-yl]carbamate (5.141):**



Flash chromatographic purification of the crude (hexane/EtOAc = 80:20) yielded the product **5.141** (128.4 mg, 63 %) as yellowish syrup. $[\alpha]_D^{20}$ = — 33.4° (c 1.04, $CHCl_3$). IR (film, $CHCl_3$) 3430, 3360, 2974, 2930, 1693, 1609, 1504, 1489, 1422, 1366, 1246, 1168, 1039, 938, 809 cm^{-1}.

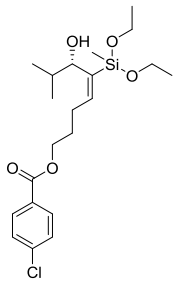
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 1.5 Hz, 1H), 6.65 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.91 (s, 2H), 5.85 (ddd, *J* = 7.6, 6.4, 1.1 Hz, 1H), 4.55 – 4.37 (m, 2H), 3.80 (q, *J* = 7.0 Hz, 2H), 3.79 (q, *J* = 7.0 Hz, 2H), 3.31 (bs, 1H), 3.15 – 3.00 (m, 2H), 2.70 (ddd, *J* = 14.1, 9.6, 5.0 Hz, 1H), 2.56 (ddd, *J* = 14.1, 9.6, 7.1 Hz, 1H), 2.08 (dq, *J* = 14.9, 7.6 Hz, 1H), 2.00 – 1.82 (m, 2H), 1.72 – 1.55 (m, 1H), 1.50 – 1.28 (m, 13H), 1.23 (t, *J* = 7.0, 6H), 0.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 147.6, 145.6, 143.1, 141.1, 136.2, 121.3, 109.1, 108.3, 100.8, 79.2, 70.8, 58.6, 40.7, 40.5, 32.1, 29.9, 28.6, 28.4, 26.5, 18.4,-2.9. HRMS (ESI): m/z calculated for $C_{26}H_{43}NO_7SiNa^+$ [M+Na^+]: 532.2707, found: 532.2701.

(*S,E*)-9-azido-1-(benzo[*d*][1,3]dioxol-5-yl)-4-(diethoxy(methyl)silyl)non-4-ene-3-ol (5.142):



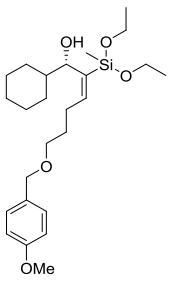
The crude was purified by flash chromatography using hexane/MTBE (85:15) to afford the product **5.142** (33 mg, 76 %) as colorless oil. $[\alpha]_D^{20}$ = — 16.3° (*c* 1.25, $CHCl_3$). IR (film, $CHCl_3$) 3484, 2972, 2927, 2880, 2094, 1609, 1503, 1488, 1441, 1244, 1071, 1038, 936, 807 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 1.6 Hz, 1H), 6.69 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.95 (s, 2H), 5.89 (t, *J* = 6.5 Hz, 1H), 4.47 (bd, *J* = 4.3 Hz, 1H), 3.83 (q, *J* = 7.0 Hz, 4H), 3.37 – 3.20 (m, 2H), 2.75 (ddd, *J* = 14.1, 9.4, 5.0 Hz, 1H), 2.61 (ddd, *J* = 14.1, 9.4, 7.3 Hz, 1H), 2.12 (dq, *J* = 15.1, 7.6 Hz, 1H), 2.05 – 1.90 (m, 2H), 1.77 – 1.64 (m, 1H), 1.64 – 1.52 (m, 2H), 1.52 – 1.40 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 0.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 145.7, 142.6, 141.5, 136.1, 121.3, 109.1, 108.3, 100.9, 70.8, 58.7, 51.3, 40.7, 32.1, 28.6, 28.3, 26.4, 18.4, -3.0. HRMS (ESI): m/z calculated for $C_{21}H_{33}N_3O_5SiNa^+$ [M+Na^+]: 458.2084, found: 458.2082.

(*S,E*)-[5-(diethoxy(methyl)silyl)-6-hydroxy-7-methyloct-4-ene-1-yl] 4-chlorobenzoate (5.143):



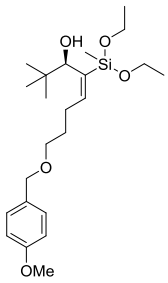
Flash chromatographic purification of the crude (hexane/MTBE = 85:15) yielded the product **5.143** (154.3 mg, 53 %) as yellow liquid. $[\alpha]_D^{20}$ = +23.7° (*c* 1.05, $CHCl_3$). IR (film, $CHCl_3$) 3498, 2970, 2925, 1722, 1596, 1489, 1402, 1389, 1271, 1103, 949, 760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 5.98 (ddd, *J* = 7.5, 6.3, 0.9 Hz, 1H), 4.40 – 4.24 (m, 1H), 4.03 (*p*d, *J* = 8.8 Hz, 1H), 3.80 (q, *J* = 7.0 Hz, 2H), 3.78 (q, *J* = 7.0 Hz, 2H) 3.26 (bs, 1H), 2.40 (td, *J* = 15.1, 7.5 Hz, 1H), 2.19 (ddt, *J* = 15.1, 8.6, 6.3 Hz, 1H), 1.97 – 1.81 (m, 2H), 1.71 (m, 1H), 1.23 (t, *J* = 7.0, 3H), 1.22 (t, *J* = 7.0, 3H) 1.04 (d, *J* = 6.6 Hz, 2H), 0.78 (d, *J* = 6.6 Hz, 2H), 0.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 142.7, 141.2, 139.5, 131.1, 128.9, 77.3, 64.8, 58.6, 35.1, 28.5, 25.7, 19.5, 19.2, 18.4, -3.0. HRMS (ESI): m/z calculated for $C_{21}H_{34}O_5ClSi^+$ [M+H^+]: 429.1854, found: 429.1859.

(*S,E*)-1-cyclohexyl-2-(diethoxy(methyl)silyl)-6-((4-methoxybenzyl)oxy)hex-2-ene-1-ol (5.144):



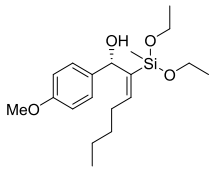
The residue was purified by flash chromatography using hexane/EtOAc (90:10) to afford the product **5.144** (251.9 mg, 59 %) as yellowish liquid. $[\alpha]_D^{20}$ = +73.1° (*c* 1.10, $CHCl_3$). IR (film, $CHCl_3$) 3502, 1970, 2922, 2851, 1612, 1513, 1449, 1339, 1247, 1171, 1099, 1074, 952, 919, 762 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.05 – 5.77 (m, 1H), 4.43 (s, 2H), 4.08 (d, *J* = 9.0 Hz, 1H), 3.85 – 3.67 (m, 7H), 3.58 – 3.35 (m, 2H), 3.37 (s, 1H), 2.30 (td, *J* = 15.1, 8.0 Hz, 1H), 2.23 – 1.94 (m, 2H), 1.94 – 1.45 (m, 6H), 1.45 – 1.30 (m, 1H), 1.30 – 1.04 (m, 9H), 1.04 – 0.89 (m, 1H), 0.88 – 0.74 (m, 1H) 0.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 144.0, 139.9, 130.8, 129.4, 113.9, 76.0, 72.7, 69.5, 58.5, 55.4, 44.8, 29.8, 29.7, 29.5, 26.7, 26.4, 26.3, 25.9, 18.4, -3.0. HRMS (ESI): m/z calculated for $C_{26}H_{42}O_4SiNa^+$ [M+Na^+]: 473.2695, found: 473.2696.

(*R,E*)-4-(diethoxy(methyl)silyl)-8-((4-methoxybenzyl)oxy)-2,2-dimethyloct-4-ene-3-ol (5.145):



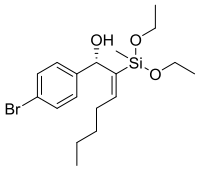
The residue was purified by flash chromatography using hexane/EtOAc (90:10) to afford the product **5.145** (151.5 mg, 54 %) as colorless syrup. $[\alpha]_D^{20}$ = —13.1° (*c* 1.00, $CHCl_3$). IR (film, $CHCl_3$) 3494, 2971, 2906, 2868, 1613, 1513, 1465, 1390, 1362, 1248, 1170, 1100, 1073, 948, 821 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.97 (ddd, *J* = 8.7, 5.2, 1.2 Hz, 1H), 4.42 (s, 2H), 4.21 (s, 1H), 3.91 (bs, 1H), 3.83-3.73 (m, 7H), 3.51 – 3.38 (m, 2H), 2.40 (td, *J* = 15.5, 8.5 Hz, 1H), 2.11 – 1.99 (m, 1H), 1.81 – 1.57 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 3H) 0.90 (s, 9H), 0.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 145.7, 138.5, 130.6, 129.3, 113.8, 79.7, 72.6, 69.3, 58.5, 58.2, 55.3, 37.1, 29.3, 26.6, 18.1, -3.15. HRMS (ESI): m/z calculated for $C_{23}H_{41}O_5Si^+$ [M+H^+]: 425.2721, found: 425.2718.

(*S,E*)-2-(diethoxy(methyl)silyl)-1-(4-methoxyphenyl)hept-2-ene-1-ol (5.146):



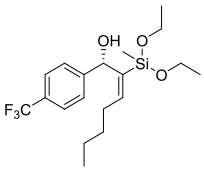
The residue was purified by flash chromatography using hexane/MTBE (95:5 to 85:15) to afford the product **5.146** (295.7 mg, 61 %) as yellow liquid. $[\alpha]_D^{20}$ = —57.9° (*c* 1.13, $CHCl_3$). IR (film, $CHCl_3$) 3498, 2957, 2929, 1607, 1508, 1465, 1442, 1390, 1293, 1250, 1176, 1075, 1035, 793, 766 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 3H), 4.67 (td, *J* = 9.0, 4.6 Hz, 1H), 3.94 – 3.76 (m, 7H), 3.11 (d, *J* = 9.0 Hz, 1H), 1.75 (dtd, *J* = 13.6, 9.4, 4.6 Hz, 1H), 1.67 – 1.52 (m, 1H), 1.52 – 1.41 (m, 1H), 1.41 – 1.19 (m, 9H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.34 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 141.9, 140.0, 130.4, 129.9, 113.7, 71.5, 58.7, 55.4, 38.2, 28.4, 22.8, 18.4, 14.2, -2.7. HRMS (ESI): m/z calculated for $C_{19}H_{32}O_4SiNa^+$ [M+Na^+]: 375.1964, found: 375.1962.

(*S,E*)-1-(4-bromophenyl)-2-(diethoxy(methyl)silyl)hept-2-ene-1-ol (5.147):



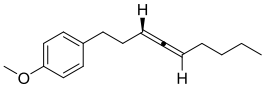
Flash chromatographic purification of the crude (hexane/MTBE = 90:10) yielded the product **5.147** (275.8 mg, 75 %) as colorless oil. $[\alpha]_D^{20}$ = —89.8° (*c* 1.11, $CHCl_3$). IR (film, $CHCl_3$) 3473, 2971, 2927, 2874, 1611, 1484, 1392, 1257, 1102, 1072, 1010, 946, 817, 764 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 6.00 (ddd, *J* = 7.6, 6.2, 1.2 Hz, 1H), 5.50 (d, *J* = 10.2 Hz, 1H), 4.06 (d, *J* = 10.2 Hz, 1H), 3.69 (q, *J* = 7.0, 2H), 3.59 – 3.36 (m, 2H), 2.26 (dq, *J* = 15.1, 7.6 Hz, 1H), 2.13 (dq, *J* = 15.1, 7.6 Hz, 1H), 1.44 – 1.19 (m, 4H), 1.12 (t, *J* = 7.0 Hz, 3H), 1.04 (t, *J* = 7.0 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H), -0.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 143.7, 139.0, 131.0, 127.6, 120.4, 71.6, 58.5, 58.4, 31.4, 28.8, 22.4, 18.2, 18.1, 13.9, -3.3. HRMS (ESI): m/z calculated for $C_{18}H_{29}BrO_3SiNa^+$ [M+Na^+]: 423.0963, found: 423.0962.

(*S,E*)-2-(diethoxy(methyl)silyl)-1-(4-(trifluoromethyl)phenyl)hept-2-ene-1-ol (5.148):



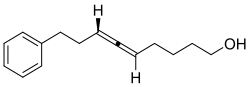
The residue was purified by flash chromatography using hexane/EtOAc (90:10) to afford the product **5.148** (292.5 mg, 83 %) as colorless oil.$[\alpha]_D^{20}$ = —97.2° (*c* 1.22, $CHCl_3$). IR (film, $CHCl_3$) 3464, 2971, 2927, 2876, 1618, 1410, 1391, 1163, 1125, 952, 829 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 6.11 (ddd, *J* = 7.6, 6.3, 1.1 Hz, 1H), 5.68 (d, *J* = 9.8 Hz, 1H), 4.24 (d, *J* = 9.8 Hz, 1H), 3.78 (q, *J* = 7.0 Hz, 2H), 3.63 – 3.48 (m, 2H), 2.39 (dq, *J* = 14.4, 7.4 Hz, 1H), 2.19 (qd, *J* = 14.4, 7.4 Hz, 1H), 1.53 – 1.29 (m, 4H, H_2), 1.21 (t, *J* = 7.0 Hz, 3H), 1.10 (t, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H), -0.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 145.4, 138.9, 129.1 (q, *J* = 32.2 Hz), 126.2, 125.8, 125.1 (q, *J* = 3.8 Hz), 124.8 (q, *J* = 272.1 Hz), 123.1, 120.4, 71.9, 58.7, 58.6, 31.5, 28.96, 22.6, 18.3, 18.2, 14.1, -3.3. HRMS (ESI): m/z calculated for $C_{19}H_{29}F_3O_3SiNa^+$ [M+Na^+]: 413.1731, found: 413.1730.

1-methoxy-4-(nona-3,4-diene-1-yl)benzene (5.157):



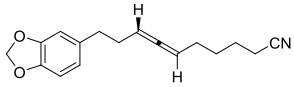
The crude was purified by flash chromatography using hexane/MTBE (99:1) to afford the product **5.157** (11.4 mg, 91 %) as colorless oil. $[\alpha]_D^{20}$ = +50.3° (*c* 1.39, $CHCl_3$). IR (film, $CHCl_3$) 2955, 2927, 2855, 1962, 1612, 1584, 1512, 1455, 1300, 1244, 1176, 1106, 1039, 821 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 1H), 5.16 – 5.02 (m, 2H), 3.79 (s, 3H), 2.66 (t, *J* = 7.8 Hz, 2H), 2.32 – 2.18 (m, 2H), 1.95 (m, 2H), 1.38 – 1.30 (m, 4H), 0.93 – 0.85 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 157.9, 134.2, 129.5, 113.8, 91.6, 90.4, 55.4, 34.8, 31.5, 31.2, 28.8, 22.3, 14.1. HRMS (ESI): m/z calculated for $C_{16}H_{22}ONa^+$ [M+Na^+]: 253.1563, found: 253.1563. The enantiomeric excess was determined to be 92 % by HLPC analysis (150 mm Chiralpack AS-3R, 4.6 mm i.D., Methanol/water gradient = 60%-10'-90% B, 1 mL/min, 35.8 MPa, 298 K, UV 220 nm).

9-phenylnona-5,6-dien-1-ol (5.158):



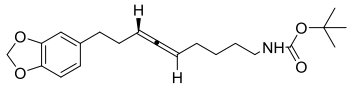
The residue was purified by flash chromatography using hexane/EtOAc (90:10) to afford the product **5.158** (5.8 mg, 29 %) as yellowish oil. IR (film, $CHCl_3$) 3336, 3063, 2927, 2855, 1963, 1604, 1496, 1453, 1264, 1066, 871, 744, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.18 (m, 3H), 5.20 – 5.05 (m, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.72 (t, *J* = 7.4 Hz, 2H), 2.39 – 2.24 (m, 2H), 2.01 – 1.93 (m, 2H), 1.63 – 1.52 (m, 2H), 1.48 – 1.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 142.0, 128.7, 128.4, 125.9, 91.3, 90.6, 63.0, 35.6, 32.3, 30.8, 28.7, 25.3. HRMS (ESI): m/z calculated for $C_{15}H_{20}ONa^+$ [M+Na^+]: 239.1406, found: 239.1406. The enantiomeric excess was determined to be 89 % by HLPC analysis (150 mm 3-Amycoat RP, 4.6 mm i.D., Methanol/water = 75:25, 0.5 mL/min, 16.3 MPa, 298 K, UV 220 nm).

10-(benzo[*d*][1,3]dioxol-5-yl)deca-6,7-dienenitrile (5.159):



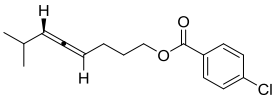
The crude was purified by flash chromatography using hexane/MTBE (90:10) to afford the product **5.159** (11.4 mg, 72 %) as brownish oil. $[\alpha]_D^{20}$ = +49.2° (*c* 0.60, $CHCl_3$). IR (film, $CHCl_3$) 2929, 2247, 1963, 1608, 1502, 1488, 1441, 1361, 1242, 1187, 1097, 1037, 934 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 1.5 Hz, 1H), 6.61 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.89 (s, 2H), 5.26 – 4.82 (m, 2H), 2.66 – 2.56 (m, 2H), 2.30 (t, *J* = 7.1 Hz, 2H), 2.27 – 2.17 (m, 2H), 2.01 – 1.90 (m, 2H), 1.71 – 1.59 (m, 2H), 1.57 – 1.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 147.6, 145.7, 135.7, 121.4, 119.8, 109.1, 108.2, 100.9, 90.9, 90.4, 35.3, 31.0, 28.0, 24.9, 17.1. HRMS (ESI): m/z calculated for $C_{17}H_{19}NO_2Na^+$ [M+Na^+]: 292.1308, found: 292.1308. The enantiomeric excess was determined to be 91 % by HLPC analysis (150 mm Chiralpack AS-3R, 4.6 mm i.D., Methanol/water = 85:15, 1.0 mL/min, 25.1 MPa, 298 K, UV 220 nm).

***tert*-butyl(9-(benzo[*d*][1,3]dioxol-5-yl)nona-5,6-diene-1-yl)carbamate (5.160):**



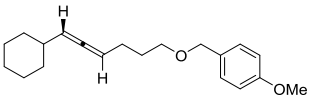
Flash chromatographic purification of the crude (hexane/EtOAc = 80:20) yielded the product **5.160** (10.9 mg, 72 %) as yellowish oil. $[\alpha]_D^{20}$ = +49.2° (*c* 0.60, $CHCl_3$). IR (film, $CHCl_3$) 3352, 2975, 2931, 2857, 1961, 1702, 1503, 1490, 1443, 1365, 1245, 1170, 1040, 937, 810 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 1.6 Hz, 1H), 6.61 (dd, *J* = 7.9, 1.6Hz, 1H), 5.89 (s, 2H), 5.13 – 4.99 (m, 2H), 4.48 (bs, 1H), 3.08 (m, 1H), 2.60 (t, *J*= 7.6 Hz, 2H), 2.26 – 2.17 (m, 2H), 1.93 (tdd, *J* = 7.0, 3.2, 0.7 Hz, 2H), 1.50 – 1.30 (m, 13H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 155.8, 147.6, 145.7, 135.9, 121.4, 109.1, 108.2, 100.9, 91.2, 90.5, 79.4, 40.6, 35.3, 31.1, 29.6, 28.6, 26.4. HRMS (ESI): m/z calculated for $C_{21}H_{29}NO_4Na^+$ [M+Na^+]: 382.1991, found: 382.1989. The enantiomeric excess was determined to be 90 % by HLPC analysis (150 mm Chiralpack AS-3R, 4.6 mm i.D., Acetonitrile/water = 70:30, 1 mL/min, 16.4 MPa, 298 K, UV 220 nm).

7-methylocta-4,5-diene-1-yl-4chlorobenzoate (5.162):



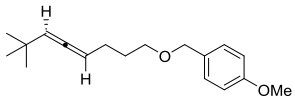
The crude was purified by flash chromatography using hexane/MTBE (98:2) to afford the product **5.162** (0.9 mg, 10% yield) as colorless oil. $[\alpha]_D^{20}$ = +5.7° (*c* 0.22, $CHCl_3$). IR (film, $CHCl_3$) 2959, 2927, 2868, 1956, 1722, 1596, 1488, 1466, 1402, 1271, 1092, 1016, 760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 5.26 – 5.09 (m, 2H), 4.36 (td, *J* = 6.5, 1.5 Hz, 2H), 4.31 (t, *J* = 6.7 Hz, 1H), 2.33 – 2.20 (m, 2H), 2.20 – 2.09 (m, 2H), 1.94 – 1.83 (m, 2H), 1.00 (dd, *J* = 6.7, 1.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 165.9, 139.4, 131.1, 129.1, 128.8, 99.5, 91.1, 64.8, 28.2, 28.1, 25.6, 22.7. HRMS (ESI): m/z calculated for $C_{16}H_{19}O_2ClNa^+$ [M+Na^+]: 301.0966, found: 301.0966. The enantiomeric excess was determined to be >90 % by HLPC analysis (150 mm 3-Amycoat RP, 4.6 mm i.D., Methanol/water = 75:25, 0.5 mL/min, 16.3 MPa, 298 K, UV 220 nm).

1-(((6-cyclohexylhexa-4,5-dien-1-yl)oxy)methyl)-4-methoxybenzene (5.163):



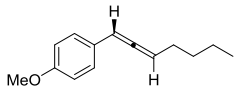
The crude was purified by flash chromatography using hexane/MTBE (96:4) to afford the product **5.163** (28 mg, 82 %) as colorless oil. $[\alpha]_D^{20}$ = +39.6° (*c* 1.07, $CHCl_3$). IR (film, $CHCl_3$) 2922, 2849, 1956, 1613, 1568, 1512, 1448, 1363, 1302, 1246, 1172, 1100, 1037, 819 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.51 – 4.91 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.48 (t, *J* = 6.6, 2H), 2.15 – 2.00 (m, 2H), 2.00 – 1.83 (m, 1H), 1.82 – 1.55 (m, 6H), 1.36 – 0.97 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 159.3, 130.9, 129.4, 113.9, 97.7, 91.4, 72.7, 69.7, 55.4, 37.4, 33.3, 33.2, 29.3, 26.3, 26.2, 25.8. HRMS (ESI): m/z calculated for $C_{20}H_{28}O_2Na^+$ [M+Na^+]: 323.1982, found: 323.1981. The enantiomeric excess was determined to be 93 % by HLPC analysis (150 mm Chiralpack AS-3R, 4.6 mm i.D., Acetonitrile/water gradient: 70% B-5'-90% B, 1 mL/min, 16.7 MPa, 298 K, UV 220 nm).

1-(((7,7-dimethylocta-4,5-dien-1-yl)oxy)methyl)-4-methoxybenzene (5.164):



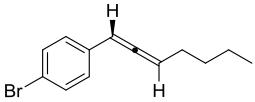
Flash chromatographic purification of the crude (hexane/MTBE = 98:2) yielded the product **5.164** (5.9 mg, 42 %) as yellow liquid. $[\alpha]_D^{20}$ = —60.5° (*c* 0.20, $CHCl_3$). IR (film, $CHCl_3$) 2958, 2901, 2861, 1959, 1613, 1586, 1512, 1462, 1362, 1302, 1246, 1172, 1099, 1037, 819 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.16 (q, *J* = 6.4 Hz, 1H), 5.09 (dt, *J* = 6.4, 3.1 Hz, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.48 (t, *J* = 6.8, 1.0 Hz, 2H), 2.12 – 1.97 (m, 2H), 1.72 (p, *J* = 6.8 Hz, 2H), 1.02 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 159.3, 131.1, 130.9, 129.4, 113.9, 103.6, 92.4, 72.7, 69.7, 55.4, 31.8, 30.4, 29.4, 25.9. HRMS (ESI): m/z calculated for $C_{18}H_{26}O_2Na^+$ [M+Na$^+$]: 297.1825, found: 297.1825. The enantiomeric excess was determined to be 80 % by HLPC analysis (150 mm Chiralpack AS-3R, 4.6 mm i.D., Acetonitrile/water = 70:30, 1 mL/min, 16.7 MPa, 298 K, UV 220 nm).

1-(hepta-1,2-dien-1-yl)-4-methoxybenzene (5.165):



Flash chromatographic purification of the crude (hexane/MTBE = 100:0 to 99:1) yielded the product **5.165** (8.6 mg, 73 %) as yellowish oil. $[\alpha]_D^{20}$ = 40.0° (*c* 0.05, $CHCl_3$). IR (film, $CHCl_3$) 2956, 2929, 2857, 1950, 1579, 1510, 1464, 1441, 1302, 1171, 1034, 832 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.850 (d, *J* = 8.7 Hz, 2H), 6.08 (dt, *J* = 6.7, 3.0 Hz, 1H), 5.54 (q, *J* = 6.7 Hz, 1H), 3.80 (s, 3H), 2.12 (ddd, *J* = 14.3, 6.7, 3.0 Hz, 2H), 1.54 – 1.35 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 158.7, 127.7, 114.5, 114.2, 95.2, 94.1, 55.6, 31.5, 28.8, 22.4, 14.0. HRMS (ESI): m/z calculated for $C_{14}H_{18}O^+$ [M$^+$]: 202.1359, found: 202.1358. The enantiomeric excess was determined to be 23 % by HLPC analysis (150 mm Chiralpack AS-3R, 4.6 mm i.D., Methanol/water gradient: 60%-10'-90% B, 1 mL/min, 37.4 MPa, 298 K, UV 220 nm).

1-bromo-4-(hepta-1,2-dien-1-yl)benzene (5.166):



The crude was purified by flash chromatography using hexane (100%) to afford the product **5.166** (9.5 mg, 74 %) as yellowish oil. $[\alpha]_D^{20}$ = +149.7° (*c* 0.98, $CHCl_3$). IR (film, $CHCl_3$) 2956, 2926, 2857, 1950. 1711, 1589, 1487, 1465, 1379, 1099, 1069, 874, 829 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 6.06 (dt, *J* = 6.7, 3.0 Hz, 1H), 5.57 (q, *J* = 6.7 Hz, 1H), 2.13 (ddd, *J* = 14.3, 6.7, 3.0 Hz, 2H), 1.51 – 1.33 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 134.4, 131.8, 128.2, 120.3, 95.7, 93.9, 31.4, 28.5, 22.4, 14.0. HRMS (ESI): m/z calculated for $C_{13}H_{15}Br^+$ [M+H+]: 250.0355, found: 250.0357. The enantiomeric excess was determined to be 88 % by HLPC analysis (150 mm Chiralpack AS-3R, 4.6 mm i.D., Methanol/water gradient: 60%-10'-90% B, 1 mL/min, 37.4 MPa, 298 K, UV 220 nm).

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NOVEL STRATEGIES FOR THE SYNTHESES OF SPHINGOSINE KINASE INHIBITORS, B-FLUOROAMINES AND ENANTIOENRICHED ALLENES
Macarena Corro Morón

CHAPTER 6

General conclusions

UNIVERSITAT ROVIRA I VIRGILI
NOVEL STRATEGIES FOR THE SYNTHESES OF SPHINGOSINE KINASE INHIBITORS, B-FLUOROAMINES AND ENANTIOENRICHED ALLENES
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Different sphingosine analogues, β-fluoroamines and enantioenriched allenes have been prepared during this PhD work and their syntheses have been extensively discussed in Chapter 3, 4 and 5, respectively.

Chapter 3 describes the syntheses of sphingosine derivatives. The following conclusions can be extracted:

i) A novel library of sphingosine analogues have been synthesized bearing the following structural features:

   a. Azo- and *N,N*-dimethyl moieties were introduced in the polar head replacing the amino group present in the natural product.
   b. A quaternary center was created at position 2, neighbouring azo- and hydrazino groups.
   c. Alkynyl, alkenyl and alkyl chains were introduced as lipophilic tails including the insaturations at C4-C5 bond.

ii) The hydrazine group was incorporated to the sphingoid base by aziridination with $PhthNH_2$ in the presence of I(III) reagents.

iii) Hydrazones were immediately formed upon hydrazine deprotection, presumably due to the presence of acetone contained in materials.

iv) *N,N*-dimethyl hydrazines were achieved by dephthaloylation followed by reductive amination with paraformaldehyde. Mono- and trimethylated hydrazines were found as by-products during the dimethylation.

v) Diversity at positions C4-C5 was introduced in a divergent way from the alkyne. Thus, alkyne was selectively reduced to the *trans* double bond by a hydrosilylation-protodesilylation processes catalyzed by ruthenium. The full saturated compound

was obtained from the alkyne by reduction with hydrogen and Pd/C as catalyst.

vi) Some final products, especially those obtained from non-quaternized aziridine, decomposed in the final step probably by a retro-aldol reaction.

vii) Docking studies have been performed to predict interactions between our designed compounds and sphingosine kinase 1 (SphK1). From these studies, we concluded that our compounds presumably interact with Leu 268, Asp 81 and/or Asp 178 in most cases.

viii) *In vitro* assays have revealed that our compounds possess an inhibitory potency against SphK1 and/or SphK2 similar than *N,N*-dimethylsphingosine (DMS). Furthermore, compounds bearing alkynyl and hydrazino moieties showed selectivity only for SphK2.

In Chapter 4, the synthesis of β-fluoroamines from cinnamyl carbamates was developed by a tandem intramolecular aziridination/ring-opening process in the presence of 4-$MePhF_2$. The following conclusions were extracted:

i) Carbamates were efficiently prepared from the corresponding cinnamyl alcohols by reaction with Cl_3CO-CN.

ii) The oxidation of 4-iodotoluene to give 4-$MePhIF_2$ was successfully achieved when this reagent was treated with Selectfluor and $Et_3N{\cdot}3HF$.

iii) Optimization of the reaction conditions allowed us to conclude that a considerable excess of 4-$MePhIF_2$ and the presence 4Å M.S. are required to achieve β-fluoroamines in good yield.

iv) The use of an external fluoride source such as CsF, KF, py·9HF or Et_3N·3HF did not improve the results.

v) The ring-opened product was afforded as a mixture of *syn/anti* diastereoisomeres, in which the *syn* one was obtained as a major product in all cases.

vi) The stereoselectivity depended on the electronic properties of substituents at the aromatic ring. Thus, electron-donating groups gave a mixture of diastereoisomers in moderate selectivity, while electron-withdrawing groups favored the formation of *syn* products.

vii) Two mechanisms haven been proposed to explain the observed selectivity. *Syn* products might be formed as a result of a pseudo-carbocation with previous interaction of the nucleophile with the nitrogen of the aziridine, thus directing the nucleophilic attack. The *syn/anti* mixture may be formed through a carbocation intermediate generated by acid activation of the aziridine. This hypothesis is supported by some specific tests in the presence of N_3SiMe_3, and by the influence of groups in the aromatic ring.

In Chapter 5, the enantioselective synthesis of chiral allenes starting from enantioenriched *cis* hydroxysilanes was studied. The following conclusions were extracted:

i) Enantioenriched *cis* hydroxysilanes were afforded in high enantioselectivity from chiral propargyl alcohols mediated by platinum.

ii) Enantioselective allenylation was achieved by reacting the resulting hydroxysilanes with mesityl copper. *Anti* or *syn* allenes could be selectively obtained by the use of appropriate

ligands. Thus, the use of phosphites and phosphines drove the reaction towards the synthesis of *anti* allenes, and also increased the enantioselectivity. However, the use of less electron donating phosphines or bulkier phosphites with similar electronic properties afforded *syn* allenes.

iii) This process is influenced by the electronic or steric properties of the substrates and tolerates different functional groups.

iv) Enantioselective allenes are prone to racemization when they react with copper at long reaction times.

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