### Total Synthesis of Alstilobanine C, Undulifoline and Alstilobanine B

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"Total synthesis is expensive, labor intense, slow, frustrating, capricious, unproductive, brutal but powerful, enabling, magic and indispensable"

Alois Fürstner

"Our greatest glory is not in never falling, but in rising every time we fall."

Confucius

"The definition of insanity is doing the same thing over and over again and expecting different results"

Albert Einstein

## Acknowledgments

I would like to start by thanking Professors Cramer, Gademann, Magauer and Waser for accepting to be part on my thesis committee, as member of the jury and taking the time to review the manuscript describing the work done during the PhD as well as being present at my private defense.

I want to express my gratitude to Jieping for having given me the opportunity to perform my PhD in his group. You are the most passionate person about chemistry I have ever met. Your devotion to chemistry is inspiring and admiring. Your door is always open and you constantly have new ideas and your guidance helped me for my projects. You allowed me to grow as an independent chemist improving my skills on total synthesis.

Besides my advisor, I would like to thank Qian who is a huge help for our group. Indeed, her attention to details improves the rigor of every co-worker. Her patience, smile and knowledge, on both practical and theoretical chemistry, is appreciate by all and I in particular. Your help from the beginning of my thesis allowed me to be a better chemist and will be remembered. You are always in a good mood and available to discuss about chemistry but also about any topic.

A very special gratitude goes to Tu, aka Tu the Machine. Direct labmate in BCH5412, you are one of the, if not the nicest person I have met. I had the chance to work beside you for two years and you were always ready to help anyone in need. I appreciate all the discussion about chemistry/politics/religion and much more we shared. Solving chemistry problems with you was really fun. I cannot thank Tu without my other colleagues of the lab; former post-doc Yang and Wangqing and actual post-doc Guang, Guihua and Zhaodong. Their hard-working attitude created a dynamic atmosphere in the lab. Spending four years with you was not enough to speak Chinese, but I caught a few words. I also wish good luck to Dina, a new PhD student, for her thesis.

Apart from my lab, I would like to thank Mathias in BCH5401 who is still struggling with his end of the thesis. After being through a lot, he kept going to the lab, fighting for this thesis. We shared many discussion about many different topics, even if some of them kept coming every day. We also shared nice time playing the guitar together. Great time! Antonin who started a year before me was another smile in the lab. Always motivated, smiling, happy, we spend a few nights out which were super fun. Bastien, who started only a year ago tackled a molecule with a similar approach than mine for the beginning. Good chemistry related discussions, you change completely of behavior once out of the lab. I will always remember one of the first night out with you for Dylan's Defense, you were amazing! Mr. Nuggets, aka Rémi, is a freshman in here. You are a great guy, lots of motivation, which you will need for the following four years. I am glad you are enjoying your single life. Enjoy young Padawan. Shuo and Hua were always here to keep the good working atmosphere.

Changing lab to the BCH5418 brings us to an interesting human being, called Dylan, another total synthesis machine. I have always appreciate you from the beginning. Super clever, you know so much about chemistry. I also enjoyed your similar humor and delicacy when it comes to talk about a certain topic. Gamer in the soul, we shared many discussions and good time together. I think I will have more chance to be read here than if I send an email to the following member of the lab, Magic Raph. Your first six months were filled with motivation and energy that none of the rest of the lab could bear. It quickly changed to a more "normal" state, which is still unbelievable with all this energy, smile and motivation. With his BG attitude, this exceptional magician was always bringing positive energy to the lab which was appreciated by all. Thank you for all the great time spent together! Omar is an excellent post-doc who is extremely nice. Always here to help another, Mexico brought us joy in every day life in the lab. Good luck with your position in your country. Lab member of this lab was Xu who could always be found in the lab every day of the year.

The group extended with a fourth lab, BCH5409, featuring the boss of the boss in total synthesis and organic synthesis in general. Summoned for the Valhalla, this ancient God, Cyril, brought his all mighty knowledge to every single member of the lab. I had the chance to study with him especially during the Master with this unending day/night in biscom. We brought joy to our day with the chair race which ended up usually roughly. You are the most dedicated person I know and I admire this. Your passion spread to people around you and you are always helping someone in need. Whenever something goes wrong in the lab, we could always count of you to know just the thing to fix it. If the lab goes so smoothly, it is thank to you. Balázs, super clever guy, always with the British class, even if Hungarian. Great chemist he was part of the good atmosphere in the lab. Alex who succeeded easily his first year exam has tremendous potential ... in dance. Of course in chemistry I mean, even if your hips are doing a good job, from what I have been told. Passionate about chemistry, skate, cooking and of course baking. Can't wait to do some Top Chef day with you. Bank who is around from time to time has still a long way to finish his thesis, good luck.

They are of course previous members who contributed to the well being of the lab, JB, Thomas, Olivier, Viktoria, Ala, Charlotte, Clémence and all the other Master students, interns who joined the lab for a period of time.

During the first two years of my PhD, we used to share a lab with the member of the group of Prof. Gerber. We kept going for lunch all together after they moved in a different building and the tradition is still on up to this day. François who just defended his PhD thesis is the coolest guy. Always chill, no rush, lots of laughs were shared during our time, which started during the Bachelor. Raph le mytho, contributed a lot in the group with his initiative for game menu, travels together. We always enjoy his stories/opinion, which had to be double checked before believing them. Super nice guy, I wish you good luck for the end of your PhD, the end is near. Jeremy is very calm, barely talk, but still hanging out with us. Luca, the Hungarian girl in the group is crazy about sport and mosly waking up so early in the morning. I am sure your French is good now, you should come back with us for lunch. Laure who recently started her PhD will move in her apartment very soon. I wish you good luck with your new home and your PhD.

In EPFL, two other research group are dedicated to organic chemistry. Ruled by Prof. Cramer, the LCSA group is all about chemistry. Many great chemists did their time in this group. The LCSO group, can be divided in three nationalities; French, Italian and Indian. We had the opportunity to share the famous molecule of the month and their barbecue, group outings and summer schools together.

A special mention to all the staff of ISIC; NMR service, HRMS service, BCH-magasin and our secretary Monique who actively participated in everyday life to make our work as easy as possible by taking care of technical issue or administrative papers. I also thank EPFL and the SNF for financial support during my PhD.

Apart from the lab and EPFL, I kept trying to see my older friends from high school. Gros lard, aka Antoine, is my sport partner. Subscribed to a gym, we kept trying to go there despite the low motivation after a hard and long day at work. Sharing lunch or dinner was always a delight. David, Janice the perfect couple, Nico the biologist, Neury, the Apple Vodka drinker, Eileen, the beauty flower, Emilien, the thinker, Zwicky, the builder and many others are always found in the Montreux Jazz Festival. This annual meeting brought us back some great memories of high school. We made and lost memories during this exceptional festival and it is always a pleasure to see you there. We, of course, try to see each other in a different time of the year, but it looks like our agenda never manage to make it happen.

Starting EPFL in 2008, I was introduced to many people by Mathieu, aka spicot, an old friend from school. We met when we were 13 years old and kept having a great friendship sharing lots of activities together. I started to hang out and have lunch with Laurent, Nadine, Adrien, Chloé, Matthias, Chu, Luisier. We kept seeing each other outside of EPFL such as in Mathieu's chalet in Vercorin for some crazy session in winter, with the famous ravioli contest, the 3-stars Michelin fondue with mint, and some other delicacies. The group increased with the boyfriend/girlfriend of the whole group and we are still organizing meeting from time to time to celebrate any excuses. We traveled to Italy together for wine tasting and for New Year Eve in different places. It is always nice to see you all.

During my time as student, I enjoyed many parties organized by EPFL and met many people. Among these, I have to point out one person with whom I have shared many adventures, Marine. Sigmund Freud can go back to sleep in comparison with Marine. I enjoyed every late discussions about fundamental questioning of the meaning of life and quantum chemistry. We also went for our Master thesis in Stanford and shared the American life together through different road trips, wine tasting and food orgies. During the PhD, we even lived together in our shared flat. Even if I saw you more before living with you, I always appreciate our talks about any topics and your motivation, despite making me tired, is inspiring.

I had the chance to work at the Montreux Jazz Festival for thirteen years in a row. I made friends and many people kept coming every year working in the same department as I was working in. I was co-responsible with Mélanie for two years and it was a great experience. I would like to thank Sandra, Virginie, Romain, Rosa, Annie, Marie and many other staffs who made this festival unforgettable.

Surprisingly, thank to my ex-girlfriend Chiara, I discovered a new world, the dance. Against all expectations and my will, I started to follow salsa classes. I kept going to and met amazing people, such as Sueda, Prasad, Vania, Elahi, Paola, Gianrocco and Clara. This world of dance talked to me and allowed me to loose and the pressure from work. After six months of salsa, we decided with Sueda to learn another dance, bachata. From this day, my horizon expended drastically. I discovered a new way of communication, sociability, happiness. I would like to thank Janine and William who taught me so much and Flo and Nino with whom I was able to be part of a group of great dancers; Ching, Maud, Céline, Jimmy, Anissa, Daniel, Lilly, Amandine and Pascal. We lived a special experience which brought us far and we lived many things together, united. Dancing allowed me to meet amazing people, Julie, Carlos, Monica, Mélissa, Patrick, Céline, Rada, Ati, Rocchi, Jess and many others. I am sorry for the ones I did not mentioned, but I would write as many pages as my thesis if I had to thank you all.

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Pour finir ces remerciements, je tiens à remercier tous les gens qui ont eu la patience de lire jusqu'ici et à tous les gens qui ont fait partie de ma vie à un certain moment lors de ma thèse que je n'ai pas pu citer.

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## Abstract

The total synthesis of pentacyclic monoterpene indole alkaloids is the focus of this thesis.

Total syntheses of (±)-alstilobanine C, (±)-undulifoline and (±)-alstilobanine B, three natural products from the *Ulean* family of alkaloids, were accomplished. The characteristic features of our synthesis included: a) a domino sequence involving a highly diastereoselective Michael addition followed by chemoselective *C*-acylation of the resulting enolate by Mander's ester; b) an unprecedented Lewis acid mediated intramolecular addition of enolate to oxonium, generated in situ from MOM protective group; c) a sequence of chemoselective reduction/indolization/intramolecular aza-Michael addition. This domino process afforded directly the (±)-alstilobanine C, a pentacyclic monoterpene indole alkaloid in 87% yield. Reductive *N*-methylation of (±)-alstilobanine C provided (±)-undulifoline which, upon *N*-oxidation, was further converted to (±)-alstilobanine B.

Enantioselective total synthesis of the same natural products through a different synthetic route is presented. After exploring different unsuccessful strategies, an enzymatic desymmetrization of a *meso* compound was adopted for the synthesis of enantioenriched cyclopentenone intermediate. Applying the two domino sequence developed previously, namely, Michael addition/*C*-acylation and oxepane formation, an efficient synthesis of the oxobicyclo[4.2.1]nonane was realized. A palladium-catalyzed decarboxylative cross-coupling, a methodology developed in our group, afforded an advanced bicyclic intermediate with all the carbon and functional groups needed to accomplish the total synthesis. However, conversion of the vinyl group to alkylazide or its synthetic equivalent proved to be difficult in spite of the efforts dedicated to this seemingly trivial transformation.

**Keywords**: total synthesis, natural product, indole alkaloids, enantioselective synthesis, alstilobanine C, undulifoline, alstilobanine B, domino reaction.

## Résumé

La synthèse totale d'alcaloïdes indolo-monoterpénique pentacyclique est présentée dans ce travail de thèse.

La synthèse totale de ( $\pm$ )-alstilobanine C, ( $\pm$ )-undulifoline et ( $\pm$ )-alstilobanine B, trois produits naturels de la famille d'alcaloïdes *Ulean* a été accomplie. La synthèse a comme caractéristiques : a) une séquence domino impliquant l'addition de Michael hautement diastéréosélective suivie par une *C*-acylation chimiosélective de l'enolate résultant avec l'ester de Mander ; b) l'addition intramoléculaire de l'enolate sur l'oxonium formé in situ à partir de MOM, introduit précédemment comme groupement protecteur de l'alcool primaire. Cette transformation inédite nous a permis de construire un oxépane ponté avec la création d'un centre quaternaire ; c) une réaction domino chimiosélective de réduction/cyclisation/aza-Michael fournissant directement la ( $\pm$ )-alstilobanine C, a pentacyclic natural product. La *N*-méthylation de la ( $\pm$ )-alstilobanine C conduit à la formation de la ( $\pm$ )-undulifoline qui est ensuite transformation en ( $\pm$ )-alstilobanine B par une réaction de *N*-oxydation.

Des études synthétiques en vue de la synthèse totale énantiosélective des mêmes produits naturels par une voie de synthèse différente sont également présentées. Après avoir exploré différentes stratégies infructueuses, une désymétrisation enzymatique d'un composé méso a été réalisée, permettant la synthèse d'un intermédiaire cyclopenténone énantiopur. A partir de ce dernier, une addition de Michael hautement diastéréosélective suivie d'une *C*-acylation chimiosélective de l'enolate résultant avec l'ester de Mander a été réalisée. L'oxobicyclo[4.2.1]nonane est ensuite synthétisé en appliquant la même cyclisation décrite précédemment en utilisant MOM comme précurseur de l'oxonium désiré. Un couplage décarboxylatif, une méthodologie développée dans notre groupe, nous a conduit à un intermédiaire bicyclique contenant tous les carbones et les fonctionnalités nécessaires pour accomplir la synthèse totale. Néanmoins, la transformation du vinyl à l'azido alkyle s'est avérée difficile malgré des efforts consacrés à cette réaction.

**Mots-clés:** synthèse totale, produit naturel, alcaloïdes indoliques, synthèse énantiosélective, alstilobanine C, undulifoline, alstilobanine B, réaction domino.

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# **EDCH Requirements**

### EDCH Course Credits

Course name	Credits
CH-621(1) Perspectives in Modern Organic Chemistry (OCS) 1	1
CH-621(2) Perspectives in Modern Organic Chemistry (OCS) 2	1
CH-708 Frontiers in Organic Synthesis. Part II Synthesis of carbo- and hetero-cycles	2
CH-709 Frontiers in Organic Synthesis. Part III Stereochemistry	2
CH-620 Efficient Synthetic Routes Towards Bioactive Molecules	2
CH-622 Synergism between Art of Total Synthesis and High Level Strategic Design	2
CH-801 Swiss Summer School 2015 in Rxn Design & Synthesis	2
Swiss Summer School 2017 – Poster presentation	2
Total	14/12

### EDCH Teaching Assistant Credits Hours

Course name	Credits
Atoms, ions, molecules and functions (exercises) – fall 2014	15
Preparative chemistry I (practical work) – spring 2015	95
Organic functions and reactions II (exercises + exam correction) – fall 2015	123
Preparative chemistry I (practical work) – spring 2016	95
Organic functions and reactions II (exercises + exam preparation) – fall 2016	147
Preparative chemistry I (practical work) – spring 2017	95
Total synthesis of natural products (Master lecture) – fall 2014	104
Total	674 / 630

# List of Abbreviations

°C	Degree Celsius
9-BBN	9-Borabicyclo[3.3.1]nonane
Ac	Acetyl
AIBN	Azobisisobutyronitrile
Aq.	Aqueous
Ar	Aromatic
atm	Atmosphere
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	tert-Butyloxycarbonyl
brsm	Based on recovered starting material
Bu	Butyl
Bz	Benzoyl
calcd	Calculated
Comins'	<i>N,N</i> -Bis(trifluoromethylsulfonyl)-5-chloro-2- pyridylamine
Су	Cyclohexyl
d	Day
DABCO	l,4-diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DCE	Dichloroethane
DCM	Dichloromethane
DIBAL	Diisobutylaluminium hydride
DIPA	Diisopropylamine
DIPEA	Diisoproylethylamine, also known as Hünig's base

DMAP	4-Dimethylaminopyridine
DMF	Demethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
DP	Desired product
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
EDC	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide
ee	Enantiomeric excess
equiv	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EtOAc	Ethyl acetate
FCC	Flash column chromatography
FGI	Functional group interconversion
g	Gram
h	Hour
HMDS	Bis(trimethylsilyl)amine
HMPA	Hexamethylphosphoramide
HOBt	Hydroxybenzotriazole
HRMS	High-resolution mass spectrometry
hu	Light
Hz	Hertz
i	iso

IBX	2-Iodoxybenzoic acid
<i>IC</i> <sub>50</sub>	Half maximal inhibitory concentration
Im	Imidazole
iORC	Integrated oxidation/reduction/cyclization
IR	Infrared
J	Coupling constant
L	Litre
LA	Lewis Acid
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
m	Milli
т	Meta
Μ	Molar (mol/L)
m/z	Mass divided by charge
тСРВА	meta-Chloroperoxybenzoic acid
Me	Methyl
MEM	2-Methoxyethoxymethyl
min	Minutes
mol	Mole
МОМ	Methoxymethyl ether
Ms	Mesyl
MS	Molecular sieves or Mass spectroscopy
MW	Microwave
NBS	N-Bromosuccinimide
n	normal
n.d.	Not determined
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide

NMR	Nuclear Magnetic resonance
Ns or nosyl	2-Nitrobenzenesulfonyl
Nu	Nucleophile
0	Ortho
р	Para
РСС	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PE	Petroleum ether
PG	Protecting group
Ph	Phenyl
PhD	Doctor of Philosophy
Pin	Pinacol
PMP	<i>p</i> -methoxyphenyl
PPA	Polyphosphoric acid
ppm	Parts per million
PPTS	Pyridinium para-toluenesulfonate
Pr	Propyl
Ру	Pyridine
pTsOH or PTSA	para-Toluenesulfonic acid
quant.	Quantitative
R	Rectus
rt	Room temperature
S	Sinister
SFC	Supercritical Fluid Chromatography
SM	Starting material
S <sub>N</sub> (1 or 2)	Nucleophilic substitution
t	tert

Т	Temperature
TBAAz	Tetrabutylammonium azide
TBAF	Tetrabutylammonium fluoride
TBDPS	tert-Butyldiphenylsilyl
TBS	tert-Butyldimethylsilyl
Tf	Trifluoromethansulfonate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Tin-layer chromatography
ТМР	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
Trityl	Triphenylmethyl
trig	Trigonal
Ts or tosyl	4-toluenesulfonyl
UPLC	Ultra performance liquid chromatography
UV	Ultraviolet
W	Watt
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Х	Halide
X-Phos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
δ	Chemical shift

## Chapter 1 - General Introduction

Nature provides a lot of diversity of molecules through different organisms. Indeed, plants, fungi and animals are made from myriads of simple to highly complex natural products and among them are found the alkaloids. The definition of this class of molecule is controversial between research fields but can be seen as a group of natural products containing basic nitrogen atoms which show many pharmaceutical activities.<sup>1</sup> Their classification is based on their characteristic skeleton and its connectivity between atoms. Mostly biosynthesized from aromatic amino acids such as phenylalanine, tyrosine and tryptophan. The latter give rise to indole, quinoline,  $\beta$ -carboline and other family of alkaloids. Indole alkaloids is one of the sub-group containing more than four thousands different compounds. Their wide diversity, interesting biological activity and challenging structures have spurred multidisciplinary interest over a century. A sub-group is called monoterpene indole alkaloid and despite the structural diversity, most of them are present in three families of dicotyledon plants: Apocynaceae (genera Alstonia, Aspidosperma, Rauwolfia and Catharanthus), Rubiaceae (Corynanthe) and Loganiaceae (Strychnos).<sup>2</sup> Lysine does not bear an aromatic ring but is the precursor of quinolizidine and piperidine alkaloids. True alkaloids are defined as bearing the origin nitrogen atom from the amino acid in the heterocycle. The biosynthesis of monoterpene indole alkaloids is believed to start from two building blocks, tryptophan and secologanine. These two units will, after minor transformations, react *via* a Pictet-Spengler reaction to give rise to strictosidine. From the latter intermediate, every sub-group of monoterpene indole alkaloid can be obtained, such as Strychnos, Iboga, Aspidosperma and many more.<sup>3</sup>

Historically, morphine was the first alkaloid to be isolated.<sup>4</sup> Until now, more than 8'000 alkaloids are listed and more than 100 are discovered yearly. This huge diversity implies a wide range of use and properties. Toxic alkaloids such as tubocarine and aconitine, discovered and used as poisons for arrows,<sup>5</sup> can however be used in medicine as analgesic. Particular frogs, snakes, spiders and mosquitos secrete toxic alkaloid through their skin or sting. On the other hand, beneficial alkaloids were used through ages to cure diseases. For instance quinine is used as anti-malarian agent, taxol and vinblastine as anticancer agents.<sup>6</sup>

<sup>&</sup>lt;sup>1</sup> Clayden, J., Greeves, N., Warren, S. and Wothers, P. 2001. Organic Chemistry. Oxford, New York, Oxford University Press.

<sup>&</sup>lt;sup>2</sup> a) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532–547. b) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2015**, *32*, 1389–1471.

<sup>&</sup>lt;sup>3</sup> Wenkert, E. J. Am. Chem. Soc. 1962, 84, 98-102.

<sup>&</sup>lt;sup>4</sup> Bynum, W. F. and Porter, R. (eds) 1994. Companion Encyclopedia of the History of Medicine. Vol. 1. London and New York: Routledge; and, Bynum, W. F. 1998.

<sup>&</sup>lt;sup>5</sup> Aniszewski, T. Alkaloids - Secrets of Life 2007.

<sup>&</sup>lt;sup>6</sup> Kaushik, N.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C.; Verma, A.; Choi, E. *Molecules* **2013**, *18*, 6620-6662.

Chemists have an important role to play. Inspired by Nature, their task can be to reproduce what is already outside. Based on isolation papers, the structure of novel alkaloids are reported and biological tests against diseases are performed depending of the mass extracted from a living organism. Their characterization permits to have a better understanding of the structure-activity relationship. The biomass is extremely low and the isolated yield after extraction of raw material in alkaline aqueous phase, separation and purification is typically around 0.002%. The poor biomass of natural products in Nature motivates us to design a strategic route to achieve their synthesis. The urge to reproduce synthetically bioactive molecules can be empathized as the biodiversity and the ecosystem have to be preserved. Moreover, chemists can bring modifications on natural products varying their structure, hence their activity.

Total synthesis is a part of chemistry which focused on the synthetic replication of a molecule, usually a natural product. It originated with the idea to build step by step, bond by bond, the target from simple molecule. Typical targets were chosen based on their molecular architecture and their bioactivities. With time, new aspects appeared relevant and important such as the biological activity of the target, a short, elegant, environmentally-friendly, protecting-group free<sup>7</sup>, atom<sup>8</sup> and redox<sup>9</sup> economical synthesis. Monoterpene indole alkaloids have been under investigation for many years in our laboratory and still continue to fascinate.

A small family, called *Ulean* alkaloids, contains a rare skeleton.<sup>10</sup> In this thesis, the total synthesis of three natural products of the *Ulean* alkaloids as well as synthetic studies towards their enantioselective total synthesis will be discussed.

<sup>&</sup>lt;sup>7</sup> Young, I. S.; Baran, P. S. Nat. Chem. 2009, 1, 193-205.

<sup>&</sup>lt;sup>8</sup> Trost, B. M. Angew. Chem., Int. Ed. Engl. 1995, 34, 259-281.

<sup>&</sup>lt;sup>9</sup> Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. Angew. Chem., Int. Ed. 2009, 48, 2854-2867.

<sup>&</sup>lt;sup>10</sup> Reviews: a) Joule, J. A. *Chemistry of Heterocyclic Compounds*, **1983**, Chapter 6, 265-292. b) Manske, R. H. F.; Rodrigo, R. G. A. In *The Alkaloids: Chemistry and Physiology*, Academic Press: London, **1979**, Chapter 3, 339-344. c) Álvarez, M.; Joule, J. A. In *The Alkaloids: Chemistry and Biology*, Academic Press: London, **2001**, Chapter 4, 235-272.

# Chapter 2 - Total Synthesis of (±)-Alstilobanine C, (±)-Undulifoline and (±)-Alstilobanine B

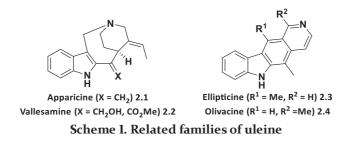
#### 2.1.Introduction

Monoterpene indole alkaloids contains a vast amount of natural product. Among these are found the uleine alkaloids.

2.1.1. Uleine Alkaloids

#### 2.1.1.1. Classification, Isolation and Structure

The uleine group of alkaloids belongs to the *Ulean* and *Vallesaman* alkaloid family which is also composed of the apparicine and vallesamine groups.<sup>11</sup> The *pyridocarbazole* alkaloid family contains the ellipticine and olivacine groups which share the same biogenetic precursor as the uleine group (Scheme 1).<sup>12</sup>

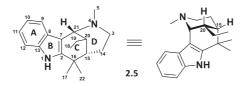


As well as the vallesamine and olivacine families, the uleine family differentiates itself from the *Strychnos* alkaloids by their lack of the original C-5 - C-6 bridge ring of tryptamine between the indole C-3 and the basic nitrogen. They are characterized by a tetracyclic 1,5-methanoazocino[4,3-b]indole moiety, by the typical C-7 - C-21 bond and C-2 - C-16 - C-15 unit as well as the ethyl substituent on C-20 (Scheme 2).<sup>13</sup> While the biosynthesis fixes the absolute configuration of C-15(S), both configurations at C-20 can be found.

<sup>&</sup>lt;sup>n</sup> Southon, I. W.; Buckingham, J. Dictionary of Alkaloids, Second Edition with CD-ROM. Taylor & Francis: **1989**.

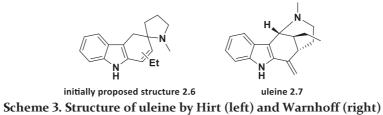
<sup>&</sup>lt;sup>12</sup> Trefonas, L. M.; Lipscomb, W. N. J. Am. Chem. Soc. **1959**, 81, 4434–4435.

<sup>&</sup>lt;sup>13</sup> Sévenet, T.; Pusset, J. In *The Alkaloids: Chemistry and Pharmacology*, Academic Press: London, **1996**, Chapter 1.

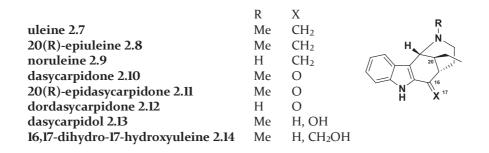


Scheme 2. General skeleton of the uleine group

Uleine was first isolated from *Aspidosperma ulei Mgf* in 1957 by Hirt and co-workers.<sup>14</sup> They proposed a spirocyclic structure **2.6** which was revised in 1959 by Warnhoff and co-workers as **2.7** (Scheme 3).<sup>15</sup>

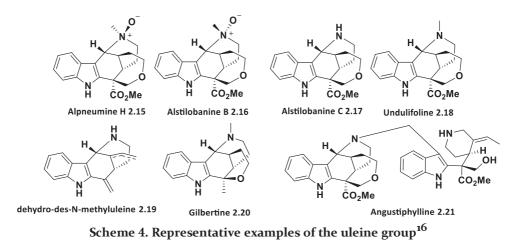


Since the isolation of uleine, several other alkaloids have been isolated and joined the uleine group (Scheme 4).



<sup>&</sup>lt;sup>14</sup> Schmutz, J. Hunziker, F. Hirt, R. Helv. Chim. Acta 1957, 134, 1189.

<sup>&</sup>lt;sup>15</sup> Büchi, G.; Warnhoff, E. W. J. Am. Chem. Soc. 1959, 81, 4433-4434.



Uleine alkaloids are mostly found in the *Apocynaceae* plant family. In particular, in the *Alstonia angustiloba* (which gave more than 40 alkaloids so far), pneumatophore, rostrate and undulifolia but also in the *Aspidosperma austral, dasycarpon, formosanum, gilbertii, subincanum, ulei* and *Winchia calophylla*.<sup>17</sup> The monoterpene indole alkaloids isolated from *Alstonia* are well-known for their biological activity, such as antibacterial, antitussive and anticancer, which makes them an interesting target to study.<sup>18</sup>

#### 2.1.1.2. Biosynthesis

Uleine can be found in the same plants along with other alkaloids, such as ellipticine, olivacine, vallesamine and apparicine.<sup>19</sup> One believes that the biogenetic formation comes from the same progenitor as the alkaloids come from the same plant. The first biosynthetic pathway proposed by Wenkert and co-workers started from a common precursor derived from glycosylideneanthranilic acid and secologanine.<sup>20</sup> However, the work by Potier and

<sup>&</sup>lt;sup>16</sup> a) Joule, J. A.; Ohashi, M.; Gilbert, B.; Djerassi, C. *Tetrahedron* **1965**, *21*, 1717–1734. b) Garcia, R. M. F.; Brown,

K. S. *Phytochemistry* **1976**, *15*, 1093–1095. (20-epiuleine) c) Miranda, E. C.; Blechert, S. *Tetrahedron Lett.* **1982**, *23*, 5395-5398. (Gilbertine) d) Borris, R. P.; Lankin, D. C.; Cordell, G. A. *J. Nat. Prod.* **1983**, *46*, 200–210. (NMR of uleine) e) Massiot, G.; Boumendjel, A.; Nuzillard, J.-M.; Richard, B.; Le Men-olivier, L.; David, B.; Hadit, H. A. *Phytochemistry* **1992**, *31*, 1078-1079. (undulifoline) f) Gan, L.-S.; Yang, S.-P.; Wu, Y.; Ding, J.; Yue, J.-M. *J. Nat. Prod.* **2006**, *69*, 18–22. (undulifoline) g) Koyama, K.; Hirasawa, Y.; Zaima, K.; Hoe, T. C.; Chan, K. L.; Morita, H. *Bioorg. Med. Chem.* **2008**, *16*, 6483–6488. (alstilobanine B,C) h) Koyama, K.; Hirasawa, Y.; Hosoya, T.; Hoe, T. C.; Chan, K. L.; Morita, H. *Bioorg. Med. Chem.* **2010**, *18*, 4415–4421. (alpneumine H) i) Ku, W. F.; Tan, S. J.; Low, Y. Y.; Komiyama, K.; Kam, T. S. *Phytochemistry* **2011**, *72*, 2212–2218. (angustiphylline) j) Bao, M.-F.; Zeng, C.-X.; Qu, Y.; Kong, L.-M.; Liu, Y.-P.; Cai, X.-H.; Luo, X.-D. *Nat. Products Bioprospect.* **2012**, *2*, 121–125. (undulifoline)

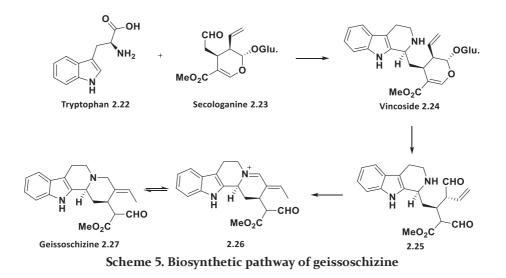
<sup>&</sup>lt;sup>17</sup> Kam, T. S.; Choo, Y. M. Phytochemistry 2004, 65, 603–608.

<sup>&</sup>lt;sup>18</sup> Gupta, R. S.; Bhatnager, A. K.; Joshi, Y. C.; Sharma, M. C.; Khushalani, V.; Kachhawa, J. B. *Pharmacology* **2005**, *75*, 57-62.

<sup>&</sup>lt;sup>19</sup> Büchi, G.; Warnhoff, E. W. J. Am. Chem. Soc. 1959, 81, 4433-4434.

<sup>&</sup>lt;sup>20</sup> Wenkert, E. J. Am. Chem. Soc. 1962, 84, 98-102.

co-workers suggested that stemmadenine-*N*-oxide would be the possible precursor, which itself could come from tryptophan.<sup>21</sup> Labelling experiments with tryptophan and stemmadenine strengthened the hypothesis as incorporation of the two compounds were found in apparicine and uleine.<sup>22</sup>

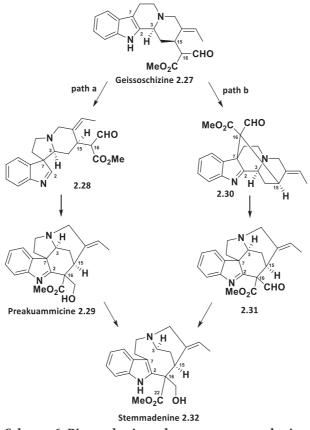


Tryptophan **2.22** undergoes a Pictet-Spengler reaction with the aldehyde of the glucosidic residue **2.23**, after enzymatic decarboxylation, to afford vincoside **2.24**. Enzymatic hydrolysis of the sugar moiety provides a dialdehyde which upon reductive condensation yields geissoschizine **2.27** (Scheme 5).<sup>23</sup>

<sup>&</sup>lt;sup>21</sup> Potier, P.; Janot, M.-M. C. R. Acad. Sc. 1973, 276C, 1727.

<sup>&</sup>lt;sup>22</sup> Kutney, J. P. *Heterocycles* **1976**, *4*, 429.

<sup>&</sup>lt;sup>23</sup> Scott, A. I. Acc. Chem. Res. 1970, 3, 151-157.

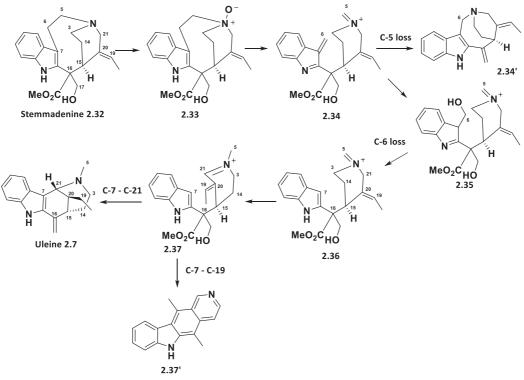


Scheme 6. Biosynthetic pathways to stemmadenine

Two different mechanisms can lead to stemmadenine **2.32**. The first one starts with protonation  $\alpha$  of the indole nitrogen of geissoschizine **2.27** followed by a 1,2-shift of C-3, from C-2 to C-7, to give spiroindole **2.28** (path a). Cyclization of C-2 to C-16 afford preakuammicine **2.29** which can be converted to stemmadenine *via* a sequence of retro-Mannich and reduction.<sup>24</sup> The second one involves a one-electron oxidative coupling between C-7 and C-16 (path b) followed by rearrangement provides **2.31** which under reductive conditions affords stemmadenine **2.32** (Scheme 6).<sup>25</sup>

<sup>&</sup>lt;sup>24</sup> Harley-Mason, J.; Waterfield, W. Tetrahedron 1963, 19, 65.

<sup>&</sup>lt;sup>25</sup> Saxton, J. E. Alkaloids **1968**, 10, 501.



Scheme 7. Biological pathway to uleine alkaloids and related families

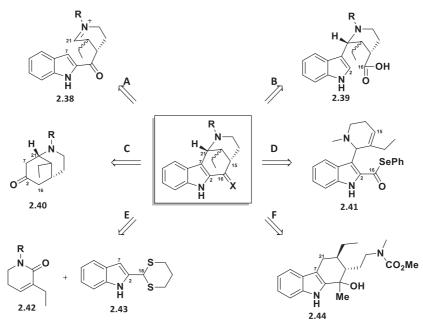
Oxidation to the *N*-oxide **2.33** leads to the precursor of the Polonovski-Potier reaction. The latter was mimicked in the laboratory of Potier and co-workers using TFAA.<sup>26</sup> Fragmentation yields alcohol **2.34**. N-4 – C-6 cyclization followed by loss of C-5 leads to the apparicine and vallesamine alkaloids **2.34**'. Isomerization of the exocyclic iminium species **2.36** to the more stable conjugated iminium **2.37** can give the ellipticine and olivacine family **2.37**' when C-7 undergoes Michael addition on C-19. The uleine alkaloid family is obtained when C-7 cyclizes on C-21 (Scheme 7).<sup>27</sup>

#### 2.1.1.3. Previous syntheses

Uleine alkaloids have been isolated and characterized since 1959, but only few total syntheses have been reported so far and many of them are based on the same disconnections (Scheme 8).

<sup>&</sup>lt;sup>26</sup> a) Ahond. A.; Cavé, A.; Kan-Fan, C.; Husson, H.-P.; de Rostolan, J.; Potier, P. J. Am. Chem. Soc. **1968**, 90, 5622-5623. b) Potier, P. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D.; Zenk, M. H., Eds; Academic Press: London, **1980**, Chapter 8.

<sup>&</sup>lt;sup>27</sup> a) Szabó, L. F. *ARKIVOC* **2008**, *(iii)*, 167-181. b) Macabeo, A. P. G.; Krohn, K.; Gehle, D.; Read, R. W.; Brophy, J. J.; Cordell, G. A.; Franzblau, S. G.; Aguinaldo, A. M. *Phytochemistry* **2005**, *66*, 1158–1162.



Scheme 8. Retrosynthetic approaches for the synthesis of uleine alkaloids

To form the tetracyclic unit, the most used disconnection in the syntheses of uleine alkaloids is the C-7 - C-2l bond. It can be formed by cyclization of C-7 onto C-2l *via* an iminium species **2.38** formed *in situ* in the piperidine ring (A).<sup>28</sup> Another strategy is the cleavage of C-2 - C-16 bond which can, in the synthetic way, be formed by Friedel-Crafts cyclization of C-2 onto the acid **2.39** (B).<sup>29</sup> Fischer indole synthesis can also be explored to afford the uleine moiety starting from bicyclic compound **2.40** (C).<sup>30</sup> Radical cyclization was studied using seleno ester at the C-16 which cyclize onto C-15 of **2.41** (D).<sup>31</sup>

The dithiane chemistry was investigated and led to a one-pot cyclization to 20epidasycarpidone from 1,4-addition of **2.43** onto enone **2.42** (E).<sup>32</sup> Finally, another approach was followed which used a cationic domino sequence from **2.44** to give the piperidine ring (F).<sup>33</sup>

To illustrate some of the strategies used for the total synthesis of uleine alkaloids, selected examples are shown (Scheme 9 to 11).

<sup>&</sup>lt;sup>28</sup> a) Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Bosch, J. J. Chem. Soc. Chem. Commun. **1991**, *6*, 1687-1688. b) Wilson, N. D. V.; Jackson, a.; Gaskell, a. J.; Joule, J. A. Chem. Commun. **1968**, *10*, 584.

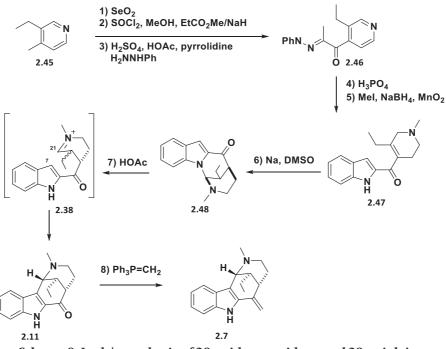
<sup>&</sup>lt;sup>29</sup> a) Amat, M.; Sathyanarayana, S.; Hadida, S.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 7123–7126. b) Dolby, L. J.; Biere, H. J. Am. Chem. Soc. **1968**, *90*, 2699–2700.

<sup>&</sup>lt;sup>30</sup> Gràcia, J.; Bonjoch, J.; Bosch, J. J. Org. Chem. 1994, 59, 3939–3951.

<sup>&</sup>lt;sup>31</sup> Bennasar, M. L.; Roca, T.; García-Díaz, D. J. Org. Chem. 2008, 73, 9033–9039.

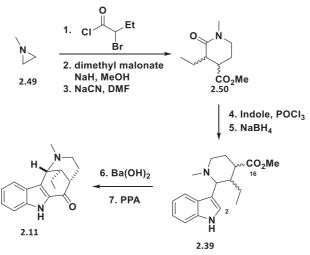
<sup>&</sup>lt;sup>32</sup> Forns, P.; Diez, A.; Rubiralta, M.; Solans, X.; Font-Bardia, M. *Tetrahedron* **1996**, *52*, 3563–3574.

<sup>&</sup>lt;sup>33</sup> Blechert, S. Liebigs. Ann. Chem. 1985, 2073-2082.



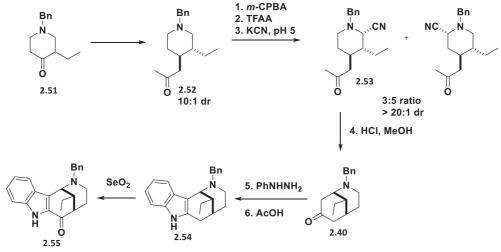
Scheme 9. Joule's synthesis of 20-epidasycarpidone and 20-epiuleine

Starting from a commercially available pyridine derivative **2.45**, an oxidation, reduction and cyclization sequence afforded indole **2.47** as the key intermediate of the synthesis.<sup>28b</sup> Cyclization and acidic rearrangement led to **2.11** with the formation of the C-7 - C-21 bond in the late stage. The cyclization was not stereoselective as the ( $\pm$ )-20-epidasycarpidone **2.11** was found to be the major isomer. Conversion to ( $\pm$ )-20-epiuleine **2.7** was performed using a Wittig reaction. A variation of the iminium species **2.38** was used by Bosch and co-workers. The charged intermediate was stabilized by a nitrile on the C-21, which avoided the enamine formation and therefore the epimerization of C-20.<sup>28a</sup>



Scheme 10. Biere's synthesis of dasycarpidone and its C-20 epimer

In Biere's synthesis,<sup>29b</sup> 1-methylaziridine **2.49** was converted to **2.50** in three steps as a mixture of diastereoisomers. Vilsmeier-Haack conditions were used and the salt intermediate was reduced with NaBH<sub>4</sub> to yield **2.39** as a mixture of stereoisomers. Hydrolysis of the ester and acid-induced Friedel-Crafts cyclization of C-2 to C-16 afforded  $(\pm)$ -20-epidasycarpidone **2.11** as a major diastereoisomer.



Scheme II. Gràcia's synthesis of 20-epidasycarpidone

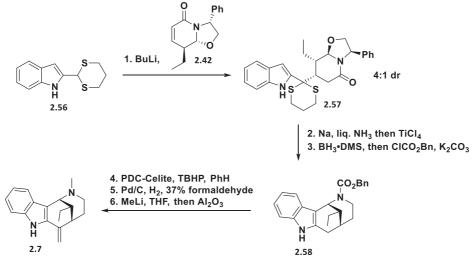
A late stage Fischer indole synthesis was used in Gràcia's synthesis.<sup>30</sup> The first steps were reported and afforded **2.52** as major diastereoisomer.<sup>34</sup> Insertion of a nitrile *via* a

<sup>&</sup>lt;sup>34</sup> Bonjoch, J.; Linares, A.; Guardià, M.; Bosch, J. Heterocycles 1987, 26, 2165.

Polonovski-Potier reaction followed by trapping of the so-formed iminium salt with KCN was not regioselective but yielded **2.53** as a minor regioisomer. Mannich cyclization led to the precursor **2.40** of the key step. Although the reaction worked and **2.40** was able to be transformed to  $(\pm)$ -20-epidasycarpidone **2.55**, the yield of the Fischer indole synthesis was low.

Most of the previous racemic syntheses showed a major stereoselective problem as the C-20 epimerized to the thermodynamically more stable configuration, which led to the 20-epidasycarpidone or 20-epiuleine as a major isomer.

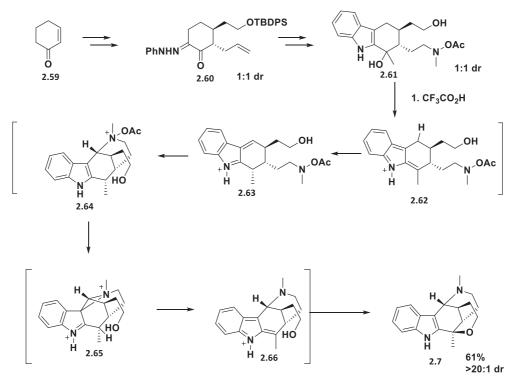
Almost 40 years were needed to produce the first enantioselective total synthesis of a member of the uleine group. Bosch and co-workers developed a diastereoselective conjugated addition of lithium dithiane **2.56** on a chiral enone **2.42** to afford **2.57** (Scheme 12).<sup>35</sup> Treatment of the latter in liquid ammonia with sodium cleaved the dithiane and the benzylic C-N bond which then cyclized using TiCl<sub>4</sub> to afford tetracyclic lactam. Reduction of the lactam carbonyl with borane followed by carbamate formation led to **2.58**. Benzylic oxidation with PDC-Celite in presence of TBHP afforded the ketone. *N*-deprotection and *N*-methylation proceeded well with formaldehyde. Finally, transformation of the ketone to the corresponding alkene **2.7** was achieved by alkylation followed by dehydration of the so-formed tertiary alcohol.<sup>36</sup>



Scheme 12. First enantioselective total synthesis of uleine by Bosch and co-workers

 <sup>&</sup>lt;sup>35</sup> Amat, M.; Pérez, M.; Llor, N.; Martinelli, M.; Molins, E.; Bosch, J. Chem. Commun. 2004, 14, 1602–1603.
 <sup>36</sup> Saito, M.; Kawamura, M.; Hiroya, K.; Ogasawara, K. Chem. Commun. 1997, 2, 765–766.

Blechert and co-worker have reported for the first time an enantioselective synthesis of a pentacyclic member of the uleine family (Scheme 13).<sup>37</sup>



Scheme B. Enantioselective synthesis of (-)-gilbertine

The Shibasaki enantioselective Michael addition set the first stereocenter, which will direct the second in  $\alpha$  *via* enolate formation and quench by allyl bromide. A modified Fischer indole synthesis was used followed by FGI of the alkene **2.60** to afford the precursor of the key step **2.61**. Acidic condition triggered the cationic domino process as well as an additional diastereomeric resolution.

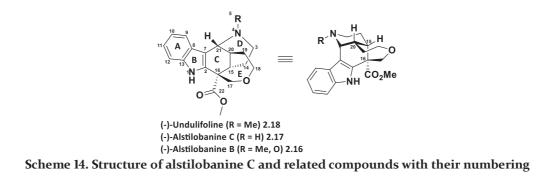
<sup>&</sup>lt;sup>37</sup> Jiricek, J.; Blechert, S. J. Am. Chem. Soc. **2004**, *126*, 3534–3538.

#### 2.1.2. Alstilobanine C, Undulifoline and Alstilobanine B

Among the few uleine alkaloids, alstilobanine C **2.17**, undulifoline **2.18** and alstilobanine B stand out from their family by their interesting structure.

#### 2.1.2.1. Isolation and chemical structure

Undulifoline was isolated from a Malaysian *Alstonia undulifolia* in 1992 by Hadi and coworkers along with eight known alkaloids.<sup>38</sup> Alstilobanine B and C as well as three other new alkaloids and three known alkaloids, including undulifoline, were isolated from a Malaysian *Alstonia angustiloba* in 2008 by Morita and co-workers (Scheme 14).<sup>39</sup>

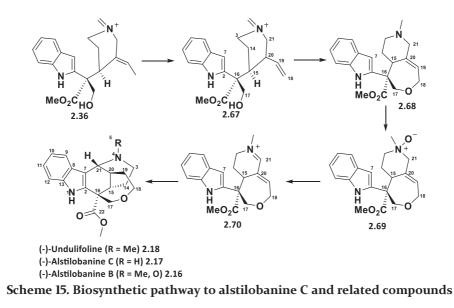


The remarkable structure of undulifoline **2.18**, alstilobanine C **2.17** and alstilobanine B **2.16** is rare within indole alkaloids. This pentacyclic framework contains four contiguous stereogenic bridgehead centers including one quaternary carbon. Ring C is doubly bridged in a 1,3-manner by the piperidine (D ring) and the oxepane (E ring) rings. The relative configuration of C-16, C-15, C-20, C-21 is fixed as the two bridged rings can only be opposite from each other. An amine, an ester and an ether are part of the structure.

<sup>&</sup>lt;sup>38</sup> Massiot, G.; Boumendjel, A.; Nuzillard, J.-M.; Richard, B.; Le Men-olivier, L.; David, B.; Hadit, H. A. *Phytochemistry* **1992**, *31*, 1078-1079.

<sup>&</sup>lt;sup>39</sup> Koyama, K.; Hirasawa, Y.; Zaima, K.; Hoe, T. C.; Chan, K. L.; Morita, H. *Bioorg. Med. Chem.* **2008**, *16*, 6483–6488.

# 2.1.2.2. Biosynthesis and biological activity



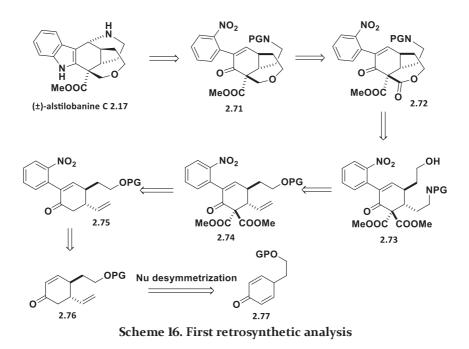
The proposed biogenetic formation of undulifoline is similar to uleine (Scheme 15).<sup>39</sup> Starting from the same intermediate **2.36** as previously described, isomerization of the double bond followed by acidic cyclization the alcohol group on C-18 forms the 7-membered ring. Oxidation of the basic nitrogen and Polonovski-Potier reaction afford iminium **2.70**. C-7 - C-21 cyclization leads to the undulifoline alkaloid.

Regarding their biological activity, undulifoline and alstilobanine B and C show a moderate  $(3 \times 10^{-7} \text{ M})$  relaxation activity against phenylephrine induced contractions of thoracic rat aortic rings with endothelium.<sup>31</sup>

The synthetically challenging motive of undulifoline and its rare family motivated us to investigate its total synthesis.

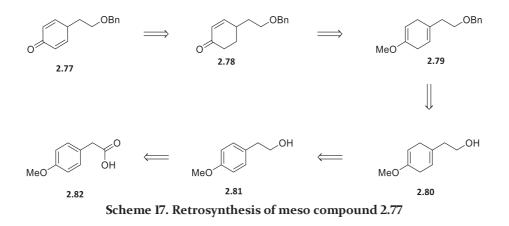
#### 2.2. First Retrosynthetic Analysis

The first retrosynthetic pathway envisioned for the synthesis of alstilobanine C and other members of the family is outlined in Scheme 16.

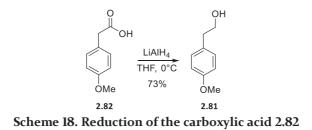


Alstilobanine C would be obtained through an intramolecular aza-Michael addition on the conjugated iminium. The latter would be formed by condensation of the reduced nitro group with the ketone **2.71**. The oxepane ring would come from the reduction of the corresponding lactone **2.72**. This unusual bridged ring would be formed from transesterification of the free alcohol **2.73** and the desired ester with a high stereoselectivity as the cyclization can only occur from the top face. Functional group interconversion of the alkene **2.74** leads us to the protected amine. A three carbons units, such as an allyl moiety, can also be used to reach the same protected amine **2.73**. Double  $\alpha$  functionalization of the formation of the desired aryl moiety. Enone **2.76** was envisioned to be formed by nucleophilic desymmetrization of the meso compound **2.77** using an organometallic vinyl or allyl moiety.

#### 2.2.1. Synthesis of the Meso Compound

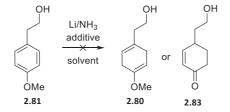


The first strategy to synthesize the desired meso compound **2.77** is shown in Scheme 17. Oxidation of enone **2.78** would provide the desired meso compound **2.77**. Protection of the alcohol **2.80** followed by hydrolysis of enol ether gives enone **2.78**. Birch reduction of the derived anisole **2.81** will lead to alcohol **2.80**.<sup>40</sup> The commercially available acid **2.82** can be reduced to the corresponding alcohol **2.81**.

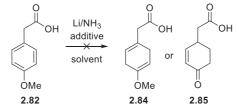


Reduction of the acid **2.82** to the corresponding primary alcohol **2.81** proceed in good yield (Scheme 18). However, the following Birch reduction did not proceed as expected. The reduced aromatic **2.80** or **2.83** was never observed while performing the reaction in various solvent systems nor using additive such as acids. Some reduction conditions were also tried on the acid **2.82** but similar outcome were observed, no desired product was obtained.

<sup>4</sup>º Birch, A. J. J. Chem. Soc. 1942, 430-436.



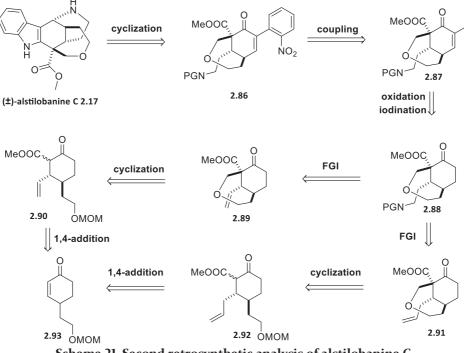




Scheme 20. Birch reduction of the carboxylic acid 2.82

# 2.3. Second Retrosynthetic Pathway

Because of the difficulties encountered, the long linear sequence and the feasibility of the chemoselective reduction of the bridged lactone, we therefore proposed a new retrosynthesis of the desired target with a shorter route and a new key step (Scheme 21).



Scheme 21. Second retrosynthetic analysis of alstilobanine C

The last step of the synthesis was hypothesized to be the formation of the bridged D ring through an intramolecular aza-Michael addition on the conjugated iminium. The latter would be formed by condensation of the reduced nitro group with the ketone 2.86 of the C ring. This type of reaction has been investigated in many total syntheses including several in our group.<sup>41</sup> The 1,4-addition will occur with a high stereoselectivity as the nitrogen can only cyclize from one face. Indeed, the C-14 - C-13 and C-5 - N-4 bonds can only be cis. The tricyclic compound 2.86 could come from a coupling between o-nitrophenylboronic acid and the iodo enone 2.87 which would be easily obtained by oxidation and iodination of **2.88**. The amino function on the alkyl chain can be obtained through different pathways; either with a two carbon unit or with a three carbon unit. The key step of this synthesis is the formation of the E ring which was thought to be built using the property of an acetal. Indeed, under specific conditions, the latter can form an oxonium species that would be trapped by the nucleophilic carbon of the  $\beta$ -ketoester. Again, the stereoselectivity of the reaction would be high as the C-15 - C-16 and C-20 - C-21 bonds have to be from the same face to afford the E ring. The unique difficulty in this reaction is the formation of the 7membered ring and a quaternary carbon center. The  $\beta$ -ketoesters 2.92 and 2.90 could come from a 1,4-addition of allylmagnesium bromide or vinylmagnesium bromide, respectively, followed by quench with Mander's ester of cyclohexenone 2.93.42 The 1,4-addition should occur with high diastereoselectivity as the cuprate would come with an anti-relationship to the C20 substituent. The formed  $\beta$ -ketoester will be in equilibrium between the keto-enol forms, losing the diastereoselectivity on the C15, but it should have no consequence on the synthesis as the formation of the D ring can occur only from one face.

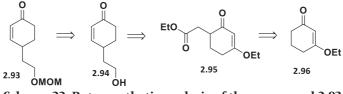
# 2.4. Synthesis of Alstilobanine C, Undulifoline and Alstilobanine B

# 2.4.1. Synthesis of the Cyclohexenone

The first strategy to synthesize the desired cyclohexenone **2.93** is shown in Scheme 22. C-alkylation of the enone **2.96** would give the compound **2.95**. Reduction of both ketone and ester groups followed by acidic workup should give rise to the free alcohol **2.94**. Protection of the latter with an acetal moiety would lead to **2.93**.

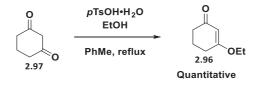
<sup>&</sup>lt;sup>41</sup> a) Xu, Z.; Wang, Q.; Zhu, J. *Angew. Chemie - Int. Ed.* **2013**, *52*, 3272–3276; b) Wagnières, O.; Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 15102–15108; c) Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2015**, *137*, 6712–6724; d) Dagoneau, D.; Xu, Z.; Wang, Q.; Zhu, J. *Angew. Chemie - Int. Ed.* **2016**, *55*, 760–763.

<sup>&</sup>lt;sup>42</sup> a) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425–5428; b) Reddy, D. S. *Org. Lett.* **2004**, *6*, 3345–3347.



Scheme 22. Retrosynthetic analysis of the compound 2.93

Although 3-ethoxycyclohex-2-en-1-one **2.96** is commercially available, it was synthesized by refluxing **2.97** in toluene and ethanol in the presence of a catalytic amount of pTsOH (Scheme 23).



Scheme 23. Synthesis of 3-ethoxycyclohex-2-enone

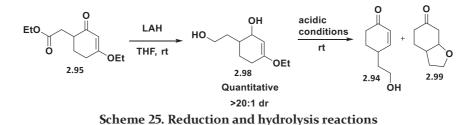
Protonation of a carbonyl group makes its carbon more electrophilic and allows ethanol to attack it. Water elimination afforded **2.96** in a quantitative yield.<sup>43</sup>



Alkylation of enone **2.96** gave the ester **2.95** in good yield (Scheme 24).<sup>44</sup> HMPA plays an important role in the reaction as in its absence, the reaction is much slower and cannot get to full conversion.

<sup>&</sup>lt;sup>43</sup> Findley, T. J. K.; Sucunza, D.; Miller, L. C.; Davies, D. T.; Procter, D. J. Chem. Eur. J. 2008, 14, 6862-6865.

<sup>&</sup>lt;sup>44</sup> Toyota, M.; Seishi, T.; Fukumoto, K. Tetrahedron 1994, 50, 3673-3686.

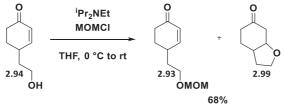


Reduction followed by acidic workup of the so-formed diol proved to be troublesome. The reduction was straightforward and gave diol **2.98** after Fieser workup as a single diastereoisomer.<sup>45</sup> Hydrolysis of enol ether **2.98** under acidic conditions afforded a mixture of the desired enone **2.94** and the oxo-Michael product **2.99** (Scheme 25). Alcohol **2.94** is not stable and cyclizes over time to **2.99** even when kept in the freezer. The hydrolysis of the enol ether **2.98** was then investigated (Table 1).

Entry	Conditions	Ratio alcohol 2.94 : bicycle 2.99 (Isolated Yield)
1	LAH, THF then 1 M HCl (until pH=4)	1:1 (45%)
2	LAH, Et <sub>2</sub> O then 1 M HCl (until pH=4)	1:1 (37%)
3	LAH, THF then 1 M HCl (until pH=1)	1:1 (65%)
4	1. LAH, THF (Fieser workup) 2. 3% HCl, THF	2:1 (91%)

Reduction of **2.95** with LAH in THF or Et<sub>2</sub>O, followed by one-pot hydrolysis by addition of 1 M HCl until pH=4 provided a 1:1 mixture of **2.94** and **2.99** in moderate yields (entries 1-2). Increasing the acidity to pH=1 improved slightly the yield to 65%, but the ratio between the two products remained the same (entry 3). Switching to the basic Fieser workup, the so-formed diol intermediate was directly used for the next step. After addition of 3% HCl in the reaction mixture, complete hydrolysis of the enol ether was observed in less than 5 minutes and afforded a 2:1 mixture of the alcohol **2.94** and the bicyclic compound **2.99** respectively in excellent yield (entry 4).

<sup>&</sup>lt;sup>45</sup> Fieser, L. F.; Fieser, M. Reagents for Organic Synthesis 1967, 581-595.



Scheme 26. Protection of the alcohol 2.94

The alcohol was converted to the acetal protected **2.93** with **2.99** as a major side product (Scheme 26).<sup>46</sup> Attempts have been made to avoid the formation of the bicyclic product by changing solvent, temperature, base, MOM-source, concentration or additive (Table 2).

Table 2. Representative conditions for the protection of alcohol 2.94

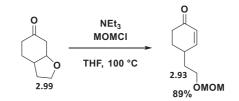
Entry	Conditions <sup>1</sup>	Isolated Yield
1	NaH, MOMCl, THF, 0 °C to rt	Decomposition
2	DIPEA, MOMCl, THF, 0 °C to rt	57%
3	2,6-lutidine, MOMCl, THF, 0 ℃ to rt	33%
4	DIPEA, MOMCl, DCM, 0 °C to rt	48%
5	DIPEA, MOMBr, THF, 0 °C to rt	42%
<b>6</b> <sup>a</sup>	MOMCl, DIPEA, THF, 0 °C to rt	21%
7	DIPEA, MOMCl, THF (1 M), 0 °C to rt	68%
8	DIPEA, MOMCl, THF (1 M), 40 °C	60%
9	DIPEA, MOMCl, NaI, THF (1 M), 0 °C to rt	65%

<sup>1</sup>: All reactions have been carried out with a concentration of 0.3 M unless otherwise noted.

<sup>a</sup>: MOMCl was added first, followed by DIPEA.

Initial conditions, using NaH as a base led to the decomposition of the starting materials (entry 1). Using DIPEA as a base under otherwise identical conditions afforded the desired MOM ether in 57% yield (entry 2). Using 2,6-lutidine as a base did not improve the yield of the desired product, nor the formation of the bicycle by-product (entry 3). Changing the solvent to DCM reduced the yield of **2.99** (entry 4). An alternative and cheaper MOMBr was tested which led to a decreased yield and considerable decomposition of the starting materials (entry 5). Addition of the base subsequent to MOMCl, afforded **2.93** as a minor product (entry 6). Increasing the concentration appeared to improve the yield of the reaction and limit the production of the byproduct **2.99** (entry 7). Raising up the temperature or addition of sodium iodide as an additive did not improve the reaction rate nor the yield of the protected enone (entries 8-9).

<sup>&</sup>lt;sup>46</sup> Paquette, L. A.; Peng, X.; Bondar, D. Org. Lett. **2002**, *4*, 937-940.



Scheme 27. Opening of the bicyclic compound 2.99

Some efforts were then headed to the re-opening of the bicyclic compound **2.99** and direct protection of the alcohol (Scheme 27).<sup>47</sup> Several conditions are shown in Table 3.

Table 3. Representative conditions for opening of compound 2.99

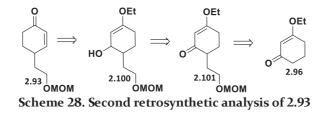
Entry	Conditions <sup>1</sup>	Isolated Yield
1	DIPEA, MOMCl, NaI, DCM, rt	Recovery of SM
2	DIPEA, MOMCl, THF, 50 °C	Recovery of SM
3	DIPEA, MOMCl, THF, 100 °C	89%
4	DIPEA, MOMCl, THF, 100 °C, 30 min, MW	67%
5	DIPEA, MOMCl, dioxane, 100 °C	81%
6	DIPEA, MOMCl, PhMe, 100 °C	84%

<sup>1</sup>: All reaction were performed for 4 days with 8 equivalents of base and 4 equivalents or MOMCl unless otherwise noted

The reaction was first performed in DCM with NaI as additive at room temperature but no reaction was observed (entry 1). By changing the solvent to THF, removal of NaI and running the reaction at 50 °C gave the same results as previously noticed (entry 2). However, conducting the reaction in a sealed tube in THF at 100 °C for 4 days gave excellent yield (entry 3). Microwaves did not increase the yield (entry 4). In order to overcome the inconveniency of using sealed tube, solvents with a higher boiling point such as dioxane and toluene were used and gave good yields (entries 5-6).

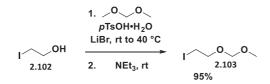
Because of the troublesome and unavoidable spontaneous formation of the bicyclic compound **2.99** through an oxo-Michael addition from the primary alcohol to the enone, we decided to investigate in parallel another pathway for the synthesis of **2.93** (Scheme 28).

<sup>&</sup>lt;sup>47</sup> Meyers, A. I.; Hanreich, R.; Wanner, K. T. J. Am. Chem. Soc. **1985**, 107, 7776-7778.



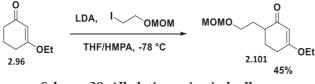
In order to avoid the intramolecular cyclization, the free alcohol **2.94** should not be formed in presence of the enone. To do so, an alternative alkylation partner should be used. Reduction of the ketone and acidic hydrolysis should afford the desired enone **2.93**.

The chosen alkylating partner is 1-iodo-2-(methoxymethoxy)-ethane **2.103** which can be easily prepared from 2-iodoethanol in a one-step procedure (Scheme 29).<sup>48</sup>



Scheme 29. Synthesis of the new alkylating partner

The alkylation of enone **2.96** using the iodoalkane **2.103** was quite difficult (Scheme 30). Under the best conditions, only 45% of the desired alkylated product **2.101** was obtained.



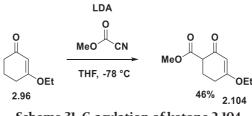
Scheme 30. Alkylation using iodoalkane

Thinking that the iodoalkane was not electrophilic enough for this reaction, the same conditions were tried with zinc(II) chloride as an additive. It was shown that this Lewis acid can improve the reactivity of the iodoalkane for such type of reaction.<sup>49</sup> Unfortunately, no reaction was observed under these conditions. The acetal might play a role for the absence of reactivity but it is still unclear to us.

<sup>&</sup>lt;sup>48</sup> Yamazaki, T. Amine compound and use thereof. U.S. Patent 0208033 Al, Sep. 6, 2007.

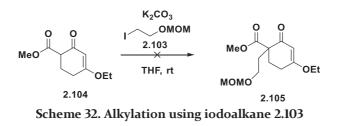
<sup>&</sup>lt;sup>49</sup> Dai, W.; Katzenellenbogen, J. A. J. Org. Chem. 1993, 58, 1900-1908.

To enhance the reactivity towards the iodoalkane, another substrate was investigated (Scheme 31).

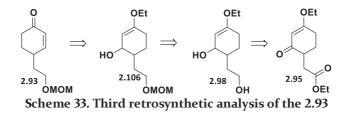


Scheme 31. C-acylation of ketone 2.104

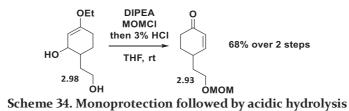
C-acylation of **2.96** using Mander's ester gave  $\beta$ -ketoester **2.104** in moderate yield. Attempts of alkylation using the iodoalkane **2.103** were unsuccessful and led to no reaction (Scheme 32).



At the same time, a third pathway was studied to prevent the self-cyclization of **2.94** (Scheme 33).



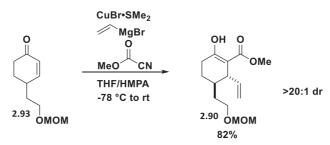
Starting from the same alkylated product **2.95** as the first route, reduction yield to the diol **2.98**. Monoprotection of the diol should affect the primary alcohol first. Acidic workup should lead to the desired enone **2.93**.



Different conditions have been tried, using additive such as potassium iodide, or different reagents to avoid the use of MOMCl without success. Conditions using excess of DIPEA and MOMCl in THF followed by hydrolysis gave the best results yielding no trace of the by-product **2.99** (Scheme 34). Fine tuning of the acidity during hydrolysis had to be optimized as the MOM protecting group can be labile in acidic media.

2.4.2. Towards the Key Step: Michael Addition Using Vinylmagnesium Bromide

With the desired enone **2.93** in hands, the next steps of the synthesis were investigated. As shown in the retrosynthesis (Scheme 21), two types of substituents bearing two of three carbon unit could be used. As the 1,4-addition using allylmagnesium bromide was less reported in the literature, we decided to study the 1,4-addition of vinylmagnesium bromide on **2.93** followed by quench with Mander's ester to afford **2.90** (Scheme 35). Several reaction conditions are presented in Table 4.



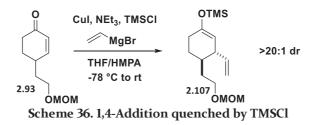
Scheme 35. 1,4-Addition followed by Mander's ester trapping

Table 4. Representative conditions for the 1,4-addition of vinylmagnesium bromide on enone 2.93

Entry	Conditions <sup>1</sup>	<b>Isolated Yield</b>
1	[Cu] (0.1 equiv), Grignard (2 equiv), ester (1.2 equiv)	SM recovered
2	[Cu] (2 equiv), Grignard (4 equiv), ester (1.2 equiv)	1,4 product
3	[Cu] (2 equiv), Grignard (4 equiv), ester (1.2 equiv), HMPA	1,4 product
4	[Cu] (2 equiv), Grignard (4 equiv), ester (1.2 equiv), HMPA, -45 °C	26%
5	[Cu] (2 equiv), Grignard (4 equiv), ester (1.2 equiv), HMPA, rt	50%
6	[Cu] (2 equiv), Grignard (4 equiv), TMSCl (3 equiv), HMPA, rt	88%
7	[Cu] (2 equiv), Grignard (4 equiv), ester (6 equiv), HMPA, rt	82%

<sup>1</sup>: All reactions were performed in THF at -78 °C unless specified otherwise.

The first trials were carried out with a catalytic amount of copper in THF and led to no reaction (entry 1). Switching to a more reactive species reported by Lipshutz,<sup>50</sup> also called higher-order cuprate, the 1,4-addition proceeded but the quench with Mander's ester was not observed due to the low reactivity of the copper enolate (entry 2). Addition of HMPA as co-solvent, which is described to help the second step of the reaction, gave the 1,4-addition product only (entry 3). Increasing the temperature to -45 °C after addition of the Grignard started to show conversion to **2.90** (entry 4). This effect was strengthened when the reaction was warmed to rt to yield **2.90** in 50% (entry 5). Based on the previous poor results, the 1,4-addition followed by trapping with TMSCI was studied (Scheme 36). The reaction proceeded in good yield with excellent diastereoselectivity to the silyl enol ether **2.107** (entry 6).



The positive result of the 1,4-addition was encouraging and indicated its good reactivity. As the resulting excess of cuprate or Grignard in the solution might consume first the cyanoformate, an excess of the electrophile was added and the reaction proceeded with good yield to product **2.90** with excellent diastereoselectivity (entry 7). It is important to mention that the work up plays an important role as a NH<sub>3</sub>/NH<sub>4</sub>Cl work up leads to almost complete decomposition whereas simple quench with saturated NH<sub>4</sub>Cl solution complexes the copper in the mixture and is not harmful for the desired ketoester.

<sup>&</sup>lt;sup>50</sup> Lipshutz, B. H.; Sharma, S.; Ellsworth, E. L. J. Am. Chem. Soc. **1990**, 112, 4032-4034.

When performing the reaction on a larger scale, one interesting side product was isolated and its X-ray structure was elucidated (Figure 1).

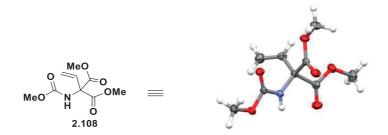
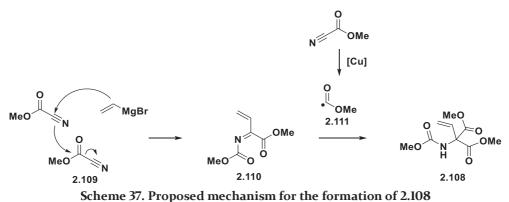


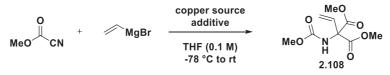
Figure 1. X-ray structure of 2.108

The side product **2.108** contains a malonate moiety, a vinyl group and a carbamate. From the reaction conditions, we can believe that one equivalent of vinylmagnesium bromide reacts with three equivalents of Mander's ester. From this hypothesis, we tried to explain the mechanism as followed (Scheme 37).



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First, vinylmagnesium bromide reacts with the nitrile moiety from the Mander's ester **2.109**. The *in situ* formed nucleophilic imine reacts with another equivalent of the Mander's ester but on the carbonyl moiety, releasing cyanide anion. Copper must cleave the third equivalent of the Mander's ester into a methoxycarbonyl radical **2.111** allowing the last C-C bond formation to occur. Several reactions were tested to have a better understanding of the mechanism (Scheme 38).



Scheme 38. Reaction between Mander's ester and a Grignard reagent

When reacting one equivalent of Grignard reagent with three equivalents of Mander's ester in presence of 0.5 equivalent of copper(I) bromide dimethyl sulfide complex, the expected product was formed in 20% yield. Control experiment showed that in the absence of copper, no desired product **2.108** was formed. When HMPA was added as additive, malonate **2.108** was not found. Increasing the equivalents of the ester to five led to decomposition and no desired product was isolated. Changing the copper source to copper(I) iodide led to lower yields. Running the reaction in diethyl ether made it messier. Increasing the copper to one equivalent resulted in lower yields. The same observation was made when 0.1 equivalent was used. As we do not form any organocuprate species, Mander's ester can be added at -78 °C directly after addition of the Grignard reagent into the solution of copper. When the mixture was warmed slowly to room temperature instead of keeping the temperature at -78 °C, the yield increased to 28%. Replacing the Grignard by phenylmagnesium bromide or allylmagnesium bromide afforded a trace amount of desired products. As the results were not satisfying enough, we decided to stop the investigation on this side reaction.

# 2.4.3. First Key step of the Synthesis: Oxepane Formation

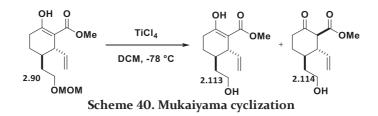
Based on a similar transformation which was recently reported, our first trials went in the same direction.<sup>51</sup> The main difference between their reaction which formed a 6-membered fused ring on a tertiary carbon and our designed reaction which would form a 7-membered and bridged ring on a quaternary carbon makes it more challenging. The search for the right conditions started with a model substrate **2.107** previously prepared by 1,4-addition and trapping of the enolate with TMSCl (Scheme 36). Titanium(IV) chloride, as reported in previous papers, was the main Lewis acid which could yield to such kind of product, through a Mukaiyama-type reaction.<sup>52</sup> Luckily, the reaction proceed directly and gave the model product **2.112** with the formation of the 7-membered ring in 53% yield over two steps (Scheme 39).

<sup>&</sup>lt;sup>51</sup> Thomas, A. A.; Hunt, K. W.; Volgraf, M.; Watts, R. J.; Liu, X.; Vigers, G.; Smith, D.; Sammond, D.; Tang, T. P.; Rhodes, S. P.; Metcalf, A. T.; Brown, K. D.; Otten, J. N.; Burkard, M.; Cox, A. a.; Do, M. K. G.; Dutcher, D.; Rana, S.; Delisle, R. K.; Regal, K.; Wright, A. D.; Groneberg, R.; Scearce-Levie, K.; Siu, M.; Purkey, H. E.; Lyssikatos, J. P.; Gunawardana, I. W. *J. Med. Chem.* **2014**, *57*, 878–902.

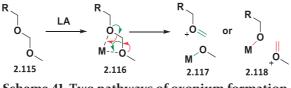
<sup>&</sup>lt;sup>52</sup> Funk, R. L.; Fitzgerald, J. F.; Olmstead, T. A.; Para, K. S.; Wos, J. A. J. Am. Chem. Soc. 1993, 115, 8849–8850.



Unfortunately, similar conditions did not give the 7-membered ring using substrate 2.90. The reaction led to the deprotected alcohol **2.113** and **2.114** (Scheme 40).

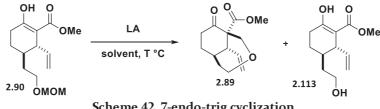


The explanation of the result can be understood as followed. Instead of forming the desired oxonium intermediate **2.117**, which could be trapped by the nucleophilic carbon of the  $\beta$ ketoester, the Lewis acid must have had coordinate with the acetal function, but the unwanted oxonium 2.118 was formed and therefore led to the observed product (Scheme 41).



Scheme 41. Two pathways of oxonium formation

A variety of Lewis acids were screened in order to achieve this intramolecular cyclization (Scheme 42) and selected results are shown in Table 5.



Scheme 42. 7-endo-trig cyclization

Entry	LA	<b>Isolated Yield</b>
1	Me <sub>2</sub> BBr	Decomposition
2	TiCl <sub>4</sub>	Deprotection
3	Al(OTf) <sub>3</sub>	Deprotection
4	TMSOTf	Decomposition
5	Ca(OTf) <sub>3</sub>	SM recovery
6	Sc(OTf) <sub>3</sub>	7%
7	FeBr <sub>3</sub>	Deprotection
8	Ga(OTf)3	Deprotection
9	$BaI_2$	SM recovery
10	$Zn(OTf)_2$	SM recovery
11	LaBr <sub>3</sub>	SM recovery
12	InCl <sub>3</sub>	Deprotection
В	GdBr <sub>3</sub>	14%
14	Yb(OTf) <sub>3</sub>	SM recovery
15	BF <sub>3</sub> •Et <sub>2</sub> O	Deprotection
16	MgBr <sub>2</sub> •Et <sub>2</sub> O	18%

Table 5. Representative conditions for the cyclization

All reactions were carried out in DCM (0.05 M) from -78 °C to rt with 1 equivalent of LA.

It is worthy to note that DCM was the solvent of choice for the first screening of Lewis acids as it was used for the model substrate and led to the desired product. A concentration of 0.05 molar and one equivalent of the Lewis acid was used. All reaction were initiated at -78 °C then the temperature was allowed to warm to room temperature while monitoring the reaction by TLC. According to the literature, dimethylboron bromide was used to cleave acetal to the desired oxonium<sup>53</sup>. Me<sub>2</sub>BBr was synthetized and tested but only decomposition was observed (entry 1). Other boron-based Lewis acids were tested upon the reaction condition, such as BCl<sub>3</sub>, BF<sub>3</sub>•Et<sub>2</sub>O but led to deprotection of the alcohol (entry 15). BF<sub>4</sub>Li and  $B(C_6F_5)_3$  led to SM recovery. Ph<sub>3</sub>CBF<sub>4</sub> decomposed quickly the substrate. Switching to aluminum-based Lewis acid showed only deprotection of the acetal protecting group when using AlCl<sub>3</sub> or Al(OTf)<sub>3</sub> (entry 3). Silicon-based Lewis acid exhibited different behaviors; when using TMSOTf, TESOTf or TBSOTf, only decomposition was observed (entry 4). However, TIPSOTf deprotected the acetal group whereas Me<sub>2</sub>SiCl<sub>2</sub> had no influence and only SM was recovered. Magnesium(II) bromide ethyl etherate complex showed promising result as the desired product was formed in 18% yield (entry 16). However, MgCl<sub>2</sub> and Mg(OTf)<sub>2</sub> had no impact on the reaction. Calcium-based Lewis acids had no effect on the substrate as CaBr<sub>2</sub>, CaCl<sub>2</sub> and Ca(OTf)<sub>2</sub> allowed us to recover the initiate substrate (entry 5). Interestingly, scandium triflate yielded the desired product in 7% yield (entry 6) but ScF<sub>3</sub> had no impact. Titanium(III) chloride deprotected the alcohol (entry 2) whereas Ti(<sup>i</sup>OPr)<sub>4</sub> had no influence on the reaction and the starting material was recovered. Iron(III) such as

<sup>53</sup> Guindon, Y.; Yoakim, C.; Morton, H. E. J. Org. Chem. 1984, 49, 3912-3920.

FeCl<sub>3</sub> and FeBr<sub>3</sub> deprotected the MOM group (entry 7) but FeBr<sub>2</sub> had no effect and only SM was recovered. Different zinc-based Lewis acids were tested (ZnBr<sub>2</sub>, ZnCl<sub>2</sub>, Zn(OTf)<sub>2</sub>) but had no impact on the substrate (entry 10). Gallium triflate and gallium(III) chloride led to deprotection. Zirconium(IV) chloride showed similar behavior. Indium(III) chloride and indium(III) bromide had the same deprotection properties (entry 12) where indium triflate exhibited destructive effect and decomposed the substrate. Not surprisingly, tin(IV) chloride acted the same. Barium(II) iodide and bismuth triflate had no effect in the reaction (entry 9). Platinum(II) chloride showed an inactivity whereas platinum(IV) decomposed the substrate. Finally, lanthanides were tested such as LaBr<sub>3</sub>, CeCl<sub>3</sub>, EuCl<sub>3</sub>, Er(OTf)<sub>3</sub>, Yb(OTf)<sub>3</sub> and Gd(OTf)<sub>3</sub> but none of them was able to form any oxonium (entries 8, 11, 14). Only gadolinium(III) bromide showed encouraging reactivity leading to the desired product in 14% yield (entry 13). Unfortunately, the results were too random to make a conclusion on the reaction.

A deeper optimization of the reaction was carried on based on the previous results (Table 6).

Entry	LA	<b>Isolated Yield</b>
1	MgBr <sub>2</sub> •Et <sub>2</sub> O	18%
2	$Mg(OEt)_2$	SM recovery
3	$Mg(ClO_4)_2$	Deprotection
4	$MgI_2$	12%
5 <sup>a</sup>	MgBr <sub>2</sub> •Et <sub>2</sub> O	SM recovery
6	MgBr <sub>2</sub> •Et <sub>2</sub> O (2 equiv)	28%
7	MgBr <sub>2</sub> •Et <sub>2</sub> O (3 equiv)	31%
8	MgBr <sub>2</sub> •Et <sub>2</sub> O (5 equiv)	14%
<b>9</b> <sup>b</sup>	MgBr <sub>2</sub> •Et <sub>2</sub> O (3 equiv)	25%
10	GdBr <sub>3</sub> (3 equiv)	34%
11	MgBr <sub>2</sub> (3 equiv)	45%
12 <sup>c</sup>	MgBr <sub>2</sub> (1.5 equiv)	48%

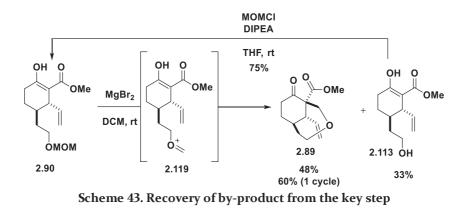
Table 6. Representative conditions with magnesium-based LA for the cyclization

All reactions were carried out in DCM (0.05 M) from -78 °C to rt with 1 equivalent of LA unless noted otherwise.

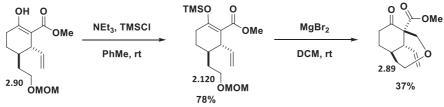
<sup>a</sup>: THF was used as solvent. <sup>b</sup>: the concentration was set at 0.25 M. <sup>c</sup>: the reaction was set up at rt.

Magnesium(II) bromide ethyl etherate seemed to be the most appropriate Lewis acid for this reaction (entry 1). Therefore, different magnesium salts were investigated.  $Mg(OEt)_2$  and  $Mg(O^tBu)_2$  had no influence on the acetal group and the substrate was recovered (entry 2).  $Mg(ClO_4)_2$  acted as deprotection reagent (entry 3). Magnesium(II) iodide allowed the formation of the cyclized product with a low 12% yield (entry 4). We then turned our attention to different solvents for the reaction. Surprisingly, running the reaction with

magnesium(II) bromide ethyl etherate in THF, Et<sub>2</sub>O, acetonitrile, EtOAc or toluene did not allow the cyclization to occur (entry 5). Only chlorinated solvent were able to carry out the reaction such as DCM, DCE or chloroform, with a better yield in DCM. The number of equivalent of the Lewis acid had an influence on the reaction outcome. Catalytic amount of Lewis acid led to traces of the cyclized product. Two equivalents of magnesium(II) bromide ethyl etherate allowed to reach 28% (entry 6) whereas 3 equivalents slightly increased the yield to a maximum of 31% (entry 7). Excess of Lewis acid was harmful for the reaction as 5 equivalents decreased the yield to 14% (entry 8). The concentration played an important role for the formation of the cyclized product. As an intramolecular reaction, we expected a low concentration to lead to a better yield. However, diluting to 0.005 molar made the reaction extremely slow. With a concentration of 0.01 molar, the reaction was still not reaching full conversion after 3 days. Increasing the molarity to 0.25 reduced the yield to 25% (entry 9). The concentration of the reaction was fixed at 0.05 molar as it was observed to give us the best yield so far. However, after changing the concentration of the reaction, the amount of Lewis acid used and the solvents, the yield was not able to go higher than 31%. The same observation was made with gadolinium(III) bromide, for which the maximum yield obtained was 34% with the best parameters (entry 10). After careful thinking of the Lewis acid used and the incompatibility with some solvent such as Et<sub>2</sub>O, we decided to change the Lewis acid to magnesium(II) bromide, removing the ethyl etherate from the reaction media. This subtle change increased substantially the yield of the desired product to 45% (entry 11). Decreasing to 1.5 equivalents of MgBr<sub>2</sub> allowed to reach 48% for this unprecedented reaction (entry 12). Studying the temperature allowed us to run the reaction at room temperature without change of the yield. Finally, additives such as Cs<sub>2</sub>CO<sub>3</sub> or NEt<sub>3</sub> were added, but none of them had a positive impact on the reaction.



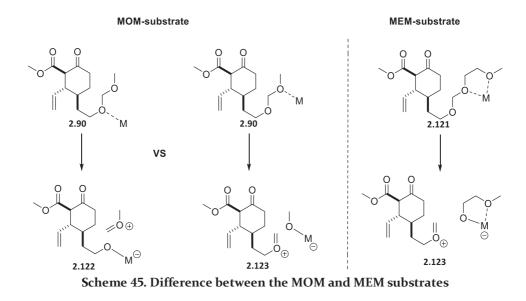
When performing the reaction on a gram-scale, the yield was reproducible and 33% of the deprotected alcohol was recovered. It can be easily converted to the precursor of the key step in one step upon MOM protection in THF (Scheme 43). Hence, upon one recovery cycle the yield of **2.89** reaches 60%.



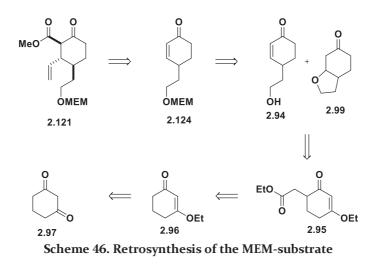
Scheme 44. Synthesis of silyl enol ether and its cyclization

The silyl enol ether substrate was synthesized from the  $\beta$ -ketoester **2.90** (Scheme 44) and some conditions were tested to study the differences that might arise from the presence of the silyl group. TMS-protection of the enol in THF or Et<sub>2</sub>O was very slow whereas using toluene for the reaction provided the silyl enol ether is good yield. Submitting the new substrate to the best conditions using selected Lewis acids did not improve the yield of the reaction but afforded the product in 37% yield, in the case of MgBr<sub>2</sub>.

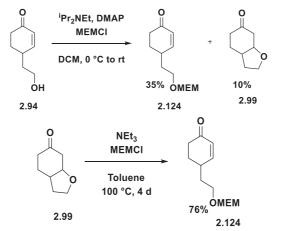
We thought to be able to improve the yield of the reaction by changing the acetal functionality of the substrate. As shown in Scheme 45, the MEM-substrate might give better results than the MOM-substrate. Indeed, with the MOM-substrate, the metal can coordinate on two different sites of the acetal without any preference. When the metal binds to the internal oxygen (Scheme 45, left), the MOM group gets deprotected. However, when the metal binds to the external oxygen (Scheme 45, right), the desired oxonium **2.123** is formed and can be trapped by the nucleophilic carbon of the  $\beta$ -ketoester moiety. On the other hand, using the MEM-substrate would prearrange the Lewis acid in a 5-membered metallacycle, which would result in the formation of the desired oxonium only.



Therefore, the new substrate was prepared according to the previous synthesis of the MOM-substrate (Scheme 46).

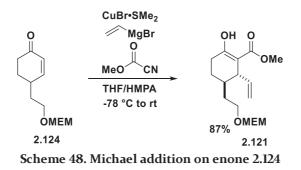


Following the same procedures until the mixture of free alcohol **2.94** and bicycle **2.99**, we were then able to protect the alcohol with the help of catalytic amount of DMAP, but only in moderate yield. In comparison to the protection using MOMCl, DCM proved to be a better solvent for the reaction. However, the intramolecular cyclization could not be prevented. Opening of the bicycle **2.99** followed by direct protection of the primary alcohol was achieved in refluxed toluene for four days with excess of NEt<sub>3</sub> and MEMCl in good yield (Scheme 47).

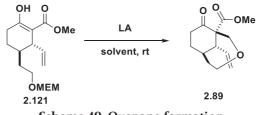


Scheme 47. Protection of alcohol 2.94 and opening of bicycle 2.99

The new substrate **2.124** was used for the Michael addition/trapping with Mander's ester sequence. Under the same conditions previously developed, the reaction proceeded with a slightly higher yield (Scheme 48).



The best conditions for the MOM-substrate were applied to the MEM-substrate and surprisingly, no reaction was observed. Changing the solvent to DCE, chloroform, EtOAc or toluene gave the same outcome. We then submit  $\beta$ -ketoester **2.124** to a variety of Lewis acid to study its reactivity for the formation of the 7-membered ring (Scheme 49). Based on the previous work done on the MOM-substrate, a selected amount of Lewis acids were tested. Some representative Lewis acids are shown in Table 7.



Scheme 49. Oxepane formation

Entry	LA	Isolated Yield
1 MgBr <sub>2</sub>		SM recovery
2	MCl <sub>2</sub>	SM recovery
3	$MgI_2$	SM recovery
4	TiCl <sub>4</sub>	Deprotection
5	Al(OTf) <sub>3</sub>	4%
6	Ca(OTf) <sub>3</sub>	SM recovery
7	Sc(OTf) <sub>3</sub>	18%
8	FeBr <sub>3</sub>	5%
9	Ga(Cl) <sub>3</sub>	Deprotection
10	$BaI_2$	SM recovery
11	$Zn(OTf)_2$	SM recovery
12	LaBr <sub>3</sub>	SM recovery
В	InCl <sub>3</sub>	4%
14	GdBr <sub>3</sub>	6%
15	Yb(OTf) <sub>3</sub>	SM recovery

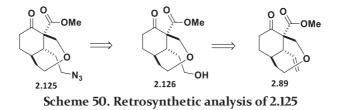
Table 7 - Representative conditions for the cyclization

All reactions were carried out in DCM (0.05 M) at rt with 2 equivalents of LA.

All magnesium-based Lewis acids (MgBr<sub>2</sub>, MgCl<sub>2</sub>, MgI<sub>2</sub>, Mg(OTf)<sub>2</sub>, Mg(O<sup>t</sup>Bu)<sub>2</sub> and Mg(OEt)<sub>2</sub>) had no influence on the MEM group. Unlike the MOM-substrate, Al(OTf)<sub>3</sub>, InCl<sub>3</sub> and FeBr<sub>3</sub>, which deprotected the acetal moiety, promoted the cyclization in 4%, 4% and 5% yield, respectively. Indium(III) bromide allowed to deprotect the MEM group but indium triflate completely decomposed the mixture. Iron(II) bromide did not play any role in the reaction such as Ca(II) chloride, Ca(II) bromide and calcium triflate. Scandium triflate gave a promising 18% isolated yield but no reactivity was observed when using Sc(III) fluoride. Titanium(IV) chloride cleanly deprotected the MEM group whereas Ti(O<sup>i</sup>Pr)<sub>4</sub> allowed to recover the starting material. A vast variety of zinc based and lanthanides Lewis acids were tested but no reaction was observed with our substrate. Only gadolinium(III) bromide afforded the cyclized product in 6% isolated yield.

After the first screening, a few conditions gave the cyclized product but only in trace amount. The only promising Lewis acid that was investigated was scandium(III) triflate. After a quick optimization, we were able to increase the yield of the reaction from 18% to 28% when using 3 equivalents of the Lewis acid.

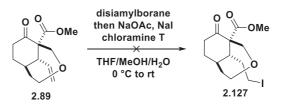
2.4.4. Functionalization of the Vinyl



The initial functional group interconversion strategy we had in mind, to get the terminal protected amine from a two carbon unit, was a hydroboration-oxidation, tosylation, azidation sequence (Scheme 50). The two first steps could also be combined in a one-pot hydroboration-iodination.<sup>54</sup>

#### 2.4.4.1. Hydroborations

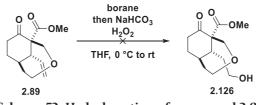
The shorter route was investigated (Scheme 51). Disiamylborane was *in situ* prepared by dropwise addition of 2-methyl-2-butene in a solution of BH<sub>3</sub> in THF. Unfortunately, no reaction was observed upon addition up to five equivalents of the borane to the substrate **2.89**. Intensive screening was made on this reaction varying the number of equivalents of the borane, the concentration and the solvents, but the desired product **2.127** was never observed.



Scheme 51. Hydroboration/iodination sequence

<sup>54</sup> Kabalka, G. W.; Gooch, E. E. J. Org. Chem. 1981, 46, 2582-2584.

We turned our attention to the hydroboration-oxidation sequence which should lead to the alcohol (Scheme 52). To do so, different boranes were tested and some results are shown in Table 8.



Scheme 52. Hydroboration of compound 2.89

Entry	Conditions <sup>1</sup>	Remarks	
1	9-BBN	SM recovery	
2	Dicyclohexylborane	Decomposition	
3	$HB(C_6F_5)_2$	Decomposition	
4	BH3•THF	Ketone reduced	
5	BH <sub>3</sub> •DMS	Decomposition	
<b>6</b> <sup>a</sup>	9-BBN	Ketone reduced	
7 <sup>a</sup> BH <sub>3</sub> •THF		Decomposition	
8 <sup>b</sup> Disiamylborane		SM recovery	
1			

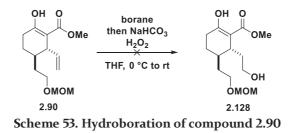
Table 8. Representative conditions for the hydroboration

<sup>1</sup>: All reactions were carried out in THF from 0 °C to rt with 2 equivalents of the borane.

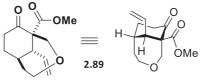
<sup>a</sup>: 5 equivalents were used. <sup>b</sup>: 12 equivalents were used.

Hydroboration using commercially available 9-BBN did not happen (entry 1) and when adding excess of the reagent, we observed a reduction of the ketone but the alkene stayed intact (entry 6). Dicyclohexylborane was extremely reactive and decomposed quickly the substrate (entry 2). As expected, the solution of borane in THF reduced the ketone prior hydroboration of the alkene (entry 4). Hoping to get a clean conversion to the diol when adding excess of borane, the outcome was different and only decomposition was observed (entry 7). Solution of borane in DMS led to complete decomposition (entry 5). The last attempt was made using an excess of disiamylborane but only starting material was recovered (entry 8). It is important to mention that when using sodium hydroxide as a base for the oxidation, it hydrolyzes the ester moiety, hence the choice of sodium bicarbonate, a milder base. Sodium perborate was also tested instead of hydrogen peroxide for the oxidation, but without success as it decomposed the substrate.

After many failures, we turned our attention to a rhodium-catalyzed method in order to increase the reactivity of the hydroboration reagents.<sup>55</sup> Using Wilkinson's catalyst, neither 9-BBN, catechol borane nor pinacol borane formed the desired alcohol **2.126** but traces of the reduction of the ketone was observed. Hydroborations on the  $\beta$ -ketoester substrate **2.90** were also tried (Scheme 53).



9-BBN had no reactivity whereas  $BH_3$  in THF reduced the ketone as observed for the previous substrate.

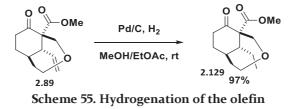


Scheme 54. 3D structure of 2.89

The unreactivity of the olefin is unexpected as it is not hindered by the 7-membered ring nor the ester group (Scheme 54).

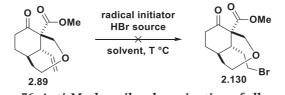
# 2.4.4.2. Other Functionalizations

To understand more about the reactivity of the double bond, a test reaction was performed (Scheme 55).



<sup>&</sup>lt;sup>55</sup> Evans, D. A.; Fu G. C. J. Am. Chem. Soc. **1992**, 114, 4667–4671.

Hydrogenation of **2.89** proceeded smoothly to afford the reduced product **2.129** in a quantitative yield. Functionalization of the olefin **2.89** is therefore doable, but for some unclear reasons, the hydroboration did not work with our substrate. With this new promising result, our effort were heading towards another approach to functionalize the alkene.



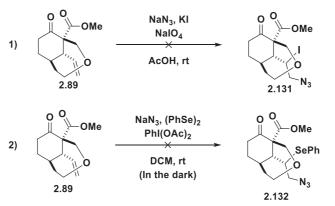
Scheme 56. Anti-Markovnikov bromination of alkene 2.89

Addition of an inorganic acid on an olefin is known to follow the Markovnikov's rule and ends up with the halide in the most substituted position. However, in some conditions, the anti-Markovnikov product is observed. This transformation is also known under the name of Kharasch reaction and goes via a radical mechanism,<sup>56</sup> which can explain the different regioselectivity (Scheme 56).<sup>57</sup> Aqueous HBr was used in presence of sulfuric acid and dibenzoyl peroxide in pentane, but no reaction was observed. Gaseous HBr was prepared mixing triphenylphosphine in aqueous HBr. The salt was used to release HBr upon heating in toluene, however, no reaction was observed even at reflux. Generation of the bromide radical using light was not successful neither. Different radical initiator were tested. Dilauroyl peroxide in benzene at 60 °C led quickly to decomposition whereas in DCE at 50 °C, only starting material was recovered. The same observation was made when using (PhCO)<sub>2</sub>. Surprisingly, no reaction was initiated by AIBN using different solvents and temperature.

Direct conversion from the alkene to the primary azide was envisioned as shown in Scheme 57.

<sup>&</sup>lt;sup>56</sup> Kharasch, M. S.; Engelmann, H.; Mayo, F. R. J. Org. Chem. 1937, 2, 288–302.

<sup>&</sup>lt;sup>57</sup> Kharasch, M. S.; Jensen, E. V; Urry, W. H. Science **1945**, 102, 128.

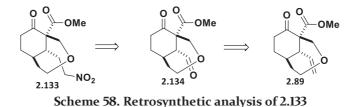


Scheme 57. Azidoiodination (top) and azidoselenation (bottom) of alkene 2.89

Azidoiodination was tested on alkene **2.89** but rapid decomposition was observed. Moving on with azidoselenation did not lead to the desired compound as no reaction was initiated by the reagents.

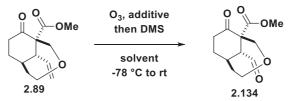
# 2.4.4.3. New Pathway via Oxidative Cleavage

We decided to follow a new pathway towards the functionalization of the olefin **2.89** (Scheme 58).



Ozonolysis of the double bond should lead to the aldehyde **2.134**. Treatment of the latter with nitromethane, also known as Henry reaction, followed by elimination of the alcohol should form the desired nitro-intermediate **2.133** after hydrogenation of the so-formed double bond.

Starting with the oxidative cleavage, some conditions were tested to afford the desired aldehyde **2.134** (Scheme 59).



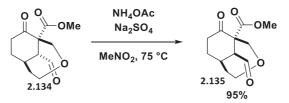
Scheme 59. Ozonolysis of the terminal alkene

Entry	Additive	Solvent	Remark
1	-	DCM/MeOH (1:1)	Messy
2	NaHCO <sub>3</sub>	DCM/MeOH (1:1)	Decomposition
3	-	DCM	94%
4	NaHCO <sub>3</sub>	DCM	42%

Table 9. Representative conditions for the ozonolysis

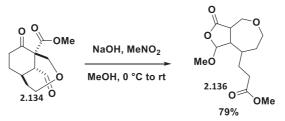
Simple oxidation using ozone in a 1 to 1 ratio of DCM-MeOH following by reduction with DMS gave a very complex mixture (entry 1). When using sodium bicarbonate as additive, complete decomposition was observed (entry 2). Solvent had a strong influence to the reaction as removing the methanol allowed to obtain the desired aldehyde **2.134** in 94% (entry 3). Adding the base as additive dropped the yield by half (entry 4).

The next step is the introduction of the nitrogen containing moiety. Different conditions for the Henry reaction were tried starting with the one showed below (Scheme 60).



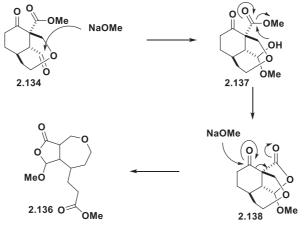
Scheme 60. Standard conditions for the Henry reaction

The outcome of the reaction was feared, as the aldehyde is enolizable. Ammonium acetate is basic enough to deprotonate in  $\alpha$  of the aldehyde and after protonation, the epimer **2.135** was observed. Several organic bases, such as pyridine, imidazole, DMAP, DIPEA were tested in DCM and THF but all gave the epimerization product or a complex mixture of products. Inorganic bases, such as cesium or potassium carbonate, did not form the desired product. Stronger base as potassium *tert*-butoxide led to decomposition. An interesting result was observed when using sodium hydroxide in methanol (Scheme 61).



Scheme 61. Unexpected reaction with NaOH and MeOH

Compound **2.B6** was formed in good yield and its structure was interesting. The formation of the lactone was unexpected and the following mechanism is proposed (Scheme 62).

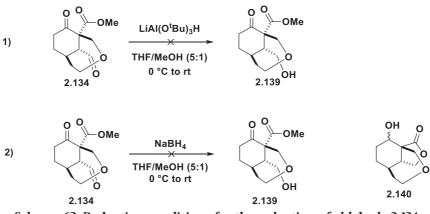


Scheme 62. Proposed mechanism for the formation of 2.136

We believe that sodium hydroxide promoted the formation of the hemiacetal **2.137** which underwent an intramolecular lactonization leading to tricyclic intermediate **2.138**. A retro-Dieckmann condensation of **2.138** afforded lactone **2.136**.

Running the reaction using other base-compatible solvents gave the same observation as previously, only the epimer was isolated. Finally, removing the base from the reagents led to no reaction and aldehyde **2.134** was recovered. Based on the previous experiments, we understood the sensitivity of the aldehyde towards base and did not pursue any base-induced reaction.

With the remaining aldehyde in hands, and as scientific curiosity, we submitted it to reductive conditions to study its behavior (Scheme 63).

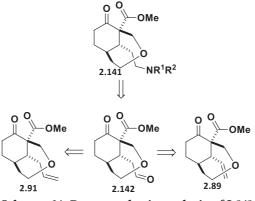


Scheme 63. Reduction conditions for the reduction of aldehyde 2.134

In the first equation, reduction using lithium tri-*tert*-butoxyaluminum hydride gave a messy reaction and nothing could get isolated from the mixture. However, using sodium borohydride as reducing agent, aldehyde **2.134** was reduced to the corresponding alcohol **2.139** and underwent direct intramolecular lactonization forming a  $\gamma$ -lactone. Moreover, some remaining hydrides were able to reduce the ketone to the corresponding secondary alcohol **2.140**.

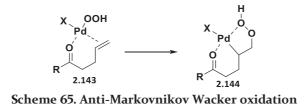
#### 2.4.4.4. New Pathway via anti-Markovnikov Oxidation

A new pathway to get to amine 2.141 from alkene 2.89 or 2.91 was pursued (Scheme 64).

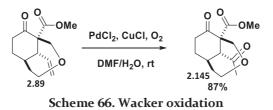


Scheme 64. Retrosynthetic analysis of 2.141

The nitrogen containing molecule **2.141** could be formed from the reduction of the *in situ* generated imine (or iminium) which could be obtained from the corresponding aldehyde **2.142**. The latter could be obtain by either oxidative cleavage of the alkene **2.91** or from oxidation of the alkene **2.89**.



We also examined the Wacker oxidation of compound **2.89**.<sup>58</sup> According to the literature, with some specific substrate and conditions, the anti-Markovnikov product can be observed.<sup>59</sup> Palladium can coordinate to a neighbor ketone which direct the insertion of the metal on the more substituted carbon of the olefin and yield to the corresponding aldehyde (Scheme 65).<sup>60</sup>



Unfortunately, the oxidation followed the Markovnikov's rule with our substrate and led to the corresponding ketone **2.145** (Scheme 66). Changing the solvent system and the palladium source to Pd(MeCN)<sub>2</sub>Cl<sub>2</sub> had no influence and the ketone was always isolated.

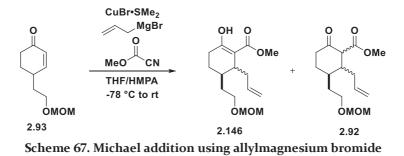
2.4.5. Few Steps Back: Michael Addition Using Allylmagnesium Bromide

As the vinyl moiety caused us some trouble for the functionalization, we decided to go a couple of steps back in the synthesis and study the 1,4-addition of an allyl moiety, which upon ozonolysis, should give the wanted intermediate as shown in Scheme 64. Using the previous optimized conditions for the Michael addition of the vinyl moiety, the outcome of the reaction was complex (Scheme 67).

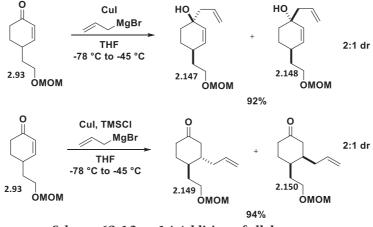
<sup>&</sup>lt;sup>58</sup> Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Ruttinger, R.; Kojer, H. Angew. Chem. 1959, 71, 176.

<sup>&</sup>lt;sup>59</sup> Dong, J. J.; Browne, W. R.; Feringa, B. L. Angew. Chem. Int. Ed. 2015, 54, 734-744.

<sup>&</sup>lt;sup>60</sup> Hosokawa, T.; Aoki, S.; Takano, M.; Nakahira, T.; Yoshida, Y.; Murahashi, S. J. Chem. Soc., Chem. Commun. **1991**, 1559–1560.



Although, the 1,4-addition product was observed, some diastereoisomers and regioisomers were present, which made the reaction too complicated to study. Indeed, up to six products could be formed in the reaction mixture. In order to understand in more details the reaction, the Michael addition was investigated (Scheme 68).



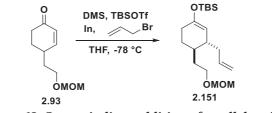
Scheme 68. 1,2- vs 1,4-Addition of allyl cuprate

So far, a lot of work has been done using different conditions for the formation of the allyl cuprate, as well as changing several parameters such as the order of the cuprate, the temperature, additives, solvent and co-solvent. Unfortunately, the 1,4-addition of the allyl moiety did not proceed with a high diastereoselectivity (2:1 ratio). Moreover, another difficulty arose with the allyl addition; the chemoselectivity. Upon different conditions, the 1,2-addition was also observed, with its two diastereoisomers. From the many experiments performed to understand the addition, the following points can be concluded. The copper-catalyzed reaction did not lead to any product, only the starting material was recovered. HMPA slowed down the reaction rate of the 1,4-addition. TMSCl played a crucial role for the 1,2- *vs* 1,4-selectivity. When the TMSCl was added to the reaction mixture, the conjugated addition was observed whereas without the additive, only the 1,2-addition was observed, even at -78 °C. Lithium chloride increased the cuprate species solubility in THF

but usually led to messy reactions. No great differences were noticeable between CuBr and CuI, however, CuCN led mostly to the 1,2-addition. Keeping the temperature at -78 °C did not change the selectivity compared to the cases in which the media was warmed to -45 °C.

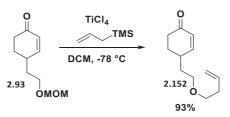
First order, second order or higher order cuprates did not change the ratio of the cis or trans product in the 1,4-addition. Finally, we believed that the trans product of the conjugated addition could come from the 1,2-addition through an anionic Oxy-Cope rearrangement.<sup>61</sup> The mixture of diastereoisomers from the 1,2-addition were submitted to one equivalent of allylmagnesium bromide, which acted as the base. No reaction was detected, therefore, no 1,4-addition product was isolated. This indicates that the rearrangement was not the explanation of the bad selectivity as, to our knowledge, copper had never been used for such transformation.

As only a few reports can be found in the literature for a 1,4-addition with allylcuprate, we turned our attention to organoindium reagent (Scheme 69).



Scheme 69. Organoindium addition of an allyl moiety

Allylindium bromide was prepared *in situ* in the presence of DMS and TBSOTf, but no reaction was observed. The Hosomi-Sakurai reaction was the next choice for this transformation (Scheme 70).

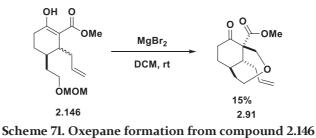


Scheme 70. Hosomi-Sakurai type reaction

<sup>&</sup>lt;sup>61</sup> Berson, J. A.; Jones, M. J. Am. Chem. Soc. 1964, 86, 5019–5020.

The Lewis acid did not only generate the nucleophilic allyl, but it also formed the oxonium species from the acetal. The result of the experiment was straightforward and led to **2.152** is excellent yield. No difference was observed when changing the order of addition of the reagents.

Although no conditions were found for a clean formation of the desired Michael adduct, the following cyclization was performed with the mixture of diastereoisomers (Scheme 71).

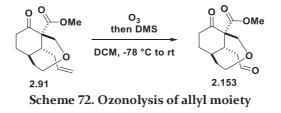


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Submitting substrate **2.146** to the previous optimized conditions with the vinyl moiety, the intramolecular cyclization proceeded and bicycle **2.91** was formed in 15% yield.

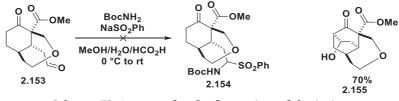
2.4.6. Functionalization of the Allyl

Oxidative cleavage of the alkene was performed (Scheme 72).



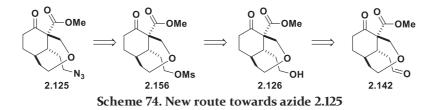
Ozonolysis of the double bond was achieved using dimethyl sulfide as reducing agent in DCM in good yield. Purification of the aldehyde **2.153** failed, therefore the crude was used for the next step.

Reductive amination was envisioned as good opportunity to introduce the *N*-containing moiety to the substrate. Hence, crude aldehyde **2.153** was treated with BocNH<sub>2</sub> and NaSO<sub>2</sub>Ph under mild conditions (Scheme 73).

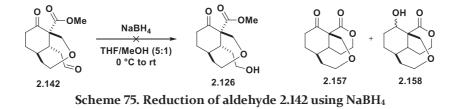


Scheme 73. Attempt for the formation of the imine.

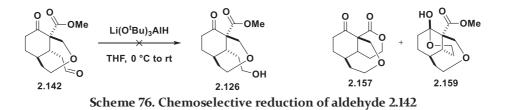
The imine precursor **2.154** was not formed and we believe that the sulfinate deprotonated in  $\alpha$  to the ketone and promoted an intramolecular aldolization to afford **2.155** in 70% yield. From our understanding of the sensitivity of aldehyde **2.153**, we envisioned a new route to introduce the nitrogen moiety (Scheme 74).



Reduction of the aldehyde should afford the corresponding alcohol, which upon mesylation becomes a good leaving group. Substitution with an azide source should provide compound **2.125**.



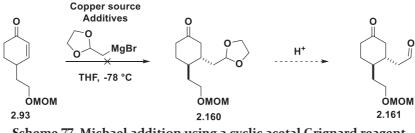
Reduction of aldehyde **2.152** using sodium borohydride in a mixture of THF and MeOH did not afford the desired alcohol **2.126**, but a mixture of lactones **2.157** and **2.158**, which shows over reduction of the ketone. As the number of equivalent of hydrides available is always difficult to predict when using NaBH<sub>4</sub>, another reducing agent was tested (Scheme 76).



Lithium tri-*tert*-butoxy aluminium hydride was used for two mains reasons. The first one is its facility to control the equivalent of hydride engaged in the reaction. Secondly, with its three bulky *tert*-butoxide groups, the hydride will only reduce the less hindered functional group available. As expected, the reduction was chemoselective, but intramolecular lactonization could not be prevented. Moreover, traces of hemiketal **2.159** was observed.

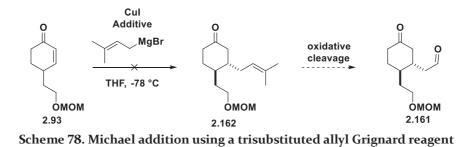
2.4.7. Few Steps Back: Michael Addition Using Different Grignard Reagents

Michael addition using an allyl moiety proved to be troublesome, we hence studied the 1,4-addition of different partners as shown below.



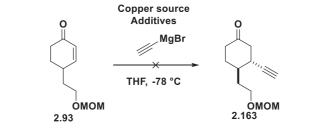
Scheme 77. Michael addition using a cyclic acetal Grignard reagent

Conjugate addition of the cuprate species to the enone **2.93** should lead to compound **2.160**. After hydrolysis of the cyclic acetal, the aldehyde **2.161** could be obtained (Scheme 77). Unfortunately, varying the source of copper, the order of the cuprate and addition of various additives were not enough and only traces amount of the product **2.160** was observed.



Cuprate addition of the dimethyl allyl moiety was tested which upon oxidative cleavage should afford the same aldehyde **2.161**. We were not able to make any type of reaction as only starting material was recovered, with or without the presence of TMSCl.

The last conjugated addition we evaluated as interesting for the synthesis was the alkyne cuprate (Scheme 79).

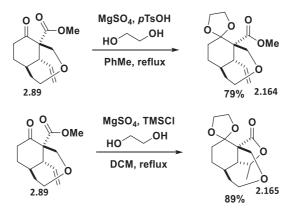


Scheme 79. Michael addition using alkyne Grignard reagent

Investigations towards the 1,4-addition of alkyne cuprate was not conclusive neither as only starting material was recovered. First order and higher order cuprate were formed but without any reactivity on enone **2.93**, even when activated by TMSCI.

#### 2.4.8. Protection of the Ketone

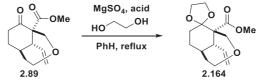
As it is known that boron has a high affinity with oxygen, we believed that the borane could coordinate with the  $\beta$ -ketoester moiety of **2.89**, creating a steric hindrance around the alkene. To prevent this binding, which could explain the low reactivity of the double bond, protection of the ketone was investigated (Scheme 80).



Scheme 80. Protection of ketone 2.89 and hydroboration

Ketal formation using ethylene glycol and *p*-toluenesulfonic acid afforded the desired product **2.164** in moderate yield. Surprisingly, the use of TMSCl as additive led to unexpected compound **2.165** in good yield. Traces of HCl might have formed *in situ* the secondary carbocation which was trapped by the ester.

Different conditions were tried to increase the yield of the ketal formation. Changing the solvent to benzene would allow the azeotropic mixture to be heated at a lower temperature to remove water and push the equilibrium towards the product (Scheme 81).



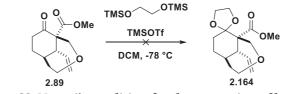
Scheme 81. Ketal formation from ketone 2.89

Table 10. Summary of the conditions for the protection of 2.89

Entry	Acid	Yield
1	рТsOH	71%
2	PPTS	Messy

In comparison with toluene, benzene afforded to desired ketal **2.164** in slightly lower yield (entry 1). Pyridinium *p*-toluenesulfonate is a weaker acid and was thought to prevent partial decomposition. Unfortunately, PPTS led to a messy reaction (entry 2).

Noyori's protocol was studied as it requires much milder conditions (Scheme 82)<sup>62</sup>.

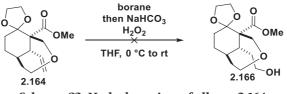


Scheme 82. Noyori's condition for the protection of ketone 2.89

When keeping the temperature at -78 °C, no reaction was observed. Rising up the temperature until 0 °C allowed only little conversion towards ketal **2.164**. Heating to reflux decomposed rapidly the substrate. In order to accelerate the speed of the reaction, excess of alkoxysilane was added, but the outcome was messier. Dropwise addition of alkoxysilane at -78 °C led to very slow conversion. The same observations were made when using THF instead of DCM.

2.4.9. Functionalization of the Olefin

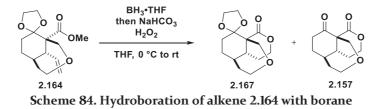
Hydroboration conditions were again tested with the new substrate 2.164 (Scheme 83).



Scheme 83. Hydroboration of alkene 2.164

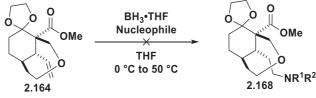
Starting with 9-BBN, no conversion towards any product was observed, no matter how many equivalents of reagent was added. When heating the reaction mixture, the same observation was made with degradation of the substrate near the reflux temperature of the solvent. We hypothesized that 9-BBN might be too bulky for the substrate. As no other functional group should be reduced than the alkene at room temperature and because of the steric hindrance issues encountered, BH<sub>3</sub> in THF was our next choice. We performed the reaction using only one equivalent, but no reaction was observed. A large excess of borane, 10 equivalents, was needed to see small conversion to a new product, but another problem has arisen. Under those conditions, intramolecular lactonization led to **2.167** with partial deprotection of the ketal **2.157** (Scheme 84).

<sup>62</sup> Tsunoda, T.; Suzuki, M.; Noyori, R. Tetrahedron Lett. 1980, 21, 1357.



Attempts to avoid the lactonization were explored. Different bases (NaOH, Na<sub>2</sub>CO<sub>3</sub>) and the use of a buffer to regulate the pH of the solution were tried without success, only complex mixtures were isolated. Sodium perborate as substitute for hydrogen peroxide for the oxidation step was tested but decomposition was observed.

In order to prevent the cyclization to happen, the formation of the free alcohol has to be avoided. We looked into methods to directly convert an alkene to the corresponding amine or azide following the anti-Markovnikov rule. The first type of reaction we investigated were hydroaminations, using a nucleophilic amine or azide (Scheme 85).



Scheme 85. Hydroamination of alkene 2.164

Entry	Nucleophile	Additive	Remark
1	H <sub>2</sub> NOSO <sub>3</sub> H	-	Decomposition
2	MeHNOSO <sub>3</sub> H	-	Decomposition
3	NaN <sub>3</sub>	-	Decomposition
4	NaN <sub>3</sub>	1 M HCl	Decomposition

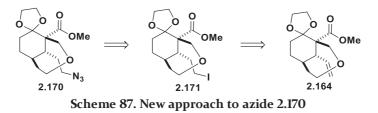
High temperatures are often needed for the hydroamination to proceed, which in our case, is harmful for the intermediate which decomposed at elevated temperatures, no matter which nucleophile was used.

Hydrozirconation of alkene using the Schwartz reagent is known to follow the unconventional regioselectivity towards the less substituted carbon. Following Hartwig's work on one-pot hydrozirconation and amination, we submitted our substrate to the new conditions as shown in Scheme 86.<sup>63</sup>



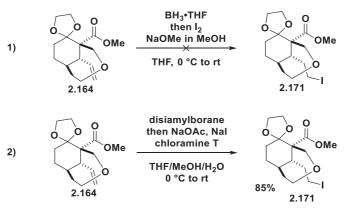
Insertion of the zirconium to the double bond was never observed. Indeed, Submitting alkene **2.164** to the Schwartz reagent in THF or DCM at different range of temperature had no influence, only the starting material was recovered.

After many failures, we decided to explore a new pathway (Scheme 87).



Azide **2.170** can be obtained by substitution of the corresponding iodoalkane **2.171** with an azide source. Different methods have to be tested for the functionalization of the alkene to the anti-Markovnikov addition of iodide (Scheme 88).

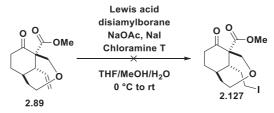
<sup>63</sup> Strom, A. E.; Hartwig, J. F. J. Org. Chem. 2013, 78, 8909-8914.



Scheme 88. Hydroboration/iodination sequence of alkene 2.164

The first reaction, using a solution of BH<sub>3</sub> in THF followed by addition of iodine and sodium methoxide, led to a complex mixture with a major decomposition of the substrate. Changing the borane source to the *in situ* generated disiamylborane followed by oxidation of the intermediate with chloramine T allowed for the first time the formation of the iodoalkane **2.171** in a moderate 35% isolated yield. Fine tuning of the reaction conditions allowed to reach 85% using 20 equivalents of the borane.

We hypothesized that the borane might coordinate on the  $\beta$ -ketoester moiety, creating a bulky environment around the double bond, which might explain the lack of reactivity of the alkene. Protection of the ketone to the corresponding ketal solved the problem but added two more steps to the synthesis. To test our hypothesis, we investigated the behavior of the addition of one equivalent of a small Lewis acid. Indeed, we believed the latter would coordinate to the  $\beta$ -ketoester moiety, leaving the alkene free of steric hindrance for the hydroboration (Scheme 89).



Scheme 89. Hydroboration/iodination using LA

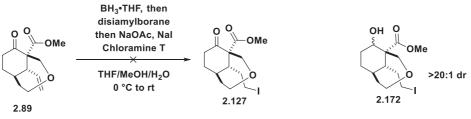
Entry	Lewis acid	Remark <sup>1</sup>
1		SM
1	BF <sub>3</sub> •OEt	(Decomposition)
2	TMSOTf	Decomposition
3	TiCl <sub>4</sub>	Decomposition
4	AuCl	Decomposition
5	AuCl <sub>3</sub>	Decomposition
<b>6</b> <sup>a</sup>	BEt <sub>3</sub>	SM (Messy)
7 <sup>a</sup>	Et <sub>2</sub> BOMe	SM (Messy)
8	B(OMe) <sub>3</sub>	Decomposition
9	BH <sub>3</sub> •THF	New product

Table 12. Representative conditions for the hydroboration/iodination sequence

 $^{\rm l}:$  All reactions were performed in DCM and THF at 0 °C and the Lewis acid was stirred for 15 min before addition of the disiamylborane

<sup>a</sup>: The Lewis acid was stirred for 1h at rt before addition of the disiamylborane at 0 °C.

A variety of small Lewis acid were tried in the reaction, but most of them led to decomposition or no reaction. On the other hand, using BH<sub>3</sub> in THF, a new product was formed, but isolation failed. A series of reactions were performed using borane as Lewis acid (Scheme 90).



Scheme 90. Hydroboration/iodination sequence using borane

We discovered that adding one equivalent of borane followed by the hydroboration/iodination sequence led to alcohol 2.172 in around 20% conversion. When adding the borane at -78 °C, traces of alcohol 2.172 was observed. Running the reaction at 0 °C seemed more appropriated. Disiamylborane has to be added very quickly after addition of the Lewis acid as only five minutes can go from 20% conversion to decomposition. The order of addition between the Lewis acid and the disiamylborane has to impact on the reaction. BH<sub>3</sub>•DMS was tested but only decomposition was observed. As the iodo substrate 2.127 could never be purified, the crude was submitted to the next step without further purification (Scheme 91).

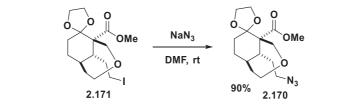


Scheme 91. Substitution using sodium azide

The nucleophilic substitution of the iodide to the azide was tested, but it appeared that the alcohol **2.172** is even more unstable than its oxidized form. Under various temperatures, the azide **2.173** was never obtained.

#### 2.4.10.Late Stage Synthesis

After many failed attempts, we came back to our previous strategy using ketal **2.171**. Subsequent substitution of the iodide to the corresponding azide is described below (Scheme 92).



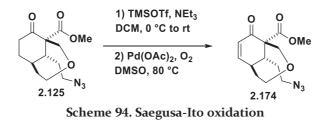
Scheme 92. Hydroboration/iodination sequence from cyclic ketal 2.171

For the first time, sodium azide in DMF afforded the desired azide **2.170** in 65% yield. It is important to mention that a purification of iodoalkane **2.171** has to be performed to remove the excess of chloramine T otherwise the following substitution becomes very messy, even with a large excess of sodium azide. However, the iodoalkane **2.171** has proven to be unstable over time. The yield of the substitution varied at first, but with the information we learned from this compound, we were able to increase the yield of the azide **2.170** up to 90%. Attempts for the one-pot hydroboration/iodination/azidation sequence were performed without success.

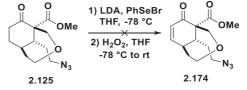
Next, the deprotection of the ketal group was studied (Scheme 93).



When submitting ketal **2.170** to an aqueous solution of hydrochloric acid, hydrolysis of the protecting group to the corresponding ketone **2.125** was obtained in high yield. The next step of the synthesis is the oxidation of the ketone **2.125** to the enone **2.174**.



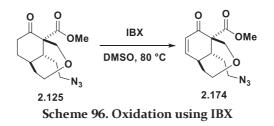
The Saegusa-Ito oxidation was the first reaction of choice (Scheme 94).<sup>64</sup> Formation of silyl enol ether followed by palladium insertion,  $\beta$ -hydride elimination afforded a complex mixture. After several trials, the desired enone **2.174** was isolated in 40% yield. The yield of the reaction was not satisfactory, hence a different reaction was investigated (Scheme 95).



Scheme 95. Oxidation of selenylated intermediate

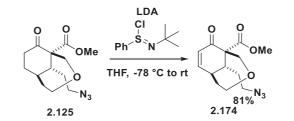
 $\alpha$ -selenylation of the ketone followed by oxidation should promote the elimination of the selenoxide allowing the formation of enone **2.174**. However, with our substrate, the reaction led to a messy mixture and the enone **2.174** was not observed. Isolation of the selenylated intermediate was attempted without success.

<sup>64</sup> Ito, Y.; Hirao, T.; Saegusa, T. J. Org. Chem. 1978, 43, 1011-1013.



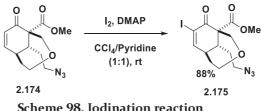
Hypervalent iodine, such as IBX, is known to oxidize ketones to the corresponding enones (Scheme 96). Submitting our ketone 2.125 to an excess of IBX produced only 4% of the corresponding enone 2.174. NMO in combination with IBX was reported to improve the yield of the oxidation but led to the formation of only 10% of the desired product.<sup>65</sup>

An unusual dehydrogenation of ketones was reported in 2000 by Mukaiyama.<sup>66</sup> Enolate formation followed by addition of *N-tert*-butyl phenylsulfinimidoyl chloride as electrophile is performed at low temperature. Thermal decomposition afforded the desired enone 2.174 in 81% yield (Scheme 97).



Scheme 97. Oxidation of 2.125 to the corresponding enone

The nitro aryl moiety was envisioned to be installed through a Suzuki cross coupling reaction. To be able to perform the coupling,  $\alpha$ -iodination of the enone was investigated (Scheme 98).



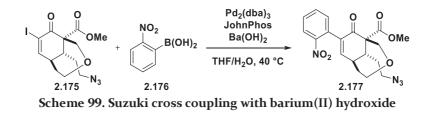
Scheme 98. Iodination reaction

<sup>65</sup> Shi, H.; Fang, L.; Tan, C.; Shi, L.; Zhang, W.; Li, C. C.; Luo, T.; Yang, Z. J. Am. Chem. Soc. 2011, 133 (38), 14944-14947.

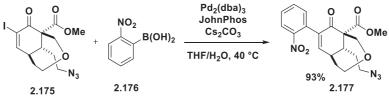
<sup>66</sup> Mukaiyama, T.; Matsuo, J.; Kitagawa, H. Chem. Lett. 2000, 29 (11), 1250-1251.

Iodination using iodine and DMAP as catalyst in a mixture of carbon tetrachloride and pyridine allowed the formation of the vinyl iodide **2.175** in good yield.

The Suzuki cross coupling was studied and standard conditions were tried first (Scheme 99).



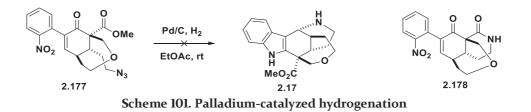
With commercially available boronic acid **2.176**, our substrate **2.175** was treated with palladium(0), JohnPhos as ligand and barium hydroxide as base in a mixture of THF and water. Under these conditions, only 45% of the cross coupling adduct was isolated with many other unidentified products. From our knowledge of the substrate **2.175**, we believed that the barium hydroxide might partially hydrolyze the ester to the corresponding acid, which could undergo side reactions or poison the catalyst. Hence, different bases were tried such as cesium fluoride which slowed down the reaction as only 30% conversion was observed. However, using cesium carbonate as base allowed the formation of the arylated product in excellent yield (Scheme 100).



Scheme 100. Suzuki cross coupling using cesium carbonate

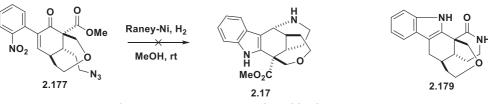
#### 2.4.11.Last Step: Reduction/Cyclization/Aza-Mannich Domino Reaction

The last step of the synthesis was envisioned to be a global reduction, indole formation followed by intramolecular aza-Mannich-type reaction allowing the formation of alstilobanine C in a one-pot sequence. The first reduction conditions tested were hydrogenation using different catalysts.



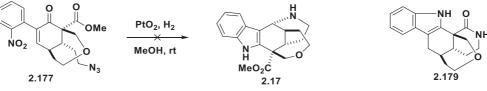
Hydrogenation using palladium on charcoal in methanol led to a messy reaction. Addition of acetic anhydride in the reaction mixture afforded a very messy reaction. However, changing the solvent to ethyl acetate led to a clean conversion to **2.178** (Scheme 101). Under these specific conditions, the nitro group was not reduced and the primary amine reacted with the ester to form lactam **2.178**.

As palladium on charcoal was not reactive enough to reduce the nitro group, we changed the catalyst to Raney nickel (Scheme 102).



Scheme 102. Raney-Ni catalyzed hydrogenation

These conditions were indeed able to reduce both azide and nitro groups, but lactam **2.179** was isolated instead of the natural product.

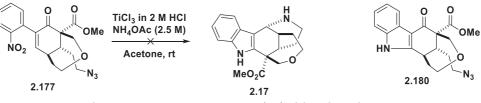


Scheme 103. Platinum oxide catalyzed hydrogenation

Platinum oxide-catalyzed hydrogenation led to the same lactam **2.179** as major product (Scheme 103). Several hypotheses can be proposed for the formation of lactam **2.179**. Reduction of nitro might be kinetically faster than the reduction of the azide group, leading to the conjugated indolenine intermediate. The  $\alpha$ , $\beta$ -unsaturation can be further reduced under these hydrogenation conditions preventing the primary amine to react as envisioned and lactam **2.179** was formed. Another hypothesis is that the reduction of the azide is faster

than the nitro group. With the primary amine intermediate, if the nitro group is not yet reduced, lactamization is fast then reduction of the nitro group can take place.

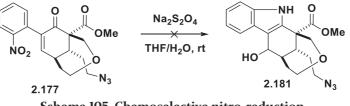
A different type of reduction conditions were investigated as there are well known in our group.<sup>67</sup> Substrate **2.177** was subject to aqueous titanium(III) chloride in acidic conditions (Scheme 104).



Scheme 104. Aqueous titanium(III) chloride reduction

Under the conditions developed in our group, the nitro group was reduced and further cyclization onto the double bond was observed leading to indole **2.180**. We observed that the presence of the buffer solution is crucial as the reaction became messy without.

Investigation of the chemoselective reduction of the nitro group was tested (Scheme 105).

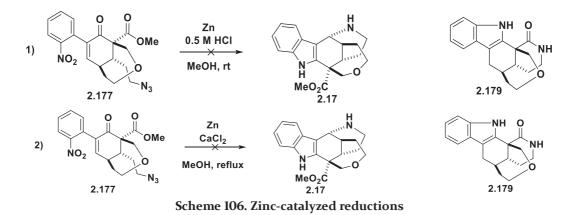


Scheme 105. Chemoselective nitro-reduction

Sodium dithionite is known to reduce aromatic nitro compounds. However, in our case, only decomposition was observed.

We turned our attention to a metal-induced reduction of both the nitro and azide groups.

<sup>&</sup>lt;sup>67</sup> Tong, S.; Xu, Z.; Mamboury, M.; Wang, Q.; Zhu, J. Angew. Chemie - Int. Ed. 2015, 54, 11809–11812.



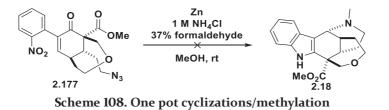
Zinc was the first metal investigated for the reductions (Scheme 106). In the first reaction, aqueous hydrochloric acid was added as additive. Both nitro and azide groups were reduced but led to a messy reaction with **2.179** as major compound isolated. In the second reaction, calcium chloride was tested in addition to zinc but the outcome of the reaction was even more complicated, with **2.179** as major product formed. Kinetics of the reductions were not in our favor, hence a milder acid was attempted (Scheme 107).



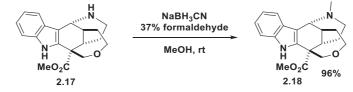
Scheme 107. Completion of the synthesis via zinc reduction in the presence of ammonium chloride aqueous solution

After fine tuning of the reaction conditions, the expected sequence performed beautifully in 5 minutes led to alstilobanine C **2.17** with an excellent **87%** yield. This powerful reaction allowed the formation of two C-N bonds as well as the construction of the indole unit and the second bridged ring. This unprecedented integrated reduction cyclization sequence allowed for the first time the total synthesis of this rare structure present in the natural product.

Attempt to reach the second natural product, undulifoline, from the same intermediate was tested (Scheme 108).

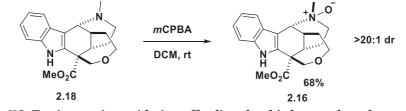


The expected one-pot reductions, cyclization, condensation and subsequent reduction sequence led to decomposition. We decided to methylate the secondary amine in a stepwise fashion (Scheme 109).



Scheme 109. Reductive amination leading to the second natural product

In order to prevent any methylation to occur on the nitrogen from the indole, reductive amination was tested and afforded undulifoline **2.18** in 96% yield. Another natural product from the same family can be obtained by oxidizing the tertiary amine to the *N*-oxide (Scheme 110).

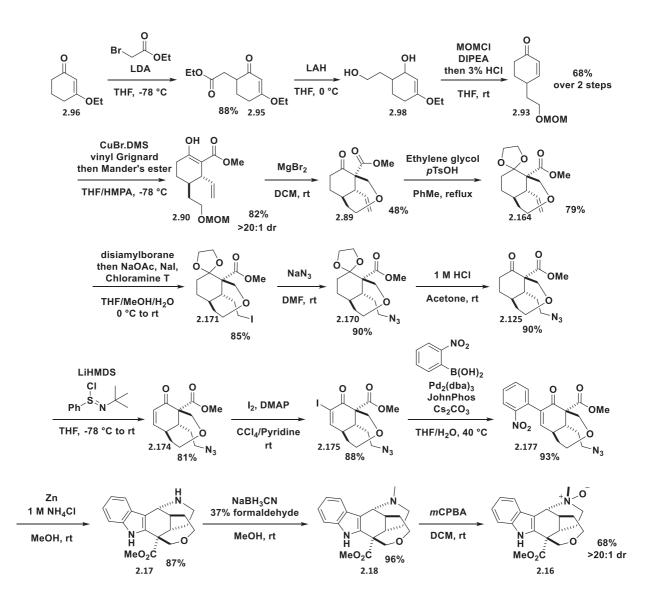


Scheme 110. Tertiary amine oxidation affording the third natural product as a single diastereoisomer

*m*CPBA oxidation led to the desired *N*-oxide compound **2.16**, alstilobanine B as a single diastereoisomer, in a good yield affording the third natural product of the uleine family.

# 2.5. Summary of the Synthesis

Scheme III summarizes the synthesis of  $(\pm)$ -alstilobanine C **2.17**,  $(\pm)$ -undulifoline **2.18** and  $(\pm)$ -alstilobanine B **2.16** from the commercially available ketone **2.97**.



Scheme III. Summary of the synthesis from the commercially available 3-ethoxy-2-cyclohexenone

(±)-Alstilobanine C **2.17** was obtained in 7.4% overall yield in 13 steps from the commercially available 3-ethoxy-2-cyclohexenone. Two additional steps afforded two other members of the uleine family, (±)-unfulifoline **2.18** and (±)-alstilobanine B **2.16**.

Table 13 shows the comparison of the <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra between the isolated natural product and the synthesized one.

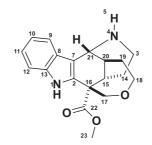


Figure 2. Numbering of alstilobanine C

Table B. Comparison of NMR data between the	isolated and the synthesized alstilobanine C
---	--

	Isolate	ed			Synthesi	ized	
N°	<sup>13</sup> C [ppm] <sup>1</sup> (100 MHz)		ppm] <sup>1</sup> MHz)	N°	<sup>13</sup> C [ppm] <sup>1</sup> (100 MHz)		opm] <sup>1</sup> MHz)
14	28.9	2.15	1.73	14	29.1	2.13	1.76
19	33.5	2.11	1.26	19	33.6	2.10	1.30
3	37.0	3.01	-	3	37.2	3.00	-
20	38.3	2.86	-	20	38.6	2.81	-
15	38.5	2.97	-	15	38.6	2.98	-
21	51.7	4.75	-	21	51.8	4.75	-
23	53.0	3.79	-	23	53.0	3.80	-
16	55.9	-	-	16	56.0	-	-
18	69.8	3.69	3.60	18	69.9	3.71	3.59
17	78.9	4.35	4.01	17	78.9	4.34	4.02
7	104.2	-	-	7	104.3	-	-
12	112.4	7.40	-	12	112.4	7.41	-
9	118.8	7.62	-	9	118.8	7.63	-
10	120.8	7.09	-	10	120.8	7.12	-
11	123.5	7.17	-	11	123.6	7.20	-
8	127.1	-	-	8	127.1	-	-
13	138.6	-	-	13	138.6	-	-
2	138.8	-	-	2	138.8	-	-
22	173.1	-	-	22	173.1	-	-

<sup>1</sup>: in CD<sub>3</sub>OD



Figure 3. Numbering of undulifoline

Table 15. Comparison of NMR data between the isolated and the synthesized undulifoline
--

	Isolated				Synt	hesized	
N°	<sup>13</sup> C [ppm] <sup>1</sup> (75 MHz)	<sup>1</sup> H [p] (300 M		N°	<sup>13</sup> C [ppm] <sup>1</sup> (100 MHz)		[ppm] <sup>1</sup> ) MHz)
14	30.7	1.65	2.12-1.91	14	30.6	1.64	2.18-1.96
19	33.1	1.35	2.12-1.91	19	33.2	1.34	2.18-1.96
3	46.1	2.45	2.12-1.91	3	46.2	2.48	2.18-1.96
20	44.0	2.73	-	20	44.0	2.74	-
15	37.9	2.78	-	15	37.9	2.79	-
21	58.7	3.95	-	21	58.7	3.99	-
23	52.3	3.79	-	23	52.5	3.79	-
16	55.4	-	-	16	55.6	-	-
18	69.6	3.72	3.50	18	69.7	3.73	3.50
17	79.2	4.18	3.89	17	79.2	4.18	3.90
7	107.4	-	-	7	107.0	-	-
12	111.2	7.55	-	12	111.4	7.54	-
9	119.7	7.36	-	9	119.9	7.37	-
10	118.9	7.20-7.07	-	10	119.0	7.11	-
11	121.9	7.20-7.07	-	11	122.2	7.17	-
8	129.0	-	-	8	128.9	-	-
B	136.9	-	-	13	137.0	-	-
2	134.6	-	-	2	135.0	-	-
1	-	8.30	-	1	-	8.43	-
5	40.4	2.30	-	5	40.2	2.32	-
22	172.7	-	-	22	172.7	-	-

<sup>1</sup>: in CDCl<sub>3</sub>

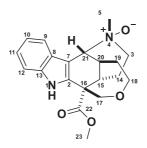


Figure 4. Numbering of alstilobanine B

Table 16. Comparison of NMR data between the isolated and the synthesized alstilobanine B

	Isolated				Synt	hesized	
N°	<sup>13</sup> C [ppm] <sup>1</sup> (75 MHz)	<sup>1</sup> H [pp (300 M		N°	<sup>13</sup> C [ppm] <sup>1</sup> (100 MHz)		opm] <sup>1</sup> MHz)
14	30.7	1.65	2.01	14	30.6	1.64	2.07
19	33.1	1.35	2.01	19	33.2	1.34	2.07
3	46.1	2.45	2.01	3	46.2	2.48	2.07
20	44.0	2.73	-	20	44.0	2.74	-
15	37.9	2.78	-	15	37.9	2.79	-
21	58.7	3.95	-	21	58.7	3.99	-
23	52.3	3.79	-	23	52.5	3.79	-
16	55.4	-	-	16	55.6	-	-
18	69.6	3.72	3.50	18	69.7	3.73	3.50
17	79.2	4.18	3.89	17	79.2	4.18	3.90
7	107.4	-	-	7	107.0	-	-
12	111.2	7.55	-	12	111.4	7.54	-
9	119.7	7.36	-	9	119.9	7.37	-
10	118.9	7.20-7.07	-	10	119.0	7.11	-
11	121.9	7.20-7.07	-	11	122.2	7.17	-
8	129.0	-	-	8	128.9	-	-
13	136.9	-	-	13	137.0	-	-
2	134.6	-	-	2	135.0	-	-
1	-	8.30	-	1	-	8.43	-
5	40.4	2.30	-	5	40.2	2.32	-
22	172.7	-	-	22	172.7	-	-

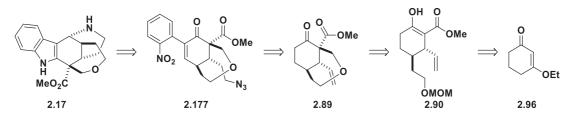
<sup>1</sup>: in CD<sub>3</sub>OD

Both proton and carbon chemical shifts of the synthetic natural products correlate well with the isolated natural products, confirming the structures.

# 2.6. Conclusion and Outlook

In conclusion, we succeeded in the first total synthesis of new unusual members of the uleine family, namely  $(\pm)$ -alstilobanine C **2.17**,  $(\pm)$ -undulifoline **2.18** and  $(\pm)$ -alstilobanine B **2.16**. The synthesis can be highlighted by several key features:

- A highly diastereoselective Michael addition followed by quenching of the resulting enolate with Mander's ester forming two new C-C bonds
- An unprecedented Lewis acid mediated cyclization forming the [4.3.1] bicycle with the creation of the quaternary carbon
- A chemoselective reduction/cyclization/aza-Michael domino reaction forming two new C-N bonds and the pentacyclic structure



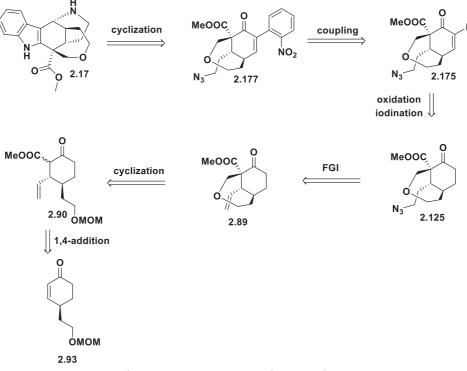
Scheme 112. Summary of the key intermediates of the total synthesis of alstilobanine C

(±)-Alstilobanine C **2.17** was obtained in only I3 steps and a good 7.4% overall yield from a simple starting material (Scheme 112).

# Chapter 3 - Synthetic Studies Towards the Enantioselective Total Synthesis

### 3.1. First Retrosynthetic Analysis

The enantioselective synthesis of alstilobanine C was first thought to be achieved through the same retrosynthesis described in the previous chapter. Only the chiral center of enone **2.93** has to be defined to induce the correct configuration of the other stereocenters as the synthesis should proceed with complete diasterecontrol (Scheme 113).



Scheme 113. First retrosynthesis pathway

Alstilobanine C should be obtained by the final reduction/cyclization/aza-Michael sequence from precursor **2.177** and can only occur in a stereoselective manner. The latter should be reached by cross-coupling reaction between **2.175** and 2-nitrophenyl boronic acid. Functional group interconversion would bring us to bicyclic intermediate **2.89**. Formation of the oxepane can only occur from the same face. Michael addition of vinyl

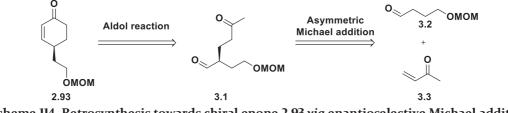
cuprate onto enone 2.93 is diastereoselective and the trans product 2.90 will be the only one obtained.

#### 3.1.1. Synthesis of Enantioenriched Cyclohexenone

The enantioselective synthesis of enone 2.93 was investigated. Several methods caught our attention and two will be presented.

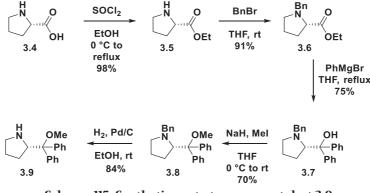
#### 3.1.1.1. By Enantioselective Michael Addition

The first retrosynthesis envisioned was by intramolecular aldol reaction followed by an enantioselective Michael addition using prolinol-derived organocatalyst (Scheme 114).



Scheme II4. Retrosynthesis towards chiral enone 2.93 via enantioselective Michael addition

Inspired by Gellman's work<sup>68</sup>, we started to synthesize the organocatalyst **3.9** required for the Michael reaction following a reported procedure (Scheme 115)<sup>69</sup>.



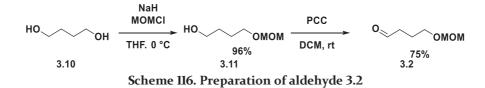
Scheme 115. Synthetic route to organocatalyst 3.9

<sup>&</sup>lt;sup>68</sup> Chi, Y.; Gellman, S. H. Org. Lett. 2005, 7, 4253–4256.

<sup>&</sup>lt;sup>69</sup> Enders, D.; Kipphardt, H.; Gerdes, P.; Brena-Valle, L. J.; Bhushan, V. Bull Soc. Chim. Belg, 1988, 97, 691-704.

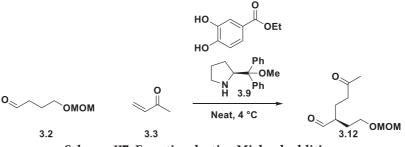
Starting with commercially available (S)-proline **3.4**, esterification using thionyl chloride in ethanol afforded **3.5** in almost quantitative yield. Then, protection of the N-pyrrolidine moiety with benzyl bromide led to **3.6**. Double Grignard additions onto the ester allowed the formation of tertiary alcohol **3.7** in good yield. Methylation of the latter was performed using sodium hydride and methyl iodide. Deprotection of the benzyl group under hydrogenation conditions afforded the desired prolinol catalyst **3.9**, in gram scale, with an overall yield of 40% over five steps.

As methyl vinyl ketone (MVK) **3.3** is commercially available, the aldehyde partner **3.2** has to be prepared (Scheme 116).



1,4-butanediol **3.10** can be monoprotected using sodium hydride in presence of MOMCl. Other bases failed to give a clean reaction. Oxidation of the primary alcohol **3.11** to the corresponding aldehyde was performed with PCC in DCM. The moderate yield of the oxidation can be explained by the volatility of the aldehyde **3.2**.

With all the substrates synthesized, we were able to try for the first time the enantioselective Michael addition (Scheme 117).



Scheme 117. Enantioselective Michael addition

Entry	Catechol (mol%)	Prolinol (mol%)	Solvent	Results
1	-	5	neat	SM recovery
2	20	5	neat	80% conversion
3	5	5	neat	85% conversion
4	20	1	neat	60% conversion
5	20	10	neat	95% conversion
6	10	5	neat	Full conversion (77% yield)
7	20	5	DCM	Full conversion

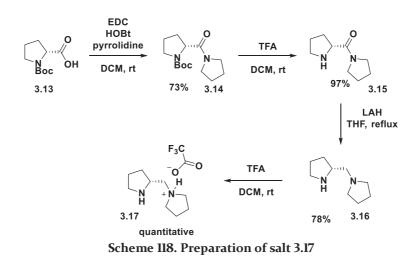
Table 14. Representative conditions for the enantioselective Michael addition

All reactions have been carried out with 1 equivalent of the aldehyde and 1.5 equivalents of MVK at 4 °C for 2 days.

When reacting aldehyde **3.2** with MVK in presence of the prolinol catalyst **3.9**, no reaction was observed (entry 1). Gellman and coworkers reported that the use of a catechol derivatives cocatalyst enhances the reaction rates of such transformation. Their hypothesis lies in the activation of the enone *via* hydrogen bonding of the catechol alcohol with the oxygen of the carbonyl. 20 mol% was enough to get 80% conversion to the desired 1,4-adduct (entry 2). When lowering the cocatalyst amount to 5 mol%, the conversion was slightly better (entry 3). Reducing the prolinol to 1 mol% reduced the conversion and only 60% of the product was observed (entry 4). Increasing the amount of catalyst to 10 mol% allowed 95% conversion of the desired product (entry 5). Keeping a 2/1 ratio between the cocatalyst and the prolinol, we succeeded to reach full conversion using 10 mol% of catechol and 5 mol% of prolinol and the desired Michael adduct was obtained in 77% isolated yield (entry 6). Despite the clean and complete reaction, the moderate yield can be explained due to the volatility of the compound. We also observed complete consumption of the starting materials using DCM as solvent, but the amount of cocatalyst has to be doubled in this case (entry 7).

The enantiomeric excess (ee) was measured based on the work of Gellman and coworkers<sup>70</sup>. When adding enantiopure (S)-methoxy-2-propylamine into the NMR tube containing the crude mixture of the reaction, imine formation occurs in only few seconds. Hence, by NMR, the ratio of diastereoisomers determines the ee. In all cases, even when the reaction did not reach full conversion, the ee were very high. Unfortunately, we were never able to clearly measure the exact ee as overlapping of several peaks made the quantitative analysis impossible.

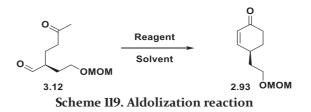
Following McQuade's work,<sup>71</sup> we started to synthesize the pyrrolidine base **3.17** required for the intramolecular aldolization (Scheme 118). As the aldehyde **3.12** is enolizable, erosion of the enantiopurity may take place. TFA salt **3.17** was reported to limit the loss of ee in such type of reaction.



Peptide coupling between *N*-protected proline **3.13** and pyrrolidine afforded amide **3.14** using EDC and HOBt. Then, Boc deprotection was achieved with TFA followed by reduction of the amide using LAH to afford the corresponding amine **3.16** in 76% yield over 2 steps. Finally, the TFA salt **3.17** was formed quantitatively and was used for the intramolecular aldol reaction (Scheme 119).

<sup>&</sup>lt;sup>70</sup> Chi, Y.; Peelen, T. J.; Gellman, S. H. Org. Lett. **2005**, *7*, 3469–3472.

<sup>&</sup>lt;sup>71</sup> Houjeiry, T. I.; Poe, S. L.; McQuade, D. T. Org. Lett. **2012**, *14*, 4394–4397.



Entry	Reagent	Solvent	Results
1	3.17	Hexane	No reaction
2	LiOH	<sup>i</sup> PrOH	Decomposition
3	$K_2CO_3$	MeOH	Decomposition
4	DABCO	PhMe	Decomposition
5	pTsOH	DCM	No reaction
6	LDA	THF	Traces of DP (1% ee)
7	LiHMDS	THF	Traces of DP (1% ee)
8	KHMDS	THF	Traces of DP (1% ee)
9	LiTMP	THF	Traces of DP (1% ee)

Table 15. Representative conditions for the aldolization

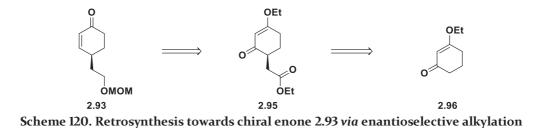
All reactions have been carried out from -78 °C and rising to rt while monitoring by TLC.

No reaction between the TFA salt **3.17** and our substrate occurred and only the starting material was recovered (entry 1). Typical conditions using LiOH in isopropanol decomposed our substrate (entry 2).<sup>72</sup> The inorganic base potassium carbonate was also harmful for the reaction (entry 3). Similar outcome was observed when nucleophilic DABCO was used (entry 4). Acidic conditions were then attempted to promote the cyclization using *p*TsOH, but no reaction took place (entry 5). Finally, strong non-nucleophilic bases, such as LDA, LiHMDS and LiTMP were tested and afforded a trace amount of the desired cyclic enone **2.93** (entries 6-9). Unfortunately, the ee of the product was close to zero, which means that racemization of the center  $\alpha$  to aldehyde **3.12** occured during the reaction.

#### 3.1.1.2. By Enantioselective Alkylation

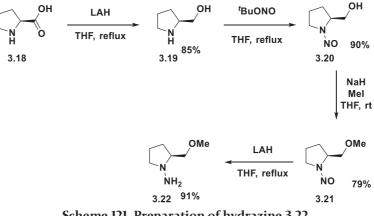
We moved to another strategy to reach the same enantioenriched key intermediate **2.93** (Scheme 120).

<sup>&</sup>lt;sup>72</sup> Zhang, P.; Wang, Y.; Bao, R.; Luo, T.; Yang, Z.; Tang, Y. Org. Lett. 2012, 14, 162–165.



Reduction of the ester, protection of the corresponding primary alcohol and hydrolysis of the enol ether would afford chiral enone **2.93**. Enantioselective alkylation of **2.96** would led to **2.95**, setting the only chiral center needed for the synthesis.

We were interested by the hydrazine compounds pioneered by Corey and Enders.<sup>73</sup> Enders further developed chiral auxiliaries that allow high enantioselectivity for alkylation reactions.<sup>74</sup> In order to have the desired stereochemistry, SAMP **3.22** was prepared (Scheme 121).



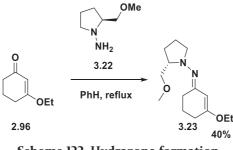
Scheme 121. Preparation of hydrazine 3.22

Reduction of (S)-proline **3.18** with LAH at reflux allowed the formation of amino alcohol **3.19**. Subsequent reaction with *tert*-butyl nitrite enable the formation of nitrosamine **3.20** in excellent yield. Finally, methylation of alcohol **3.20** and reduction of the nitroso amine group to the corresponding hydrazine led to SAMP **3.22**.

<sup>&</sup>lt;sup>73</sup> Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, *17*, 3–6.

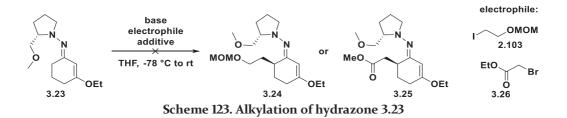
<sup>74</sup> Enders, D.; Kipphardt, H.; Fey, P. Org. Synth. 1987, 65, 183.

Condensation of the chiral auxiliary with the carbonyl moiety of **2.96** yielded hydrazone **3.23** (Scheme 122).



Scheme 122. Hydrazone formation

The reaction never reached full conversion but hydrazone **3.23** could be isolated. Trials for the alkylation were then performed (Scheme 123).

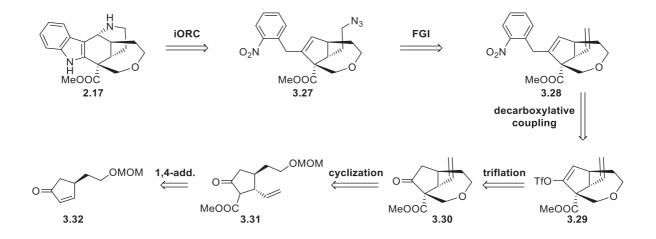


It is important to note that both electrophiles **2.103** and **3.26** were tested in each case. Moreover, we realized that hydrazone **3.23** is unstable and decomposed even at -20 °C.

We started the investigation of this transformation using LiHMDS as base, but no reaction was observed with neither of the electrophile. Adding HMPA as additive had no influence on the reaction. Changing the base to LDA, "BuLi, "BuLi or 'BuLi did not modify the outcome. We hypothesized that the electrophiles might be too bulky for the deprotonation to occur, hence we performed control experiments using D<sub>2</sub>O as quench, but no deuterium incorporation was observed. Using LDA as base and LiCl as additive, a new product was observed but we failed to isolate it. As the starting material and the product seemed unstable, we decided to drop this strategy.

#### 3.2. Second Retrosynthetic Analysis

A new synthetic route was envisioned as described in Scheme 124.



Scheme 124 – Enantioselective route towards alstilobanine C

We thought to build the whole pentacyclic scaffold of alstilobanine C from cyclopentene **3.27** by a one-pot oxidation/reduction/cyclization sequence recently developed from our group (iORC).<sup>75</sup> The azide functional group would be incorporated from alkene **3.28**. Palladium-catalyzed decarboxylative coupling vinylation of potassium nitrophenyl acetate with enol triflate **3.29**, obtained from ketone **3.30**, would afford **3.28**.<sup>76</sup> The oxepane moiety would be formed by *in-situ* generation of the oxonium from the MOM group followed by intramolecular trapping with the  $\beta$ -ketoester **3.31**. This last intermediate would be obtained from a Michael addition of vinylmagnesium bromide onto cyclopentenone **3.32** followed by quenching the resulting enolate with Mander's ester.

<sup>75</sup> Wagnières, O.; Xu, Z.; Wang, Q.; Zhu, J. J. Am. Chem. Soc. 2014, 136, 15102-15108.

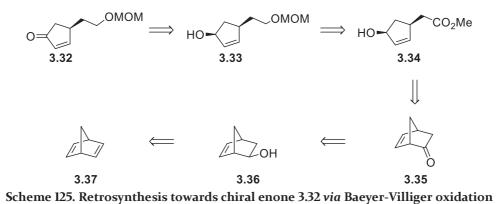
<sup>&</sup>lt;sup>76</sup> Xu, Z.; Wang, Q.; Zhu, J. Angew. Chemie - Int. Ed. 2013, 52, 3272-3276.

#### 3.2.1. Synthesis of Enantioenriched Cyclopentenone

Various routes for the synthesis of chiral cyclopentenone **3.32** were studied and four of them will be presented.

# 3.2.1.1. By Baeyer-Villiger Oxidation of Norbornenone

The first attempt was based on the work of Greene and Hayashi groups (Scheme 125).77



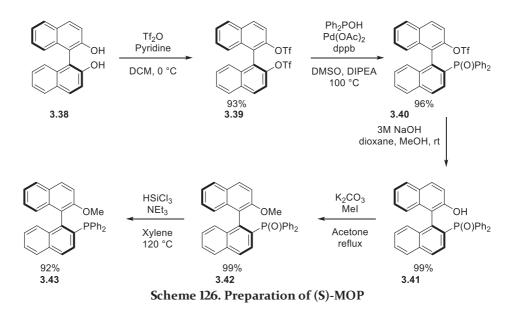
Cyclopentenone **3.32** would be obtained from oxidation of the allylic alcohol **3.33**. The latter would be formed after a reduction/protection sequence of ester **3.34**. Baeyer-Villiger oxidation of enantiopure norbornenone **3.35** and opening of the obtained lactone with NaOMe is reported to give ester **3.34**.<sup>78</sup> Finally, norbornenone **3.35** can be obtained in a two-step manner starting from an enantioselective hydrosilylation/oxidation of norbornadiene **3.37** and Swern oxidation of the so-formed alcohol **3.36**.<sup>79</sup>

For this first enantioselective step, (S)-MOP **3.43** catalyst had to be synthesized (Scheme 126).

<sup>&</sup>lt;sup>77</sup> Nicolaou, K. C.; Heretsch, P.; Hale, C. R. H.; Ghzaoui, A. M.; Pulukuri, K. K.; Yu, R.; Grove, C. Synthesis of *delta* 12-pgj3 and related compounds. WO2015048268A1, **2013**.

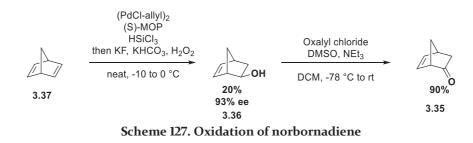
<sup>&</sup>lt;sup>78</sup> Greene, A. E.; Drian, C. Le; Crabbé, P. J. Am. Chem. Soc. **1980**, 102, 7583–7584.

<sup>&</sup>lt;sup>79</sup> Uozumi, Y.; Sang-Yong, L.; Hayashi, T. Tetrahedron Lett. 1992, 33, 7185–7188.



Bis triflation of (S)-BINOL followed by monophosphinylation of the resulting ditriflate **3.39**, using a modified Morgan's procedure, allowed the synthesis of phosphinate **3.40** in excellent yield.<sup>80</sup> Hydrolysis of the remaining triflate led to phenol **3.41** with was further alkylated with MeI and K<sub>2</sub>CO<sub>3</sub> to give ether **3.42** in almost quantitative yield. Final reduction of the phosphinate to the corresponding phosphinite **3.43** was triggered with trichlorosilane and triethylamine in xylene.

With (S)-MOP in our hands, we were able to work on the enantioselective hydrosilylation/oxidation sequence and the subsequent oxidation step, as depicted in Scheme 127.

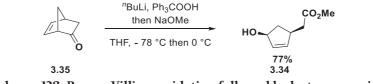


The silvlated intermediate proved to be extremely unstable and spontaneously exploded if the temperature of the mixture was above 0 °C. After troublesome experiments, alcohol

<sup>&</sup>lt;sup>80</sup> Kurz, L.; Lee, C.; Morgans, Jr., D.; Waldyke, M. J.; Ware, T. *Tetrahedron Lett.* **1990**, *31*, 6321.

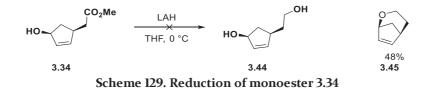
**3.36** was finally isolated in only 20% yield. Regardless of the screening of other reaction conditions, no further improvement of the yield was observed. Oxidation of the obtained alcohol using Swern's protocol afforded norbornenone **3.35** in 90% yield. Rapid oxidation has to be performed as the alcohol **3.36** is also not stable and dimers have been observed reducing considerably the yield of the desired ketone **3.35**.

The Baeyer-Villiger oxidation/opening sequence of the formed lactone was then tested (Scheme 128).



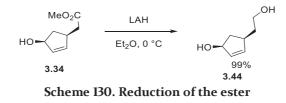
Scheme 128. Baeyer-Villiger oxidation followed by lactone opening

The classical peroxide mCPBA did not promote the desired oxidation. Following Nicolaou's patent,<sup>77</sup> trityl hydroperoxide was prepared from trityl chloride in presence of sodium bicarbonate and hydrogen peroxide and after two recrystallizations.<sup>81</sup> The oxidation with this freshly prepared peroxyde was successful and the opening of the obtained lactone with sodium methoxide gave ester **3.34** in 77% yield.

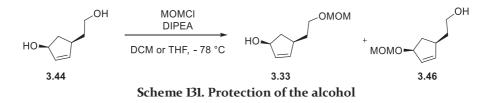


Reduction of the ester led to interesting results as shown in Scheme 129. Indeed, when LAH was used in THF, the expected diol **3.44** was not observed. Instead, self-cyclized ether **3.45** was obtained in 48% yield after Fieser work up.<sup>45</sup> Other types of work up did not increased the yield of the bicycle. The volatility of such small molecule could explain the moderate isolation yield. The reduction of ester **3.34** had to be investigated and after screening of several reducing agents in different solvent systems, we were able to obtained diol **3.44** (Scheme 130).

<sup>&</sup>lt;sup>81</sup> Stepovik, L. P.; Gulenova, M. V. Russ. J. Gen. Chem. 2006, 76, 235–244.



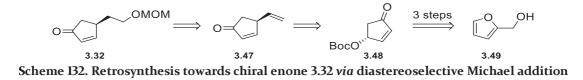
By changing the solvent to diethyl ether, LAH reduction afforded diol **3.44** in quantitative yield after Fieser work up. The next challenge was the chemoselective monoprotection of the primary alcohol using MOMCI (Scheme 131).



After careful monitoring of the reaction in both DCM and THF, from -78 °C to room temperature, we observed reactivity only starting from -20 °C. However, despite the dropwise addition, both alcohol **3.33** and **3.46** were formed in a 1:1 ratio. Due to this chemoselectivity issue and the problematic hydrosilylation step, this approach was put in stand-by and other routes were explored.

## 3.2.1.2. By Diastereoselective Michael Addition

Our second retrosynthetic analysis, inspired by the work of Reiser and coworkers, in order to reach enantioenriched enone **3.32** is described in Scheme 132.<sup>82</sup>

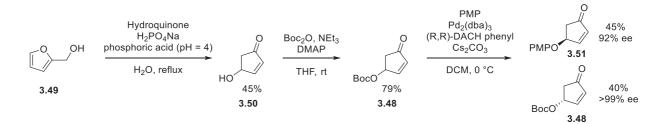


The acetal group of enone **3.32** would come from the functionalization of the corresponding vinyl **3.47**. The 2-carbon unit would arise from 1,4-addition followed by carbonate

<sup>82</sup> Arisetti, N.; Reiser, O. Org. Lett. 2015, 17, 94-97.

elimination of enone **3.48**. A reported 3-step sequence from furfuryl alcohol **3.49** would give the precursor **3.48** for the Michael addition.

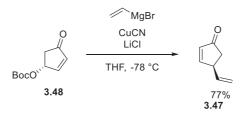
Synthesis of the chiral enone 3.32 was conducted following Reiser's protocole (Scheme 133).



Scheme 133, Preparation of chiral enones 3.51 and 3.48

Piancatelli rearrangement of furfuryl alcohol under acidic conditions afforded enone **3.50**. Boc protection of the hydroxyl group led to the racemic precursor **3.48** of the Michael addition. Kinetic resolution of **3.48** utilizing Trost's method allowed formation of **3.48** (40% yield, >99% ee).<sup>83</sup>

The diastereoselective 1,4-addition of the vinyl moiety was then studied (Scheme 134).

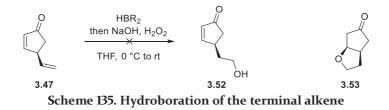


Scheme 134. Michael addition followed by elimination

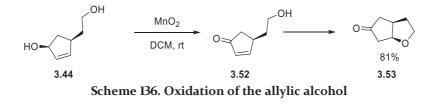
Michael addition of vinylmagnesium bromide, using a catalytic amount of copper gave only traces of the desired product **3.47**. The *in*-situ generation of second order cuprate gave messy reaction mixtures. However, first order cuprate was a more suitable choice for this substrate and gave full conversion with lithium chloride as additive and afforded 77% of the desired product **3.47**.

<sup>83</sup> Trost, B. M.; Toste, F. D. J. Am. Chem. Soc. 1999, 121, 3543-3544.

Functionalization of the alkene was envisioned by a hydroboration/oxidation sequence followed by MOM protection (Scheme 135).

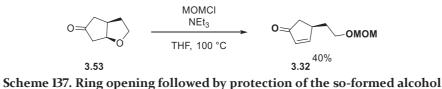


Regardless of the type of borane and its amount, only complex mixtures were obtained. However, traces of bicyclic compound **3.53** was observed. As scientific curiosity, we decided to submit our previously synthesized diol **3.44** to oxidative conditions to study its behavior. Oxidation of the allylic alcohol **3.44** would lead to enone **3.52** (Scheme 136).



Upon treatment with manganese dioxide, the expected oxidation proceeded smoothly but the subsequent intramolecular oxo-Michael addition could not be avoided and bicyclic compound **3.53** was formed exclusively.

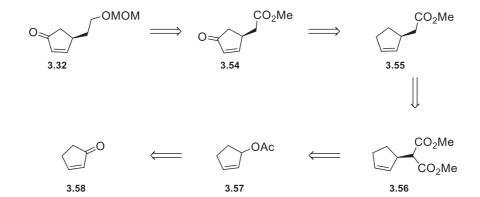
Attempts for the one-pot ring opening/protection sequence were tested (Scheme 137).



Under the same conditions previously developed (see Chapter 2.4.1), enone **3.32** was formed but the yield was not satisfying to pursue this pathway.

### 3.2.1.3. By Enantioselective Tsuji-Trost Coupling

At the same time, we were working on a different strategy to reach intermediate **3.32**, following the work of Nicolaou on the total synthesis of prostaglandin J<sub>3</sub> (Scheme 138).<sup>84</sup>

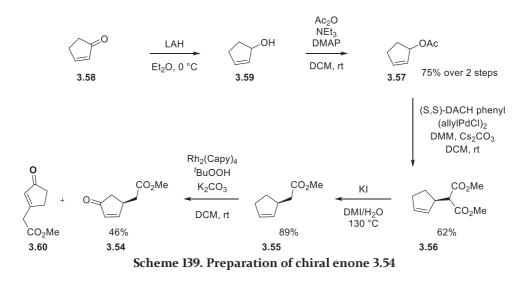


Scheme 138. Retrosynthesis towards chiral enone 3.32 via enantioselective Tsuji-Trost coupling

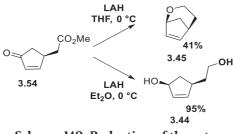
Key intermediate **3.32** would come from the corresponding ester **3.54** after reduction and protection. Functionalization of **3.55** to its corresponding enone, *via* a C-H activation mechanism, is described using a rhodium-catalyzed procedure. The ester would come from **3.56** after Krapcho monodecarboxylation. The malonate moiety would be installed through an enantioselective palladium-catalyzed Tsuji-Trost coupling reaction from cyclopentenol acetate **3.57**. The latter would be formed from commercially available 2-cyclopentenone **3.58** by reduction followed by acetylation.

We quickly obtained enone **3.54** through the reported procedures (Scheme 139).

<sup>&</sup>lt;sup>84</sup> Nicolaou, K. C.; Heretsch, P.; ElMarrouni, A.; Hale, C. R. H.; Pulukuri, K. K.; Kudva, A. K.; Narayan, V.; Prabhu, K. S. *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 10443–10447.



Commercially available 2-cyclopentenone was reduced with LAH to get allylic alcohol **3.59** which was directly acetylated to afford **3.57** in 75% yield over two steps. Enantioselective palladium-catalyzed Tsuji-Trost coupling using DMM led to malonate **3.56** in good yield and excellent ee.<sup>85</sup> Krapcho decarboxylation using potassium iodide in a mixture of DMI and water gave cleanly ester **3.55**. Finally, the allylic oxidation using a rhodium catalyst and *tert*-butylhydroperoxide provided enone **3.54** in 46% yield. Unfortunately, this last reaction was not reproducible and the main side product was a regioisomer of the oxidized product **3.60**.



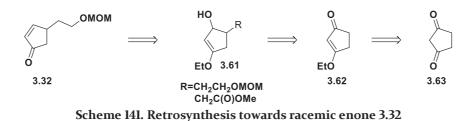
Scheme 140. Reduction of the ester

Reduction of enone **3.54** led to the same problem encountered with the first strategy (Scheme 140). Upon treatment with LAH, reduction of both the ketone and the ester occurred and bicyclic compound **3.45** was the only isolated product when THF was used as solvent. By switching to  $Et_2O$  instead, the desired diol **3.44** was formed in 95% yield. However, from previous experiments, we knew this intermediate was a dead end.

<sup>&</sup>lt;sup>85</sup> Trost, B. M.; Bunt, R. C. Angew. Chem. Int. Ed. Engl. 1996, 35, 99–102.

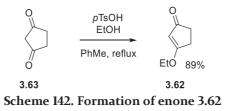
### 3.2.1.4. Synthesis of Racemic Cyclopentenone

Simultaneously, the racemic synthesis of key intermediate **3.32** was attempted in order to obtain a reference for the measurement of the enantiomeric excess using chiral SFC. The retrosynthetic analysis is shown below (Scheme 141).



Enone **3.32** would come from acidic hydrolysis of enol ether **3.61**. The latter would be formed by an  $\alpha$ -alkylation of enone **3.62** followed by reduction of the carbonyl. The enone **3.62** can easily be formed from commercially available 1,3-cyclopentanedione **3.63**.

Hence the synthesis started with refluxing the diketone **3.63** in toluene in presence of ethanol and a catalytic amount of pTsOH to form **3.62** in 89% yield (Scheme 142).



Alkylation of **3.62** was performed with two different alkylating agents (Scheme 143). Bromoethyl acetate **3.26** would allow insertion of the two carbons unit needed for the synthesis, but after reduction, further protection would be required. Iodo acetal **2.103** would be a more clever choice of electrophile as the MOM protecting group is already installed.

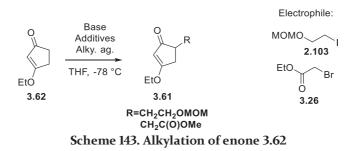
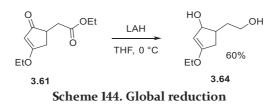


Table 16. Representative conditions for the alkylation of enone 3.62

Entry	Base	Additive	Results with 2.103	Results with 3.26
1	LDA	HMPA	No reaction	Decomposition
2	LiHMDS	HMPA	No reaction	Decomposition
3	LDA	HMPA, LiCl	No reaction	Decomposition
4	KDA	HMPA	No reaction	Decomposition
5	KHMDS	HMPA	No reaction	52%

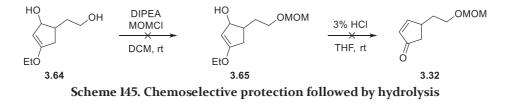
Typical reaction conditions were used with LDA or LiHMDS as strong base and in presence of HMPA as co-solvent. In both cases, no reaction were observed with **2.103** as electrophile and complete decomposition with bromoethyl acetate (entries 1 and 2). Similar trend was noted when LiCl was used as additive (entry 3). Switching from lithium base to potassium base, such as KDA,<sup>86</sup> the same behavior was observed (entry 4). However, when KHMDS was employed in the reaction, the enolate reacted with bromoethyl acetate to give the desired C-alkylated product **3.61** in 52% yield (entry 5).

We were then able to move forward with the next step, which was the reduction of both carbonyls (Scheme 144).



<sup>&</sup>lt;sup>86</sup> Raucher, S.; Koolpe, G. A. J. Org. Chem. 1978, 43, 3794–3796.

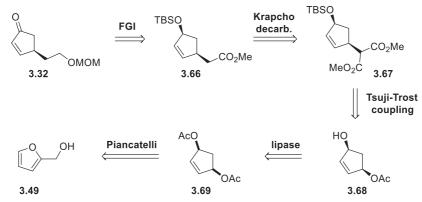
LAH reduction in THF was clean but afforded the diol **3.64** in only 60% yield. MOM protection of the primary alcohol followed by hydrolysis of enol ether **3.65** should lead to the desired enone **3.32** (Scheme 145).



Unfortunately, after many attempts, this pathway led to complex mixtures and enone **3.32** was never isolated.

# 3.2.1.5. By Enzymatic Desymmetrization of Meso Compound

After examination of the problems encountered through the different approaches to key intermediate **3.32**, we proposed a new route for the synthesis of enone **3.32** which would avoid all the complications previously faced (Scheme 146).

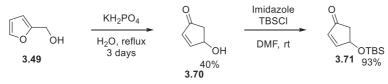


Scheme 146. Retrosynthesis towards chiral enone 3.32 *via* enzymatic desymmetrization of meso compound 3.69

Chiral enone **3.32** would be obtained from cyclopentene **3.66** through a reduction/protection/deprotection/oxidation process. The ester would be formed by decarboxylation of the malonate **3.67** which would be installed by a Tsuji-Trost coupling from **3.68** after protection. Chiral alcohol **3.68** would be synthesized from meso compound

**3.69** using lipases. Prochiral diacetate **3.69** is literature known and can be obtained from furfural alcohol **3.49** in five steps.<sup>87</sup>

The beginning of the synthesis started with the Piancatelli rearrangement of furfuryl alcohol **3.49** to enone **3.70** followed by TBS-protection (Scheme 147).



Scheme 147. Piancatelli rearrangement followed by protection

The first attempts were set up by microwave irradiation and afforded the desired alcohol **3.70** in a range of 70-80% yield. However, the scale of the reaction was limited, hence not convenient for the first step of a total synthesis. Furfuryl alcohol **3.49** was dissolved in acidic water and reflux for 3 days to form alcohol **3.70** in 40% yield on 0.3 mol. The obtained alcohol was protected with TBS under Corey's conditions to afford **3.71** in excellent yield. Careful handling of the silylated intermediate **3.71** has to be taken into consideration due to its volatility. Reduction of the ketone **3.71** had to be optimized as only the cis product can be used for the enzymatic reaction (Scheme 148).

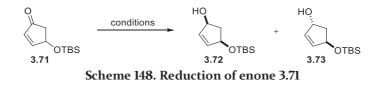


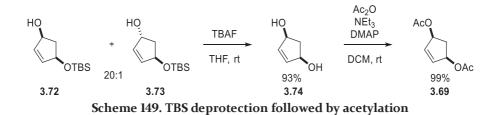
Table 17. Representative conditions for the reduction of enone 3.71

Entry	Conditions	Results (ratio cis:trans)
1	DIBAL, PhMe, -40 °C	80% (9:1)
2	LAH, Et <sub>2</sub> O, -78 °C	73% (11:1)
3	LAH, LiCl, Et <sub>2</sub> O, -20 °C	72% (11:1)
4	NaBH4, CeCl3, MeOH, -20 °C	91% (8:1)
5	NaBH <sub>4</sub> , CeCl <sub>3</sub> , MeOH, -78 °C	85% (20:1)

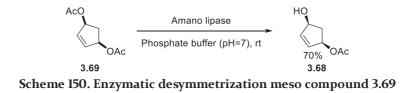
DIBAL reduction in toluene afforded the desired alcohols in 80% with a 9:1 ratio between the cis- and trans-products (entry 1). When switching to LAH, the generation of cis-product

<sup>&</sup>lt;sup>87</sup> Specklin, S.; Dikova, A.; Blanc, A.; Weibel, J. M.; Pale, P. Tetrahedron Lett. 2014, 55, 6987–6991.

was slightly higher than with DIBAL (entry 2) but addition of lithium chloride as additive did not improve further the selectivity (entry 3). Luche reduction of **3.71** in methanol at -20 °C afforded in high yield both alcohols but the ratio was less good than the previous trials (entry 4). Cooling down the reaction mixture to -78 °C allowed high selectivity (20:1) towards the desired cis-product (entry 5). After many failed attempts for the separation of the two diastereoisomers, we decided to continue the synthesis with this mixture and to separate them at a later stage (Scheme 149).

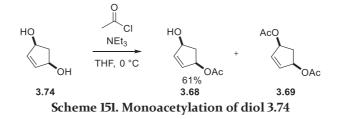


Removal of the TBS protecting group with TBAF in THF proved to be very efficient and allowed separation of the two diastereoisomers to obtain pure cis-diol **3.74**. DMAP catalyzed the acetylation of the diol and afforded diacetate **3.69** in excellent yield.

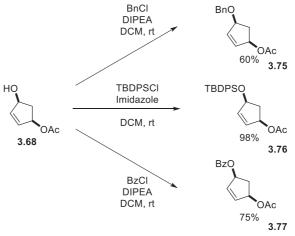


Desymmetrization of diacetate **3.69** was performed with amano lipase (Scheme 150).<sup>88</sup> The reaction proceeded very cleanly to the desired hydroxyl acetate **3.68**, but the pH of the reaction mixture had to be adjusted over time using NaOH. Indeed, the acidity of the mixture increased as the deacetylation occurred, which can be harmful for the enzymes. In order to determine the ee of the reaction, the racemic form of **3.68** had to be prepared (Scheme 151).

<sup>&</sup>lt;sup>88</sup> Morgan, B.; Dodds, D. R.; Zaks, A.; Andrews, D. R.; Klesse, R. J. Org. Chem. **1997**, 62, 7736–7743.

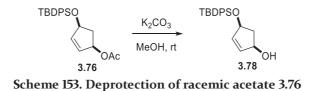


Monoacetylation of the cis-diol **3.74** was tested under various conditions. When acetic anhydride was used in presence of a weak base, only traces of the desired alcohol **3.68** was observed. The use of stronger base such as sodium hydride made the reaction very messy. Substoechiometric amount of acetyl chloride with triethylamine allowed the formation of the monoprotected alcohol **3.68** as major product together with traces of the starting material and a small amount of the diacetate **3.69**. Alcohol **3.68** cannot be seen under UV irradiation, hence derivatization into a UV active compound was necessary (Scheme 152).

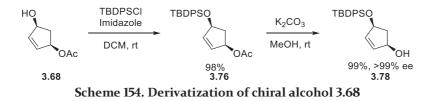


Scheme 152. Derivatization of racemic alcohol 3.68

Three different UV-active compounds have been prepared. First, alcohol protection with benzyl chloride afforded ether **3.75** in 60%. Then, silylation using the bulky TBDPSCl protecting group gave **3.76** in excellent yield. Finally, protection with benzoyl chloride allowed the formation of ester **3.77** in 75% yield. Unfortunately, the two antipodes were unseparable, with each of the three UV-visible compounds, using various elution methods on 7 different columns of the SFC. Hydrolysis of the acetate was thought to increase the polarity of the product which would help for the separation of the two enantiomers (Scheme 153).

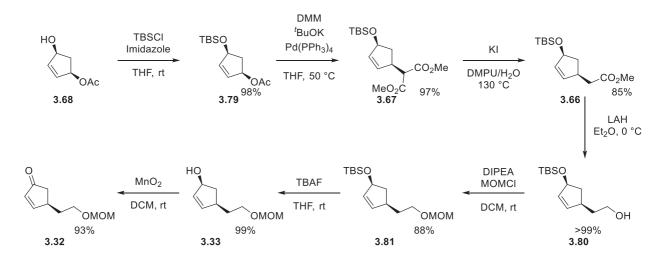


Treatment of **3.76** with basic methanol led to allylic alcohol **3.78** in quantitative yield and in this case, distinct separation of the two enantiomers was observed by SFC. Therefore, derivatization of the enantioenriched alcohol **3.68** to allylic alcohol **3.78** was performed (Scheme 154).



TBDPS-protection followed by hydrolysis of the acetate group afforded alcohol **3.78** in 97% over two steps. Comparison of the later with the racemic compound showed exceptional enantiopurity of >99% ee.

Synthesis of key intermediate **3.32** was performed from enantiopure alcohol **3.68**, as described in Scheme 155.



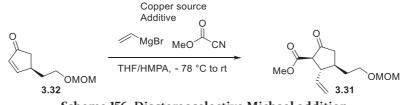
Scheme 155. Preparation of chiral enone 3.32

TBS-protection of the allylic alcohol **3.68** was carried out in THF with TBSCl and imidazole to produce **3.79** in excellent yield. Palladium-catalyzed Tsuji-Trost coupling with dimethyl malonate afforded malonate **3.67** almost quantitatively. Krapcho decarboxylation with KI in a mixture of DMI and water afforded the desired monoester **3.66** in 70% yield. Various salts have been tested, such as LiCl, NaCl and KOAc, but all of them led to decomposition. Changing the solvent system to DMF/H<sub>2</sub>O and DMSO/H<sub>2</sub>O afforded the desired product in 58% and 61%, respectively. Using DMPU with water, the yield increased to 85% when heating at 130 °C. The use of higher temperature only led to decomposition. Monohydrolysis of the malonate **3.67** using five equivalents of KOH in methanol allowed the formation of the corresponding acid in 88% yield. Decarboxylation was then attempted under numerous conditions but ester **3.66** was never obtained.

LAH reduction of the ester **3.66** to the corresponding alcohol **3.80** was quantitative when performing the reaction in Et<sub>2</sub>O, but reached only 90% in THF. MOM-protection gave the best results using Hünig's base in DCM, affording 85% of the protected alcohol **3.81**. A slower reactivity was observed in THF and a catalytic amount of DMAP had no influence on the yield in DCM nor in THF. Silyl-deprotection was efficient using TBAF and led to allylic alcohol **3.33** in 92% yield. PCC-oxidation of the latter yielded enone **3.32** in 81%. Cleaner oxidation was observed using MnO<sub>2</sub> in DCM and the desired enone **3.32** was isolated in this case in 93% yield.

# 3.2.2. Towards the Key Step: Michael Addition Using Vinylmagnesium Bromide

The diastereoselective Michael addition of a vinyl unit onto cyclopentenone **3.32** followed by quenching of the resulting enolate with Mander's ester was then investigated (Scheme 156).



Scheme 156. Diastereoselective Michael addition

Entry	Copper source	Grignard	Additive	Results
1	CuBr•DMS (2 equiv)	4 equiv	-	Decomposition
2	CuCN (2 equiv)	4 equiv	-	Decomposition
3	Cul (2 equiv)	4 equiv	-	Decomposition
4	Cul (0.5 equiv)	l equiv	-	Slow 1,4-addition
5	CuCN (0.5 equiv)	l equiv	-	Messy
6	CuBr•DMS (0.1 equiv)	1.9 equiv	TMEDA (1.8 equiv)	Messy
7	CuCN (0.1 equiv)	1.9 equiv	TMEDA (l.8 equiv)	48%
8	Cul (0.1 equiv)	1.9 equiv	TMEDA (l.8 equiv)	66% (83%) <sup>a</sup>

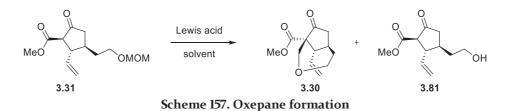
Table 18. Representative conditions for the diastereoselective Michael addition

<sup>a</sup>: Isolated yield on 25 mmol.

Second order cuprate were the first organometallic reagents to be prepared. Using the best reaction conditions optimized for the previous Michael addition of vinyl onto cyclohexenone (see Chapter 2.4.2) were not successful. Indeed, under these conditions, only decomposition was observed (entry 1). Studying the influence of the copper source did not result in any formation of product (entries 2 and 3). We decided to decrease the amount of copper and Grignard reagent. In the case of copper iodide, the 1,4-addition occurred, but the reactivity was very slow (entry 4). Under the same conditions but using copper cyanide, the reaction was much more messy (entry 5). Then, we moved to the catalytic cuprate addition with TMEDA as additive. Catalytic amount of copper source to copper cyanide has a positive outcome, as 48% of the desired product **3.31** was isolated (entry 7). The reaction became much cleaner when using copper iodide and 83% of the  $\beta$ -ketoester was isolated on 25 mmol.

### 3.2.3. First Key Step of the Synthesis: Oxepane Formation

With the newly formed trisubstituted cyclopentanone **3.31**, we were able to investigate the first key step of the synthesis; the formation of the oxepane skeleton (Scheme 157). Based on the previous screening for the construction of the oxabicyclo[4.3.1]decanone, a selection of Lewis acids were tested (Table 19).



Entry	Lewis acid	solvent	Isolated Yield <sup>a</sup>
1	MgBr <sub>2</sub>	DCM	41% (3:2)
2	MgBr <sub>2</sub>	DCE	41% (3:2)
3	$MgI_2$	DCM	37% (3:2)
4	$MgI_2$	DCE	45% (2:1)
5	MgBr <sub>2</sub> •OEt	DCM	n.d. (1:1.2)
6	MgBr <sub>2</sub> •OEt	DCE	n.d. (2:3)
7 <sup>b</sup>	InBr <sub>3</sub>	DCE	n.d. (1:2.3)
8	ScOTf <sub>3</sub>	DCE	n.d. (1:1.1)
<b>9</b> <sup>c</sup>	MgBr <sub>2</sub>	DCE	37%
10 <sup>d</sup>	MgBr <sub>2</sub>	DCE	33%
11 <sup>c</sup>	$MgI_2$	DCE	Decomposition
12 <sup>e</sup>	$MgI_2$	DCE	32%
$\mathbf{B}^{\mathrm{f}}$	$MgI_2$	DCE	49%

Table 19. Representative conditions for the oxepane formation

Entries 1 to 8 were performed with 3 equivalents of Lewis acid and a concentration of 0.05 M at rt. Entries 9 to 11 were performed at 50 °C.

<sup>a</sup>: Isolated yield of **3.30** and the ratio between the desired product and the free alcohol **3.81** is in bracket.

<sup>b</sup>: A mixture of diastereoisomers of **3.81** were isolated, both with the ketone moiety.

<sup>c</sup>: The concentration was 0.1 M.

<sup>d</sup>: The concentration was 0.02 M.

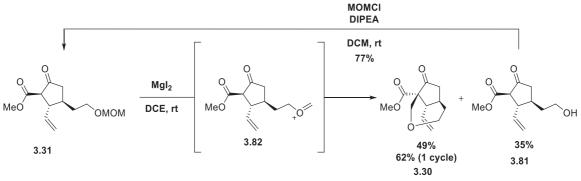
<sup>e</sup>: 2 equivalents of Lewis acid were used with a concentration of 0.05 M at rt.

<sup>f</sup>: The reaction was performed with a concentration of 0.02 M at rt with 3 equivalents of Lewis acid.

The first Lewis acid chosen for this transformation was MgBr<sub>2</sub> in DCM, as this was the best system in our racemic synthesis (see Chapter 2.4.3). Under these conditions, the oxabicyclo[4.2.1]nonanone was formed with an encouraging yield of 41%. This Lewis acid also promoted the deprotection of the MOM group and afforded the corresponding alcohol in 27% (entry 1). Changing the solvent from DCM to DCE had no influence on the ratio nor the yield (entry 2). Magnesium(II) iodide was tested and gave a slightly lower yield in DCM with the same ratio (entry 3). However, when performing the reaction in DCE, the yield increased to 45% and the ratio for the formation of the oxepane was higher than before (entry 4). A few other Lewis acids were tested to observe the variation of the ratio between the two products. MgBr<sub>2</sub>•OEt in DCM favored slightly the formation of alcohol **3.81** (entry 5), but when DCE was used, the ratio towards this side product increased considerably (entry 6). Indium(III) bromide provided some interesting results. Although it favored the deprotection, we observed the formation of two diastereoisomers of **3.81** (entry 7). The  $\beta$ -

ketoester moiety can tautomerize between the keto and enol forms, epimerizing the center. Finally, scandium triflate was used for the transformation but did not have any selectivity for the reaction (entry 8).

Further optimization of the reaction was accomplished using MgBr<sub>2</sub> and MgI<sub>2</sub> in DCE. At 0 °C, the reaction was much slower and after two days, a mixture of starting material, desired product and deprotected alcohol was observed with MgBr<sub>2</sub>. Only traces of alcohol **3.81** could be detected in the case of MgI<sub>2</sub>. At this temperature, the concentration had only little impact on the ratio of the products formed. When increasing the temperature to 50 °C, no formation of the alcohol **3.81** was observed with each Lewis acid. MgBr<sub>2</sub> was not harmful for the reaction at this temperature and afforded as a major product the desired oxepane **3.30** (entries 9-10). However, increasing the concentration to 0.1 molar decomposed the compounds when MgI<sub>2</sub> was used at 50 °C (entry 11). Lowering the amount of this Lewis acid to 2 equivalents decreased the yield to 32% (entry 12). Screening of the concentration at room temperature showed that lowering to 0.02 molar did not slow down the reaction rate and improved the yield of **3.30** to 49% with MgI<sub>2</sub>, but it indeed slowed down the reactivity when MgBr<sub>2</sub> was used (entry 13). It is important to note that scaling up the reaction under the best conditions allowed a reproducible yield and 35% of the deprotected alcohol **3.81** was recovered (Scheme 158).

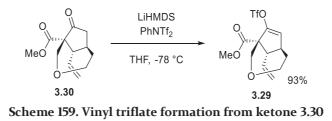


Scheme 158. Recycling of by-product 3.81 from the key step

The overview of the first key step shows that the portion which was deprotected can be recycled. Indeed, upon submission to MOMCl, DIPEA in DCM, 77% of the key step precursor **3.31** was regenerated. Hence, upon one recovery cycle, the yield of **3.30** reached 62%.

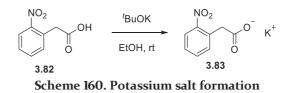
## 3.2.4. Second Key Step of the Synthesis: Decarboxylative Coupling

Vinyl triflate had to be prepared for the second key step of the synthesis (Scheme 159).



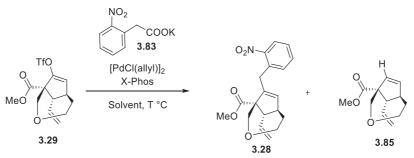
Deprotonation of **3.30** at low temperature with LiHMDS formed *in-situ* the enolate which was further quenched with phenyl triflimide to afford the vinyl triflate **3.29** in 93% yield. When employing Comin's reagent to generate **3.29**, the yield dropped to 58%.

The second partner **3.83** for the coupling was prepared by deprotonation of commercially available 2-nitrophenylacetic acid **3.83** with potassium *tert*-butoxide (Scheme 160).



The second key step of our synthesis is the palladium-catalyzed decarboxylative vinylation of potassium nitrophenyl acetate, a methodology developed in our group (Scheme 161).<sup>89</sup>

<sup>&</sup>lt;sup>89</sup> Xu, Z.; Wang, Q.; Zhu, J. Angew. Chemie - Int. Ed. 2013, 52, 3272-3276.



Scheme 161. Palladium-catalyzed decarboxylative coupling

Entry	[PdCl(allyl)] <sub>2</sub>	X-Phos	Temperature	Solvent	Isolated Yield
1	5 mol%	15 mol%	100 °C	DMF	31%
2	5 mol%	15 mol%	100 °C	diglyme	31%
3	5 mol%	15 mol%	140 °C	DMF	Decomposition
4	5 mol%	15 mol%	140 °C	diglyme	Decomposition
5	5 mol%	15 mol%	120 °C	DMF	20%
6	5 mol%	15 mol%	120 °C	diglyme	37%
7 <sup>a</sup>	5 mol%	15 mol%	140 °C	diglyme	45%
<b>8</b> <sup>a</sup>	10 mol%	30 mol%	140 °C	diglyme	60%
<b>9</b> <sup>a,b</sup>	10 mol%	30 mol%	140 °C	diglyme	69%

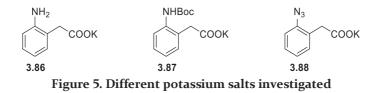
Table 20. Representative conditions for the decarboxylative coupling

<sup>a</sup>: O<sub>2</sub>-free diglyme was used.

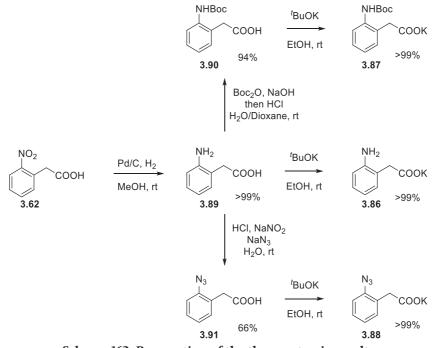
<sup>b</sup>: 2 mmol scale.

The first conditions tested for this coupling afforded the desired product **3.28** in a modest 31% yield (entry 1). DMF was substituted by diglyme but led to the same yield (entry 2). Increasing the temperature to 140 °C decomposed quickly the compound, in both DMF and diglyme (entries 3-4). Diminishing the temperature to 120 °C gave a low yield in DMF (entry 5), most probably because of the self-decomposition of the solvent at this temperature. However, using diglyme as solvent, a slightly higher yield was observed (entry 6). The use of degassed diglyme, by freeze-pump-thaw technic, allowed to rise up the temperature to 140 °C without noticeable decomposition. Indeed, under these conditions, 45% of the coupling adduct was formed (entry 7). Increasing the amount of palladium and ligand further improved the yield to 60% (entry 8). When the reaction was scaled up, protodepalladation product **3.85** was observed in only 5% yield and the yield of the cross-coupling reached 69% (entry 9). The formation of **3.85** could be explained by the steric hindrance generated by the quaternary carbon  $\alpha$  to the vinyl triflate functionality of **3.29**.

As synthetic usefulness, we decided to investigate other coupling partners which could be used for the synthesis (Figure 5).



Free aniline **3.86**, Boc-protected aniline **3.87** and aryl azide **3.88** potassium-salts could be prepared from the same commercially available 2-nitrophenylacetic acid **3.82** (Scheme 162).

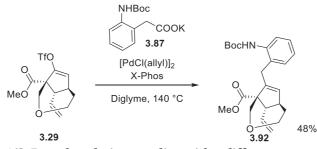


Scheme 162. Preparation of the three potassium salts

Reduction of the nitro group was performed by palladium-catalyzed hydrogenation in methanol and afforded the corresponding aniline **3.89** in quantitative yield. Protection of the latter with Boc<sub>2</sub>O allowed the formation of **3.90** with an excellent yield. Aniline **3.89** was transformed to aryl azide **3.91** using the Sandmeyer's conditions.<sup>90</sup> The three different acids were converted into their corresponding potassium salt using potassium *tert*-butoxide in ethanol in quantitative yield.

<sup>90</sup> Sandmeyer, T. Berichte der Dtsch. Chem. Gesellschaft 1884, 17, 1633–1635.

The three potassium salts were tested for the palladium-catalyzed decarboxylative coupling (Scheme 163).

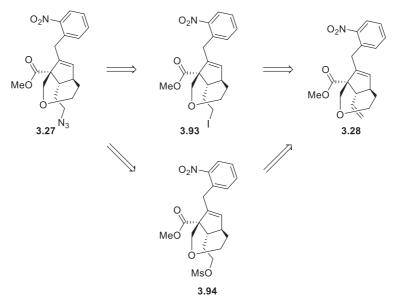


Scheme 163. Decarboxylative coupling with a different potassium salt

Under the optimized conditions used for potassium nitrophenyl acetate, only the Bocprotected aniline afforded the corresponding coupling product **3.92** in 48% isolated yield, the two other potassium salts leading to only decomposition.

3.2.5. Functionalization of the Terminal Olefin

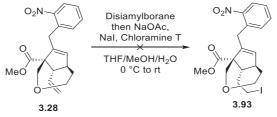
Functionalization of the terminal double bond was investigated (Scheme 164).



Scheme 164. Retrosynthesis pathways for the functionalization of the olefin

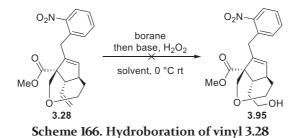
The original idea was similar to the functionalization of the vinyl for the racemic synthesis. A hydroboration/iodination sequence would afford intermediate **3.93** and subsequent substitution by an azide source would provide **3.27**. An alternative route would be by hydroboration/oxidation followed by mesylation of the so-formed alcohol leading to **3.94**. Substitution of the mesylate by an azide source should also afford the desired intermediate **3.27**.

Hence, the first sequence of the shorter route was studied (Scheme 165).



Scheme 165. Hydroboration/iodination sequence

The hydroboration of the terminal alkene **3.28** followed by oxidation to introduce the iodide led to complete decomposition. Changing the solvent for Et<sub>2</sub>O or DCM had no difference on the outcome of the reaction. Various boranes have been tested for this reaction, such as 9-BBN, BH<sub>3</sub>•THF, but the same results were observed. We decided to follow the alternative route to reach the alcohol (Scheme 166).

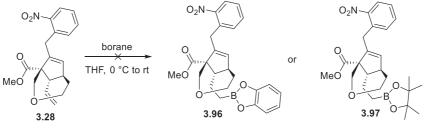


Entry	Borane	Borane Base		Remarks
1	9-BBN	NaOH buffered pH=7	THF	Decomposition
2	Disiamylborane	NaOH buffered pH=7	THF	Decomposition
3	BH <sub>3</sub> •THF	NaOH buffered pH=7	THF	Decomposition
4	Disiamylborane	NaOAc	THF	Decomposition
5	Disiamylborane	NaBO <sub>3</sub> .H <sub>2</sub> O	THF	Decomposition
6	Disiamylborane	Na <sub>2</sub> CO <sub>3</sub>	THF	Decomposition
7	9-BBN	NaHCO <sub>3</sub>	THF	Decomposition
8	Disiamylborane	NaHCO <sub>3</sub>	THF	Decomposition
9	BH <sub>3</sub> •THF	NaHCO <sub>3</sub>	THF	Decomposition
10	Disiamylborane	NaHCO <sub>3</sub>	DCM	Decomposition
11	Disiamylborane	NaHCO <sub>3</sub>	Et <sub>2</sub> O	Decomposition

Table 21. Representative conditions for the hydroboration of vinyl 3.28

Unfortunately, using either 9-BBN, disiamylborane or BH<sub>3</sub>•THF, the oxidation step decomposed the compound rapidly (entries 1-3). Replacing the base by NaOAc, NaBO<sub>3</sub>.H<sub>2</sub>O or Na<sub>2</sub>CO<sub>3</sub>, when disiamylborane was used for the hydroboration, led to the same observation (entries 4-6). We moved to a weaker base, sodium bicarbonate and tested the hydroboration using the three different boranes, but only decomposition was again observed (entries 7-9). Finally, changing the solvent to DCM or Et<sub>2</sub>O gave no different outcome (entries 10-11).

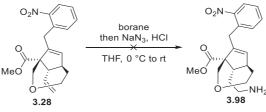
As the previous boranes gave very poor results, we chose to move to the use of less activated boranes for the hydroboration step in order to try to isolate the intermediate (Scheme 167).



Scheme 167. Hydroboration with less activated boranes

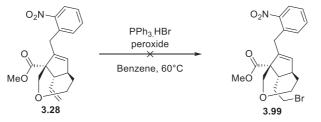
Catecholborane, pinacolborane and its dimer form have been tested for this reaction but no reactivity was observed. Upon heating, the starting material began to decompose starting from 45  $^{\circ}$ C.

Hydroamination is synthetically more challenging, but is a more straightforward approach, as a nitrogen atom is required in our case (Scheme 168).



Scheme 168. Hydroamination of vinyl 3.28

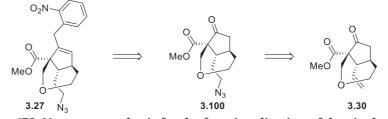
Unfortunately, the choice of borane had no influence as all of them led to decomposition. Finally, radical bromination was attempted (Scheme 169).



Scheme 169. Anti-Markovnikov bromination of the terminal double bond

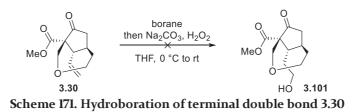
Initiated by a peroxide, homolytic cleavage of the hydrogen-bromide bond should occur, leading to the anti-Markovnikov bromination of the double bond. Benzoyl peroxide and lauroyl peroxide were tested but both conditions decomposed the starting materials.

The intermediate **3.28** appeared to be very unstable towards any type of conditions, whether acidic, basic or radical. We also observed simple decomposition of the intermediate when stored in the freezer after a few weeks. Then, we decided to slightly change the route to **3.27** by incorporating the azide functionality before the decarboxylative vinylation step (Scheme 170).



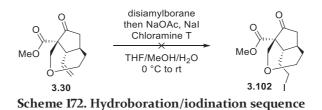
Scheme 170. New retrosynthesis for the functionalization of the vinyl moiety

Functionalization of the terminal double bond was tackled similarly as previously (Scheme 171).



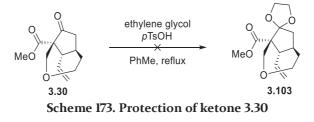
Standard hydroboration/oxidation process should afford alcohol **3.101**. However, neither 9-BBN nor disiamylborane led to the desired compound. Oxidation using sodium perborate gave the same outcome as the previous conditions, only decomposition was observed.

The hydroboration/iodination sequence was also attempted (Scheme 172).

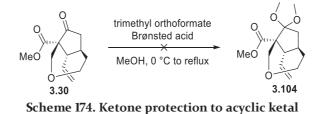


At first, we observed no reactivity, even when heating the reaction mixture to 45 °C. Excess of reagents were added at 0 °C but a rapid decomposition was perceived.

We hypothesized that the  $\beta$ -ketoester moiety from **3.30** might cause a problem as it could coordinate with the borane, increasing considerably the bulk around the alkene. To avoid any complexation, we thought to protect the ketone **3.30** (Scheme 173).

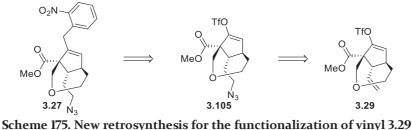


Surprisingly, with excess of reagents, no reaction was observed. Pushing the reaction with a Dean-Stark system or by adding molecular sieves had no impact on the reactivity, only the starting material was recovered. Although 1,4-dioxaspiro[4.4]nonane bearing a quaternary center in  $\alpha$  are reported, we believed that it might be too strained to be formed with our substrate. Hence, protection of the ketone **3.30** with trimethyl orthoformate was tested (Scheme 174).



Reaction of ketone **3.30** with trimethyl orthoformate catalyzed by a Brønsted acid, such as pTsOH or HCl should provide dimethyl ketal **3.104**. TBABr<sub>3</sub> was also used to activate the orthoformate but none of the above conditions afforded the desired product, even at reflux in methanol.

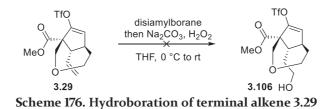
An alternative route to avoid the presence of the  $\beta$ -ketoester moiety, thus bypassing the tedious and steppy protection/deprotection sequence, would be to functionalize the alkene from the triflate intermediate **3.29** (Scheme 175).



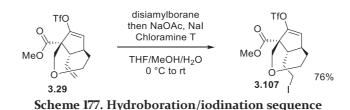
Scheme 1/3. New retrosynthesis for the functionalization of viny 5.29

Very similar as the previous strategy, the precursor for the iORC **3.27** would be formed by decarboxylative coupling of the azide **3.105** with potassium salt **3.83**. The azide intermediate **3.105** would be obtained by functionalization of the vinyl moiety of **3.29**.

Hydroboration/oxidation of substrate 3.29 would afford alcohol 3.106 (Scheme 176).



Once again, hydroboration of the double bond, followed by oxidation, led to decomposition. With little hope, we tested the hydroboration/iodination sequence to obtain directly the alkyl iodide moiety (Scheme 177).



Traces of the iodide **3.107** were observed when two equivalents of disiamylborane were used. Increasing the amount of borane to 5 equivalent afforded 32% of the product but almost 50% of the starting material was recovered. Finally, 15 equivalents of disiamylborane were required for the reaction to proceed to full conversion and 76% of the desired iodide intermediate **3.107** was isolated.

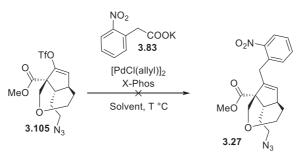
It is important to mention that the purification is needed for the next step as chloramine T cannot be removed during the work up. Also, we realized that the iodide intermediate is highly unstable and decomposes very quickly at room temperature. It cannot be stored even in the freezer without decomposing in a couple of days. Hence, the iodide has to be freshly prepared. Different types of purification have been tested but the main factor for the highest yield is the time taken to perform the column chromatography.



Scheme 178. Substitution with sodium azide

Substitution with sodium azide afforded compound **3.105** in 70% yield (Scheme 178). However, we observed inconsistent yields for this substitution. We believe the starting material partially decomposes under the reaction conditions. To minimize any decomposition due to light, the flask was covered with aluminum foil.

Azide intermediate **3.105** was then submitted to the decarboxylative coupling step (Scheme 179).



Scheme 179. Palladium-catalyzed decarboxylative coupling with azide 3.105

Entry	[PdCl(allyl)] <sub>2</sub>	X-Phos	Temperature	Solvent	Remark
1	10 mol%	30 mol%	140 °C	Diglyme	Decomposition
2	10 mol%	30 mol%	120 °C	Diglyme	Decomposition
3	10 mol%	30 mol%	100 °C	Diglyme	Very messy
4	10 mol%	30 mol%	100 °C	DMF	DP observed
5 <sup>a</sup>	10 mol%	30 mol%	100 °C	Diglyme	Very messy
<b>6</b> <sup>a</sup>	10 mol%	30 mol%	100 °C	DMF	DP observed
7	5 mol%	15 mol%	100 °C	DMF	DP observed
8	2 mol%	6 mol%	100 °C	DMF	Slow conversion
9	1 mol%	3 mol%	100 °C	DMF	Slow conversion

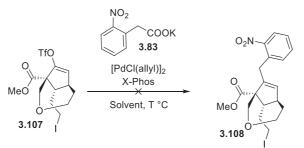
Table 22. Representative conditions for the decarboxylative coupling with azide 3.105

<sup>a</sup>: S-Phos was used instead of X-Phos.

Running the reaction in diglyme at 140 °C or 120 °C decomposed the triflate partner (entries 1-2). Lowering further to 100 °C in diglyme led to a very messy reaction, without traces of the desired compound **3.27** (entry 3). However, when carrying the reaction in DMF, the desired product was seen in traces amount in the crude (entry 4). Changing the ligand to S-Phos showed the same results in diglyme or DMF (entries 5-6). Decreasing the amount of palladium and ligand by half afforded a trace amount of the desired compound **3.27** (entry 7). Lowering further the catalyst and ligand loading decreased the rate of the reaction hence, more decomposition was observed (entries 8-9). Unfortunately, after several

attempts, the isolation of pure desired product failed, due to the presence of only tiny amount of materials in the messy mixtures.

The coupling was also tested with the iodo compound 3.107 (Scheme 180).



Scheme 180. Palladium-catalyzed decarboxylative coupling with iodo 3.107

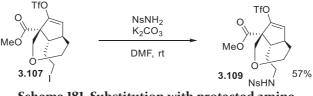
Entry	[PdCl(allyl)] <sub>2</sub>	X-Phos	Temperature	Solvent	Remark
1	10 mol%	30 mol%	140 °C	Diglyme	Decomposition
2	10 mol%	30 mol%	120 °C	Diglyme	Decomposition
3	10 mol%	30 mol%	100 °C	Diglyme	Decomposition
4	10 mol%	30 mol%	100 °C	DMF	Decomposition
<b>5</b> <sup>a</sup>	10 mol%	30 mol%	100 °C	Diglyme	Decomposition
<b>6</b> <sup>a</sup>	10 mol%	30 mol%	100 °C	DMF	Decomposition

Table 23. Representative conditions for the decarboxylative coupling with iodo 3.107

<sup>a</sup>: S-Phos was used instead of X-Phos.

When employing the best conditions for the vinyl substrate **3.29**, the iodo intermediate **3.107** quickly decomposed (entry 1). Lowering the temperature to 120 °C or 100 °C led to the same observation (entries 2-3). Switching solvent to DMF at 100 °C was not suitable for the substrate (entry 4). Replacing the ligand by S-Phos at 100 °C in either diglyme or DMF did not afford any product (entries 5-6). We believe the stability of the iodo intermediate **3.107** was not sufficient for bearing these harsh conditions, even if the reaction time was short.

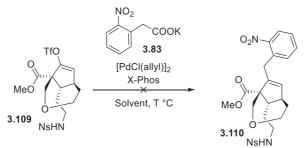
After the multiple failures encountered with the last two substrates, for the decarboxylative coupling step, we thought to substitute the iodide by a more stable nitrogen-containing moiety (Scheme 181).



Scheme 181. Substitution with protected amine

The substitution of iodide by nosyl amide in presence of cesium carbonate proved to be ineffective when acetone was used as solvent. Changing to DMSO improved slightly the amount of product formed, but the reaction was messy. However, replacing the base to potassium carbonate allowed a cleaner reaction. Finally, using the latter base and DMF as solvent afforded the desired protected amine **3.109** in 57% isolated yield.

With the new substrate in hand, we were able to submit it to the coupling conditions (Scheme 182).



Scheme 182. Palladium-catalyzed decarboxylative coupling with protected amine 3.109

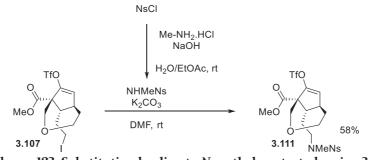
Entry	[PdCl(allyl)] <sub>2</sub>	X-Phos	Temperature	Solvent	Remark
1	10 mol%	30 mol%	140 °C	Diglyme	Decomposition
2 <sup>a</sup>	10 mol%	30 mol%	140 °C	Diglyme	Decomposition
3	10 mol%	30 mol%	100 °C	DMF	Decomposition
4	10 mol%	30 mol%	100 °C	Diglyme	Decomposition
2 1 6	1. 1 (37.7	21			

Table 24. Representative conditions for the decarboxylative coupling with protected amine 3.109

<sup>a</sup>: dppf was used instead of X-Phos.

Previously optimized for the vinyl substrate **3.29**, the best conditions were tested with the protected amine **3.109** but led to decomposition (entry 1). Changing the ligand by dppf did not afford any product (entry 2). Decreasing the temperature to 100 °C afforded only decomposition in both diglyme and DMF (entries 3-4).

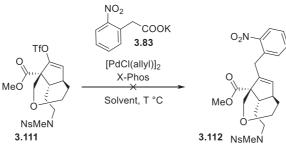
We believed that the free N-H- bond of the amine might prevent the reaction to proceed, by coordination of the substrate to palladium. Hence, a new coupling partner was synthesized (Scheme 183).



Scheme 183. Substitution leading to N-methyl-protected amine 3.111

First, N-methyl-*p*-nitrobenzenesulfonamide was prepared from nosyl chloride and methyl amine in 87% yield. Substitution of the iodo from **3.107** using *N*-methyl nosylamide was performed in DMF with potassium carbonate as base and allowed formation of the desired *N*-methylamine **3.111** in 58% yield.

The new substrate was tested under the coupling conditions (Scheme 184).



Scheme 184. Palladium-catalyzed decarboxylative coupling with N-methyl-protected amine 3.111

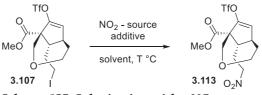
 Table 25. Representative conditions for the decarboxylative coupling with N-methyl-protected amine 3.111

Entry	[PdCl(allyl)] <sub>2</sub>	X-Phos	Temperature	Solvent	Remark
1	10 mol%	30 mol%	140 °C	Diglyme	Decomposition
2	10 mol%	30 mol%	100 °C	DMF	Decomposition
3	10 mol%	30 mol%	100 °C	Diglyme	Decomposition
<b>4</b> <sup>a</sup>	10 mol%	30 mol%	100 °C	DMF	Decomposition
5 <sup>a</sup>	10 mol%	30 mol%	100 °C	Diglyme	Decomposition

<sup>a</sup>: dppf was used instead of X-Phos.

Under the optimized conditions used for the vinyl substrate **3.29**, the *N*-methylamine **3.111** decomposed (entry 1). Decreasing the temperature to 100 °C was not sufficient enough to prevent the decomposition (entries 2-3) and replacing the ligand by dppf led to the same results (entries 4-5).

As the azide substrate **3.105** and the two different sulfonamides **3.109** and **3.111** did not afford, under any conditions, the desired coupling product, we envisioned a new functional group containing the needed nitrogen. Iodo intermediate **3.107** could be substitute to reach a new substrate containing a nitro alkyl group **3.113** (Scheme 185).



Scheme 185. Substitution with a NO<sub>2</sub>-source

Entry	NO <sub>2</sub> -source	Additive	Solvent	Temperature	Remark
1	NaNO <sub>2</sub>	-	DMF	rt	Decomposition
2	AgNO <sub>2</sub>	-	$Et_2O/H_2O$	rt	Decomposition
3	$NaNO_2$	-	DMF	0 °C	Decomposition
4	AgNO <sub>2</sub>	-	$Et_2O/H_2O$	0 °C	Decomposition
5	NaNO <sub>2</sub>	-	DMF	50 °C	Decomposition
6	NaNO <sub>2</sub>	-	DMSO	50 °C	Decomposition
7 <sup>a</sup>	NaNO <sub>2</sub>	-	DMF	50 °C	Decomposition
<b>8</b> <sup>a</sup>	NaNO <sub>2</sub>	-	DMSO	50 °C	Decomposition
9	$NaNO_2$	Phloroglucinol	DMF	rt	70% isolated yield
10	NaNO <sub>2</sub>	Phloroglucinol	DMSO	rt	DP observed, messy

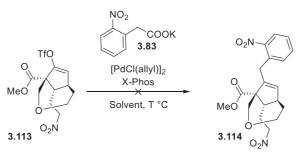
Table 26. Representative conditions for the substitution with a NO<sub>2</sub>-source

<sup>a</sup>: The reaction was performed in the microwave for 15 min.

The substitution was explored with two different NO<sub>2</sub>-source; sodium nitrite and silver nitrite. When mixing NaNO<sub>2</sub> with the iodo intermediate **3.107** in DMF, only decomposition was observed (entry 1). The same conclusion was seen with AgNO<sub>2</sub> in a mixture of diethyl ether and water (entry 2). Decreasing the temperature to 0 °C did not prevent the decomposition to happen (entries 3-4). As the iodo compound **3.107** is unstable, we wanted to shorten the reaction time, hence increasing the temperature to 50 °C, but both DMF and DMSO as solvent failed to produce any product (entries 5-6). Experiments using

microwaves were tested, without success (entries 7-8). Phloroglucinol was added as additive to sodium nitrite to minimize the formation of the nitrite ester.<sup>91</sup> Indeed, the desired nitro alkyl **3.113** was isolated in 70% in DMF (entry 9) and was also formed in DMSO (entry 10), although the reaction was more messy in the last case.

We submitted this new nitro-substrate **3.113** to the decarboxylative coupling conditions to study its reactivity and stability (Scheme 186).



Scheme 186. Palladium-catalyzed decarboxylative coupling with nitro 3.113

Entry	[PdCl(allyl)] <sub>2</sub>	X-Phos	Temperature	Solvent	Remark
1	10 mol%	30 mol%	140 °C	Diglyme	Decomposition
2	10 mol%	30 mol%	100 °C	DMF	Decomposition
3	10 mol%	30 mol%	100 °C	Diglyme	Decomposition
4	5 mol%	15 mol%	100 °C	DMF	Very messy
5	5 mol%	15 mol%	100 °C	Diglyme	Very messy
6	2 mol%	6 mol%	100 °C	DMF	Very messy
7	2 mol%	6 mol%	100 °C	Diglyme	Very messy
<b>8</b> <sup>a</sup>	10 mol%	30 mol%	115 °C	Diglyme	Decomposition
<b>9</b> <sup>b</sup>	10 mol%	30 mol%	115 °C	Diglyme	Decomposition

Table 27. Representative conditions for the decarboxylative coupling with nitro 3.113

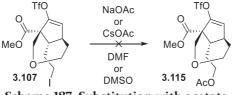
<sup>a</sup>: dppf was used instead of X-Phos. <sup>b</sup>: XanthPhos was used instead of X-Phos.

We believed that the nitroalkyl **3.113** would not be harmed by the harsh reaction conditions previously optimized for the vinyl substrate, but after 2 hours at 140 °C, we observed only decomposition (entry l). Decreasing the temperature to 100 °C led to decomposition in both DMF and diglyme (entries 2-3). Lowering the catalyst and ligand loading afforded also messy reaction mixtures (entries 4-7). Many products were formed but the desired coupling product **3.114** was not detected. Elimination of the nitro group, to form the corresponding

<sup>&</sup>lt;sup>91</sup> Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. *J. Am. Chem. Soc.* **1956**, *78*, 1497–1501.

vinyl **3.29**, was observed as one of the side product. Finally, changing the ligand to dppf (entry **8**) or XanthPhos (entry **9**) resulted in decomposition.

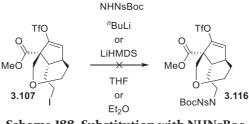
As none of the designed substrate did convert to their corresponding coupling product, we wanted to explore the reactivity of two other potential substrates towards the decarboxylative coupling conditions. The first one would contain an acetate moiety (Scheme 187).



Scheme 187. Substitution with acetate

Sodium acetate was first used in a polar solvent in order to substitute the iodide of **3.107**. As the nucleophilicity of the acetate is diminished by the hard cation, no reaction was observed at room temperature. Rising the temperature only led to decomposition of the starting material. Switching to the more nucleophilic cesium acetate, no substitution was observed after 2 days. Increasing the temperature from the beginning of the reaction to shorten the reaction time failed to yield any product.

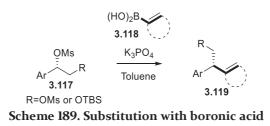
The second substrate which attracted our attention contained a doubly protected amine, as shown in Scheme 188.



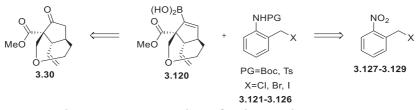
Scheme 188. Substitution with NHNsBoc

LiHMDS was used as base to deprotonate the proton from the sulfonamide carbamate at -78 °C in both THF and Et<sub>2</sub>O. No deprotonation was observed, although the temperature was increased to -40 °C. We believed that the base was too bulky, hence the use of <sup>*n*</sup>BuLi. With the new base, under similar conditions, no product was observed.

Due to the relative instability of the vinyl triflate substrates in the decarboxylative coupling conditions, we decided to investigate a different type of coupling that requires milder conditions. Tang and coworkers reported in 2016 a stereoinvertive nucleophilic substitution of secondary benzylic halides and mesylates by various boronic acids (Scheme 189).<sup>92</sup>

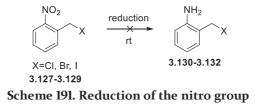


Following our strategy, primary benzyl halide and vinyl boronic acid **3.120** have to be prepared (Scheme 190).



Scheme 190. Retrosynthesis for the coupling partners

No primary benzyl halide has been reported in Tang's paper, hence 6 different coupling partners were prepared for the screening of the reaction. To reach the desired substrates, reduction of the nitroaryl followed by protection of the resulting aniline was envisioned (Scheme 191).



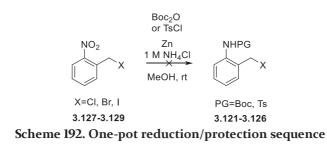
<sup>92</sup> Li, C.; Zhang, Y.; Sun, Q.; Gu, T.; Peng, H.; Tang, W. J. Am. Chem. Soc. 2016, 138, 10774-10777.

Table 28. Representative conditions for the reduction of the nitro group

1 Pd/C, H <sub>2</sub> , EtOH No read	
$\mathbf{I}$ Fu/C, 112, EtOIT NO read	ction
2 Zn, 1 M HCl, MeOH Dimer for	mation
<b>3</b> Zn, 1 M NH <sub>4</sub> Cl, MeOH Dimer for	mation

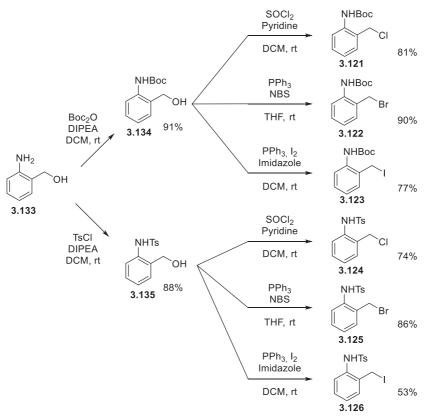
All reactions have been tested using the three different substrates.

Palladium-catalyzed hydrogenation did not reduce the nitro group and only the starting material was recovered (entry 1). Zinc reduction with hydrochloric acid or ammonium chloride proceeded but dimers were obtained as major products (entries 2-3). We believe the so-formed aniline can undergo an intermolecular nucleophilic substitution onto the primary benzyl halide. To avoid formation of polymers, the reduction was performed in presence of the protecting reagents to *in-situ* quench the reactive aniline (Scheme 192).



By using metal zinc in presence of an aqueous solution of ammonium chloride and a large excess of either Boc<sub>2</sub>O or TsCl, the desired product was not formed.

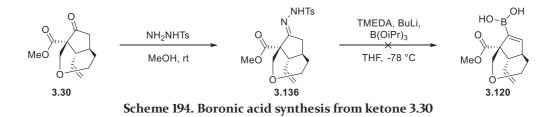
After careful thinking, the route to the desired coupling partners was changed and started from commercially available 2-aminobenzyl alcohol (Scheme 193).



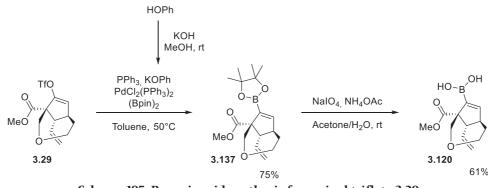
Scheme 193. Preparation of the coupling partners

Chemoselective protection of the aniline **3.133** with Boc<sub>2</sub>O afforded carbamate **3.134** in 91%. Subsequent nucleophilic substitution of the alcohol using thionyl chloride led to benzyl chloride **3.121** in 81%. Benzyl bromide **3.122** was obtained, *via* an Appel-type reaction using NBS and PPh<sub>3</sub>, in 90%. Similarly, benzyl iodide **3.123** was formed in 77%. Three other coupling partners have been prepared from the tosylated aniline **3.135**. Benzyl chloride **3.124**, benzyl bromide **3.125** and benzyl iodide **3.126** were isolated in moderate to good yield using the same chemistry employed for the carbamate derivatives.

Boronic acid **3.120** had to be prepared and attempts from ketone **3.30** were investigated (Scheme 194).<sup>93</sup>



The condensation of tosylhydrazide onto the ketone provided the desired hydrazone **3.136**, but the latter appeared to be very unstable. Indeed, the subsequent reaction never afforded boronic acid **3.120**. A different route towards the desired boronic acid was studied from vinyl triflate **3.29** (Scheme 195).



Scheme 195. Boronic acid synthesis from vinyl triflate 3.29

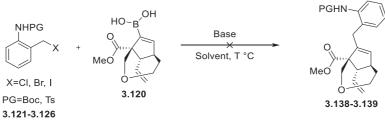
Vinyl triflate **3.29** can be converted to its corresponding vinyl pinacol boronate ester **3.137** by palladium-catalyzed cross-coupling with bis(pinacolato)diboron in 75% yield.<sup>94</sup> Oxidative cleavage of the so-formed boronate afforded boronic acid **3.120** in 61% yield, using sodium periodate and ammonium acetate in a mixture of acetone and water.<sup>95</sup>

The cross coupling of our six different benzyl halides with the alkenylboronic acid partner was then investigated (Scheme 196).

<sup>&</sup>lt;sup>93</sup> Shi, W. M.; Liu, F. P.; Wang, Z. X.; Bi, H. Y.; Liang, C.; Xu, L. P.; Su, G. F.; Mo, D. L. *Adv. Synth. Catal.* **2017**, *359*, 2741–2746.

<sup>94</sup> Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. J. Am. Chem. Soc. 2002, 124, 8001-8006.

<sup>&</sup>lt;sup>95</sup> Patil, A. S.; Mo, D. L.; Wang, H. Y.; Mueller, D. S.; Anderson, L. L. *Angew. Chemie - Int. Ed.* **2012**, *51*, 7799–7803.



Scheme 196. Cross-coupling reaction

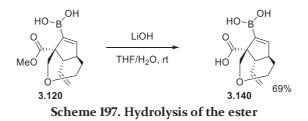
Entry	Base	Solvent	Temperature	Remark
1	K <sub>3</sub> PO <sub>4</sub>	Toluene	80 °C	When X=Cl: boronic acid recovered
1	K3F U4	Toluelle	00 C	When X=Br, I: decomposition
С	Cs <sub>2</sub> CO <sub>3</sub>	Toluene	80 °C	When X=Cl: boronic acid recovered
2	CS2CO3	Toluelle	00 C	When X=Br, I: decomposition
3	КОН	Toluene	80 °C	When X=Cl: ester is hydrolyzed
J	NULL	Toluelle	00 C	When X=Br, I: decomposition
4	K <sub>3</sub> PO <sub>4</sub>	DCE/H <sub>2</sub> O	rt to 50 °C	When X=Cl, Br: start to decompose at 50 °C
4	K3F U4	(50:1)	11 to 50 C	When X=I: start to decompose at rt
5	$C_{\alpha\alpha}C_{\alpha\alpha}$	DCE/H <sub>2</sub> O	50 °C	When X=Cl: boronic acid recovered
5	$CS_2CO_3$	$C_{s_2CO_3}$ (50:1) 50 °C		When X=Br, I: decomposition

Table 29. Representative conditions for the cross-coupling reaction

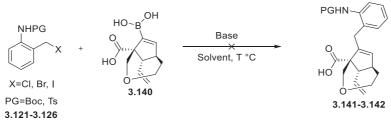
NHTs an NHBoc coupling partners had the same behavior for each condition.

Tang and coworkers have reported their best conditions using the base potassium phosphate in toluene at 80 °C. These conditions did not promote the coupling and benzyl bromide and iodide decomposed at this temperature (entry 1). Changing the base to cesium carbonate showed similar results (entry 2). When potassium hydroxide was used, partial hydrolysis of the ester was observed (entry 3). A mixture of DCE with water proved to be optimal in a similar coupling performed in our group for a different project. Hence, the conditions were tested from room temperature to 50 °C (entry 4) but unfortunately, no reaction was observed. Benzyl iodide started to decompose from 23 °C while the two other partners decomposed at 50 °C. Keeping the same solvent system, cesium carbonate was used but did not promote the reaction, while benzyl bromide and iodide decomposed at this temperature (entry 5).

Hydrolysis of the ester was thought to change the reactivity of the boronic acid *via* intramolecular hydrogen bonding (Scheme 197).



Lithium hydroxide in a mixture of THF and water afforded the carboxylic acid **3.140** in 69% yield. The latter was then tested for the cross-coupling reaction with the six halide partners (Scheme 198).



Scheme 198. Cross-coupling reaction

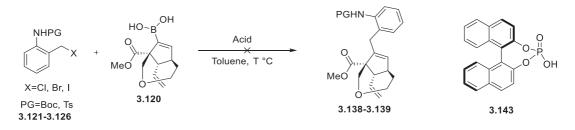
Table 30. Representative conditions for the cross-coupling reaction

Entry	Base	Solvent	Temperature	Remark
1	K <sub>3</sub> PO <sub>4</sub>	Taluana	rt to 100 °C	When X=I: decomposition at rt
1	K3PU4	Toluene	rt to 100 C	When X=Cl, Br: boronic acid recovered
C	$C_{\alpha} C_{\alpha}$	Toluene	rt to 100 °C	When X=I: decomposition at rt
Z	$CS_2CO_3$	Toluelle	ft to 100 C	When X=Cl, Br: boronic acid recovered
3	K <sub>3</sub> PO <sub>4</sub>	DCE/H <sub>2</sub> O	rt to 50 °C	When X=I: decomposition at rt
3	K3PU4	K <sub>3</sub> PO <sub>4</sub> (50:1) <sup>rt</sup>		When X=Cl, Br: boronic acid recovered

NHTs an NHBoc coupling partners had the same behavior for each condition.

Potassium phosphate in toluene was not able to initiate the reaction. Increasing the temperature had no influence on the cross-coupling and only degradation of the benzyl halide was observed (entry 1). Changing the base to cesium carbonate led to the same results (entry 2). Running the reaction in a mixture of DCE and water was not successful neither (entry 3).

We decided to explore the cross-coupling under acidic conditions as the bases tested did not promote the desired transformation and seemed to be harmful for our substrates (Scheme 199).



Scheme 199. Cross-coupling reaction Table 31. Representative conditions for the cross-coupling reaction

Entry	Acid	Temperature	Remark
1	H <sub>3</sub> PO <sub>4</sub>	-20 °C	No reaction
2	H <sub>3</sub> PO <sub>4</sub>	0 °C	When X=Cl: slow decomposition When X=Br, I: decomposition
3	3.143	-20 °C	No reaction
4	3.143	0 °C	When X=Cl: slow decomposition When X=Br, I: decomposition
5	BINOL	rt	When X=I: decomposition When X=Cl, Br: boronic acid recovered
6	BINOL	80 °C	Decomposition
	1.		

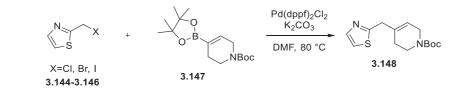
NHTs an NHBoc coupling partners had the same behavior for each condition.

Phosphoric acid was added at -20 °C in toluene but no reaction was observed (entry 1). Increasing the temperature to 0 °C did not promote the cross-coupling and benzyl halides started to decompose (entry 2). Chiral phosphoric acid was thought to have a different behavior towards the reaction but similar results were observed (entries 3-4). In 2012, Schaus and coworkers reported the addition of boronates onto *o*-quinone methides catalyzed by chiral BINOL.<sup>96</sup> Hence, the catalyst was tested but no reaction was observed at room temperature except for the benzyl iodide which decomposed (entry 5). Heating up the reaction mixture to 80 °C showed only decomposition of the chloride and bromide subsstrates (entry 6).

Takhi and coworkers have reported in 2013 a palladium-catalyzed cross-coupling involving vinyl pinacol boronate ester as nucleophile on alkyl halides (Scheme 200).<sup>97</sup>

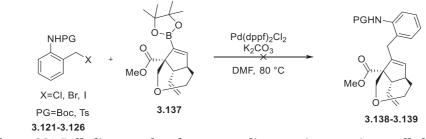
<sup>96</sup> Luan, Y.; Schaus, S. E. J. Am. Chem. Soc. 2012, 134, 19965-19968.

<sup>&</sup>lt;sup>97</sup> Takhi, M.; Hosahalli, S.; Panigrahi, S. K.; Mahadari, M. K.; Kottam, C. R.; Rahman, N.; Yusof, R. *Substituted pyridine derivatives as fabi inhibitors*. WO20I3080222AI, **2011**.



Scheme 200. Takhi's palladium-catalyzed cross-coupling reaction on primary alkyl halide

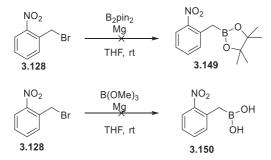
Inspired by this coupling on primary alkyl halide, we tested Takhi's conditions with our coupling partners and studied their reactivity (Scheme 201).



Scheme 201. Palladium-catalyzed cross-coupling reaction on primary alkyl halide

The six benzyl halides were tried, but in each case the result was the same, only decomposition was observed. 2-nitrobenzyl bromide was also tested in the reaction conditions and also led to decomposition.

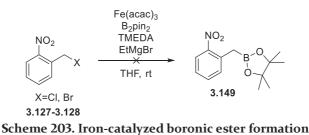
After many failed cross-coupling reactions with alkenylboronic acid as nucleophile, we envisioned to reverse the role of each partner. To do so, 2-nitrobenzyl bromide has to be converted to the corresponding pinacolboronate **3.149** and boronic acid **3.150** by transmetallation (Scheme 202).



Scheme 202. Preparation of boronic ester and boronic acid

The Grignard reagent, obtained from benzyl bromide **3.128** and magnesium, would react with bis(pinacolato)diboron to afford pinacolboronate **3.149**. Similarly, reaction with trimethyl borate followed by hydrolysis would yield boronic acid **3.150**. Activated magnesium was used in each case, but no reaction was observed. Activating reagents such as dibromoethane and iodine were used to further activate the magnesium, but the results were the same and the starting material was recovered.

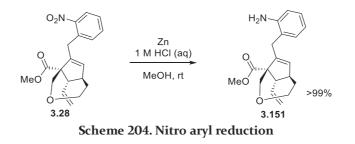
Cook and coworkers reported in 2014 an iron-catalyzed Miyaura-type borylation of alkyl electrophiles.<sup>98</sup> Attempts using 2-nitrobenzyl bromide and chloride were tested (Scheme 203).



Under the reported conditions, both electrophiles decomposed. No trace of the desired product **3.149** was found.

Based on the previous results, the different couplings did not seem to be compatible with our substrates. Hence, we decided to continue with the most advanced intermediate **3.28** obtained and pursue the synthesis.

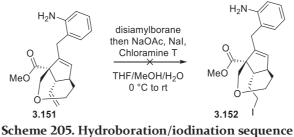
Reduction of the nitro group to the corresponding aniline was thought to stabilize the intermediate, increasing the pKa of the benzylic protons. Indeed, the instability of the nitro aryl compound **3.28** was thought to come from the highly reactive benzylic position as an oxidation could easily occur and further decompose the intermediate (Scheme 204).



<sup>98</sup> Atack, T. C.; Lecker, R. M.; Cook, S. P. J. Am. Chem. Soc. 2014, 136, 9521-9523.

Reduction with zinc and aqueous HCl afforded the aniline **3.151** in quantitative yield and the latter could be stored in the freezer without noticeable decomposition. Reduction of the nitro compound **3.28** with zinc in aqueous NH<sub>4</sub>Cl led to the desired product **3.151** albeit a longer reaction time and a lower yield.

Hydroboration of the vinyl of the aniline intermediate **3.151** was then investigated (Scheme 205).



Scheme 203. Hydroboration/logination sequence

The desired iodo intermediate **3.152** was observed in the crude after the hydroboration/iodination sequence. Unfortunately, the alkyl iodide **3.152** is highly unstable and decomposed under any type of purification. In the case of previous alkyl iodide substrates, the subsequent substitution step proved to be less efficient or unsuccessful when chloramine T was still present in the reaction mixture. Nevertheless, nucleophilic substitutions were investigated from the crude of iodo intermediate **3.152** (Scheme 206).

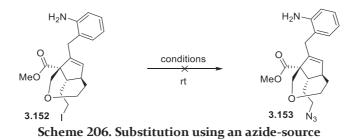
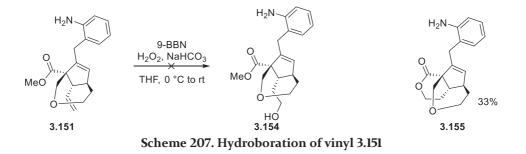


Table 32. Representative conditions for the substitution reaction

Entry	Conditions	Remarks
1	NaN3, DMF	Decomposition
2	TMSN <sub>3</sub> , DMF	Decomposition
3	TMSN <sub>3</sub> , CH <sub>3</sub> CN	Decomposition
4	TBAAz, DMF	Decomposition
5	TBAAz, CH₃CN	Decomposition

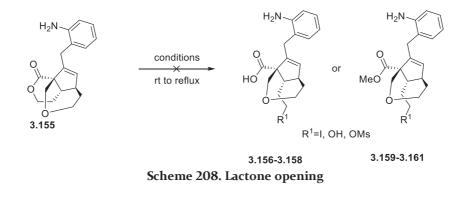
Excess of sodium azide in DMF decomposed the substrate **3.152** (entry 1). The azide source was substituted by TMSN<sub>3</sub>, but running the reaction in both DMF and acetonitrile led to decomposition (entries 2-3). TBAAz was used for the substitution in both DMF and acetonitrile but did not afford any product (entries 4-5). The one-pot hydroboration/iodination/substitution sequence was tested using different azide sources, but only decomposition was seen.

Iodo compound **3.152** being too unstable for any subsequent reaction, we focused on the classical hydroboration leading to the corresponding alcohol **3.154** (Scheme 207).



Anti-Markovnikov addition using 9-BBN followed by oxidation with hydrogen peroxide and sodium bicarbonate led *in-situ* to alcohol **3.154** but the spontaneous trans-lactonization afforded **3.155** in 33% yield. Changing the oxidation conditions did not prevent the intramolecular cyclization to proceed.

We then studied the opening of the lactone **3.155** under neutral or basic conditions (Scheme 208).

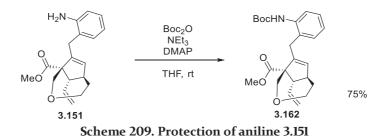


Entry	Conditions	Remarks
1	TMSI, DCM	Decomposition
2	TMSCl, NaI, MeCN	Decomposition
3	KOH(aq), MeOH	Lactone recovery
4	KOH(aq), Dioxane	Lactone recovery
5	KOH(aq), MsCl, MeOH	Lactone recovery
6	NaOH(aq), MeOH	Lactone recovery
7	NaOH(aq), EtOH	Lactone recovery
8	NaOH(aq), MsCl, MeOH	Lactone recovery
9	NaOMe, MeOH	Lactone recovery
10	NaOMe, Dioxane	Lactone recovery
11	NaOMe, MsCl, MeOH	Lactone recovery
12	NaOMe, MsCl, Dioxane	Lactone recovery

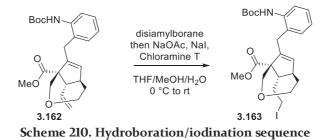
Table 33. Representative conditions for the lactone opening

The first idea was to open the lactone on the  $\delta$  position using an iodide anion which would lead to the iodo alkyl 3.156. Lactone 3.155 was subjected to TMSI but no reaction was observed at room temperature. Refluxing in DCM led to complete decomposition (entry 1). Combining TMSCl and NaI did not promote any reaction. However, when increasing the temperature to 80 °C, only decomposition was observed (entry 2). We believe that rising up the temperature might have promoted the opening of the lactone, but the product was unstable and decomposed. We turned to a more classical method and attempted to hydrolyze the lactone, which would give the free alcohol and carboxylic acid. Aqueous potassium hydroxide in both methanol and dioxane did not afford the desired product, albeit at reflux temperature (entries 3-4). The reaction being reversible, we attempted the opening of the lactone and the subsequent trapping of the so-formed alcohol with mesyl chloride but failed (entry 5). Aqueous solution of sodium hydroxide in methanol or ethanol was not able to afford the carboxylic acid (entries 6-7) and the one-pot lactone opening/alcohol trapping sequence did not work neither (entry 8). Opening of the lactone with sodium methoxide should afford the methyl ester but attempts in both methanol and dioxane were not successful, leading to the lactone recovery (entries 9-10). Finally, trials to allow the formation of the methyl ester and mesylate simultaneously failed (entries 11-12).

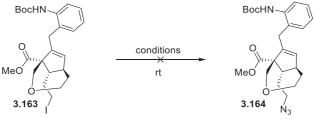
We believed that the aniline **3.151** could get oxidized during the oxidation step of the hydroborations. Hence, protection of the aniline **3.151** was carried out with Boc<sub>2</sub>O (Scheme 209).



The protected aniline **3.162** was isolated in 75% yield and the use of DMAP proved to be important as it accelerates considerably the reaction time. Functionalization of the vinyl was investigated and started with the hydroboration/iodination sequence (Scheme 210).



Once again, the desired product **3.163** was observed in low amount in the crude mixture, but any attempt of isolation failed. The crude was then directly submitted to the substitution step (Scheme 211).



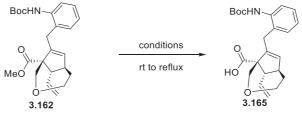
Scheme 211. Substitution with an azide-source

Table 34. Representative conditions for the substitution reaction

Entry	Conditions	Remarks
1	NaN3, DMF	Very messy
2	TMSN <sub>3</sub> , CH <sub>3</sub> CN	Very messy
3	TMSN <sub>3</sub> , DMF	Very messy
4	TBAAz, CH <sub>3</sub> CN	Very messy
5	TBAAz, DMF	Very messy

Sodium azide in DMF did not allow the formation of the desired azide **3.164** (entry 1). TMSN<sub>3</sub> was used as substitute to NaN<sub>3</sub>, in both acetonitrile and DMF, but led to a very messy mixture (entries 2-3). TBAAz was also tested but gave similar results as TMSN<sub>3</sub> and no desired product was detected (entries 4-5). As the iodo alkyl **3.163** seemed to be very unstable, attempts for the one-pot hydroboration/iodination/substitution sequence from alkene **3.162** were explored using different azide sources but none of them succeeded.

Hydrolysis of the ester to the corresponding acid **3.165** was thought to prevent the lactonization to occur during the hydroboration/oxidation step (Scheme 212).



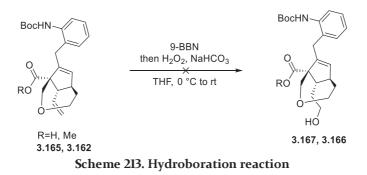
Scheme 212. Hydrolysis of the ester

Tabl	e 35. Repres	entative conditions for	the hydrolysis of the ester
	Entry	Conditions	Remarks

Entry	Conditions	Remarks
1	NaOH, MeOH	Traces of DP
2	KOH, MeOH	Very messy
3	NaOH, EtOH	5% yield
4	NaOH, EtOH/THF	10% yield

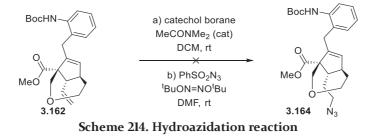
Hydrolysis proved to be harder than expected. Indeed, sodium hydroxide in methanol led to only traces of the desired acid **3.165** (entry 1). Switching to potassium hydroxide made the reaction very messy (entry 2). Changing the solvent to ethanol allowed the formation of 5% of the carboxylic acid (entry 3). When a mixture of ethanol and THF was used with sodium hydroxide, 10% of the desired product was isolated (entry 4).

Although the yield of the reaction was very low, we were able to test the new substrate for different reactions (Scheme 213).



Both substrates **3.165** and **3.162** were tested for the hydroboration, but in both cases, no reaction was observed and the starting material was recovered. Changing the borane to disiamylborane did not improve the outcome of the reaction.

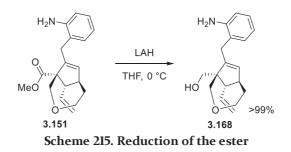
Following the work of Renaud and coworkers, the radical anti-Markovnikov hydroazidation of the vinyl **3.162** was attempted (Scheme 214).<sup>99</sup>



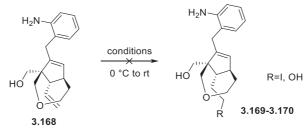
Unfortunately, after several trials, the catechol boronate ester intermediate was not isolated. One-pot hydroboration/azidation led to complete decomposition.

At the same time, to prevent the lactonization, we reduced the ester **3.151** to the corresponding alcohol **3.168**, prior to any functionalization of the vinyl (Scheme 215).

<sup>99</sup> Kapat, A.; König, A.; Montermini, F.; Renaud, P. J. Am. Chem. Soc. 2011, 133, 13890-13893.



LAH reduction in THF afforded the corresponding primary alcohol **3.168** in quantitative yield. Hydroboration on the newly synthetized substrate could be investigated (Scheme 216).



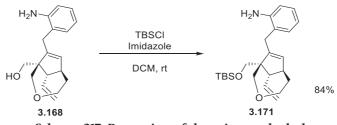
Scheme 216. Hydroborations

Table 36. Representative conditions for the hydroborations

Entry	Conditions	Remarks
1	Disiamylborane then NaOAc, NaI, Chloramine T, THF/MeOH/H2O	Decomposition
2	9-BBN, then NaHCO <sub>3</sub> , H <sub>2</sub> O <sub>2</sub> , THF	Very messy

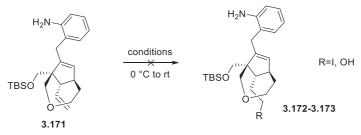
The hydroboration/iodination sequence was tested but led to decomposition (entry 1). Attempt to include the substitution step in the same reaction mixture failed. Hydroboration with 9-BBN followed by oxidation did not lead to the corresponding alcohol and the reaction was very messy (entry 2).

Albeit no tetracyclic compound was observed, which could have been formed from the nucleophilic substitution of the iodide by the alcohol to form a tetrahydropyran, we decided to protect the hydroxyl moiety (Scheme 217).



Scheme 217. Protection of the primary alcohol

TBS-protection afforded the desired silvlated product **3.171** in 84% yield. Hydroboration conditions were then tested (Scheme 218).



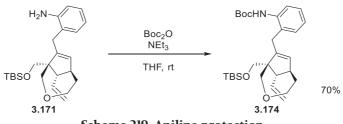
Scheme 218. Hydroborations

Table 37. Representative conditions for the hydroborations

Entry	Conditions	Remarks
1	Disiamylborane then NaOAc, NaI, Chloramine T, THF/MeOH/H <sub>2</sub> O	Decomposition
2	9-BBN, then NaHCO <sub>3</sub> , H <sub>2</sub> O <sub>2</sub> , THF	Messy
3	9-BBN, then NaOH, H <sub>2</sub> O <sub>2</sub> , THF	Decomposition

The hydroboration/iodination sequence afforded a trace amount of the desired product, but decomposed again upon any purification (entry l). Subsequent substitution using the crude mixture led to further decomposition. Hydroboration using 9-BBN afforded a new product which decomposed during the purification step (entry 2). When the stronger base sodium hydroxide was used for the oxidation step of the hydroboration, no product was seen (entry 3).

In order to handle a more stable substrate, aniline protection was carried out with Boc<sub>2</sub>O (Scheme 219).



Scheme 219. Aniline protection

Aniline protection afforded the desired carbamate **3.171** in 70% yield. The use of DMAP as catalyst led surprisingly to a messy reaction. With the protected substrate **3.174** in hands, functionalization of the vinyl was investigated (Scheme 220).

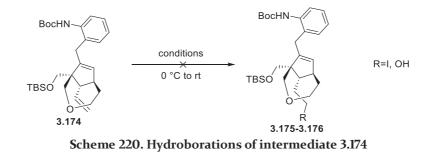
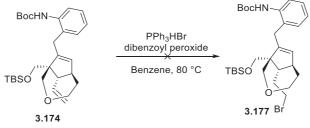


Table 38. Representative conditions for the hydroborations of 3.174

Entry	Conditions	Remarks
1	Disiamylborane then NaOAc, NaI,	Decomposition
1	Chloramine T, THF/MeOH/H <sub>2</sub> O	Decomposition
2	9-BBN, then NaHCO <sub>3</sub> , H <sub>2</sub> O <sub>2</sub> , THF	Decomposition
3	9-BBN, then Na <sub>2</sub> CO <sub>3</sub> , H <sub>2</sub> O <sub>2</sub> , THF	Decomposition
4	Disiamylborane, then NaHCO <sub>3</sub> , H <sub>2</sub> O <sub>2</sub> , THF	Decomposition
5	Disiamylborane, then Na <sub>2</sub> CO <sub>3</sub> , H <sub>2</sub> O <sub>2</sub> , THF	Decomposition
6	Disiamylborane, then NaOH, H <sub>2</sub> O <sub>2</sub> , THF	Decomposition

Hydroboration/iodination sequence led once again to traces of the iodo compound, but decomposed upon purification (entry 1). Attempts to directly substitute the iodine to the azide were tried but without success. We turned to the more classical hydroboration/oxidation conditions which should lead to the corresponding alcohol. The latter should be isolable as no further intramolecular cyclization can occur. However, hydroboration with 9-BBN led to decomposition using sodium carbonate or sodium bicarbonate as base for the oxidation step (entries 2-3). Changing the borane to disiamylborane afforded no isolable product, no matter which base was used in tandem with hydrogen peroxide (entries 4-6).

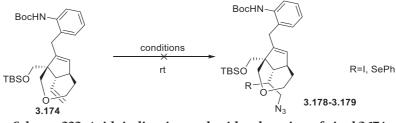
Functionalization of the vinyl moiety of the carbamate **3.174** using radical chemistry was studied (Scheme 221).



Scheme 221. Anti-Markovnikov bromination

The first reaction tested was the anti-Markovnikov bromination, also called Kharasch reaction. Bubbling dry HBr in benzene in presence of a radical initiator led to decomposition of the starting material.

Azidoiodination and azidoselenation were also tried with our new substrate **3.174** (Scheme 222).



Scheme 222. Azidoiodination and azidoselenation of vinyl 3.174

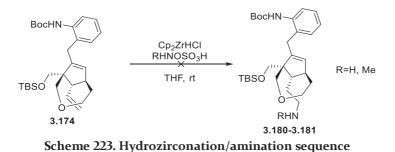
Table 39. Representative conditions for the anti-Markovnikov insertion of azide

Entry	Conditions	Remarks
1	NaN3, KI, NaIO4, AcOH	Decomposition
2	NaN <sub>3</sub> , (PhSe) <sub>2</sub> , PhI(OAc) <sub>2</sub> , DCM	Decomposition

Combination of sodium azide, potassium iodide and sodium periodate in acetic acid should afford the iodo azide **3.178**, but these conditions decomposed our substrate (entry 1). Using hypervalent iodine with (diacetoxyiodo)benzene in presence of sodium azide and diphenyl

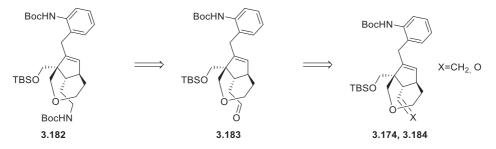
diselenide in DCM should allow the anti-Markovnikov azidation of the vinyl moiety. However, with our substrate, only decomposition was observed (entry 2).

Finally, hydrozirconation/amination sequence was investigated (Scheme 223).



Two different amination reagents were tested to afford a primary amine or a secondary amine. No reaction was observed at room temperature and the substrate in both conditions started to decompose upon heating.

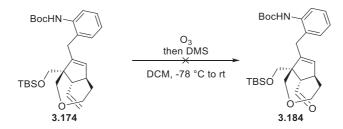
Running out of option for the direct functionalization of the vinyl moiety, a new strategy was explored for the transformation of the terminal olefin (Scheme 224).



Scheme 224. Retrosynthetic analysis of protected amine 3.182 via condensation

Protected amine **3.182** would be obtained by condensation of Boc-amine onto aldehyde **3.183** followed by reduction of the so-formed imine. The carbonyl would arise from the homologation of the oxidized product of alkene **3.174**.

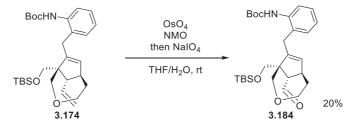
First, chemoselective ozonolysis of the monosubstituted alkene **3.174** was attempted (Scheme 225).



Scheme 225. Ozonolysis reaction

As expected, the reaction was very messy and several aldehydes were observed. Sodium bicarbonate was added as buffer but the outcome of the reaction remained the same. Methanol was used as co-solvent but did not allow a clean formation of the product.

Then, a different oxidation of the double bond to the corresponding aldehyde **3.184** was studied (Scheme 226).



Scheme 226. Johnson-Lemieux oxidation

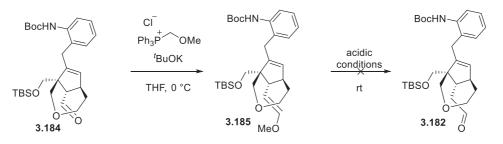
Oxidation of the terminal olefin **3.174** to the corresponding diol and further oxidative cleavage was carried out using osmium tetroxide and NMO followed by addition of sodium periodate. Under these Johnson-Lemieux conditions, 20% conversion to the desired aldehyde **3.184** was observed.<sup>100</sup> Changing the solvent to diethyl ether did not improve the results. Phenylboronic acid was used as additive to stabilize the diol into its boronate ester form but the intermediate could not be isolated.<sup>101</sup> Increasing the amount of equivalents of the reagents led to decomposition. Other oxidative agents have been tested, such as lead(IV) acetate, but only decomposition was observed.

Aldehyde 3.184 was submitted to the Wittig reaction (Scheme 227).<sup>102</sup>

<sup>&</sup>lt;sup>100</sup> Pappo, R.; Allen, D. S.; Johnson, W. S.; Lemieux, R. U. J. Org. Chem. 1956, 21, 478–479.

<sup>&</sup>lt;sup>101</sup> Iwasawa, N.; Kato, T.; Narasaka, K. *Chem. Lett.* **1988**, 1721-1724.

<sup>&</sup>lt;sup>102</sup> Wittig, G.; Schollkopf, U. Chem. Ber. **1954**, 87, 1318–1330.



Scheme 227. Homologation of aldehyde 3.184

Methoxymethylenetriphenylphosphonium chloride is a Wittig reagent which should allow us, after hydrolysis of the enol ether, to reach the homologated aldehyde.<sup>103</sup> In combination with potassium *tert*-butoxide in THF, full conversion of the aldehyde **3.184** was observed. Although the reaction was messy, desired enol ether was detected in the crude. Subsequent hydrolysis in acidic conditions was investigated and results are shown in Table 40.

Table 40. Representative conditions for the hydrolysis of enol ether intermediate 3.185

Entry	Acidic conditions	Remarks
1	1 M HCl, THF	Traces of aldehyde
2	47% HBr, Acetone	Decomposition
3	TFA/DCM	Decomposition
4	pTsOH, Acetone	Decomposition
5	<i>p</i> TsOH, THF/H <sub>2</sub> O	Decomposition

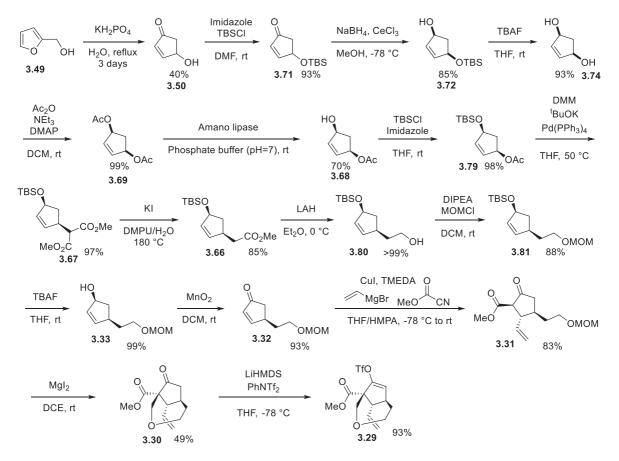
All reactions have been carried out from 0 °C to rt.

Several conditions have been tested for the hydrolysis of the enol ether. Aqueous solution of hydrochloric acid in THF led to a messy reaction, but traces of an aldehyde was observed (entry 1). 47% hydrobromic acid was added to the crude enol ether and turned black in a few minutes (entry 2). A mixture of TFA and DCM as solvent was tested but only decomposition was observed (entry 3). *p*TsOH was used in both acetone and a mixture of THF and water, but no product could be isolated (entries 4-5).

<sup>&</sup>lt;sup>103</sup> Levine, S. G. J. Am. Chem. Soc. 1958, 80, 6150-6151.

## 3.3. Summary of the Synthetic Studies

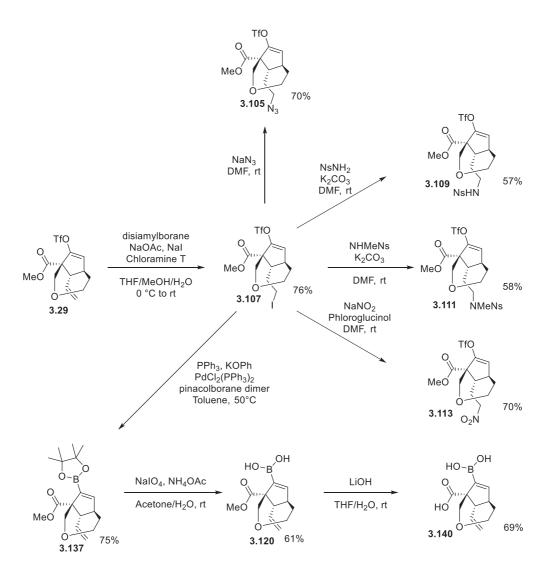
Scheme 228 summarizes the synthesis of vinyl triflate **3.29** from the commercially available furfural **3.49**.



Scheme 228. Summary of the synthesis of vinyl triflate 3.29

Vinyl triflate **3.29** was obtained in 5.0% overall yield in 16 steps from the cheap and commercially available furfural **3.49**.

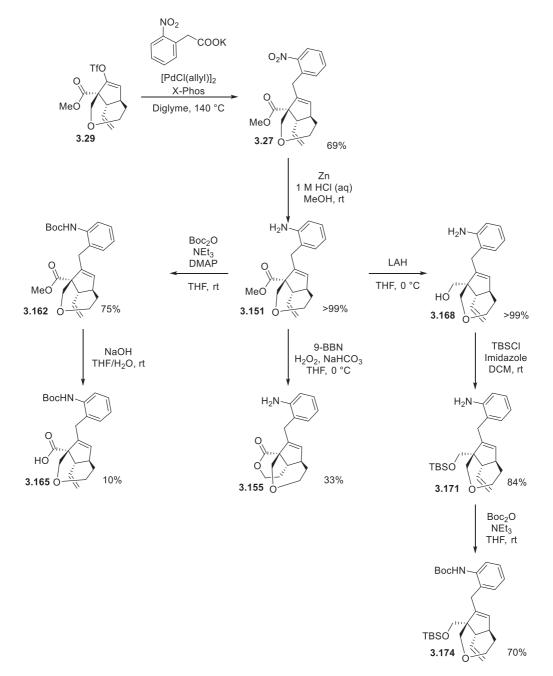
Scheme 229 summarizes the efforts made on the functionalization of the olefin of the vinyl triflate intermediate **3.29** and the subsequent cross-coupling reactions.



Scheme 229. Summary of the functionalization of vinyl triflate 3.29

Vinyl triflate **3.29** was able to be converted into 5 precursors for the palladium-catalyzed decarboxylative coupling however, none of them was able to be transformed into the desired coupling product. Different cross-coupling were investigated, hence the preparation of the boronic ester, the boronic acid and the hydrolyzed ester. Unfortunately, neither substrate was suitable for the coupling.

Scheme 230 summarizes the efforts made through decarboxylative coupling and further functionalization.

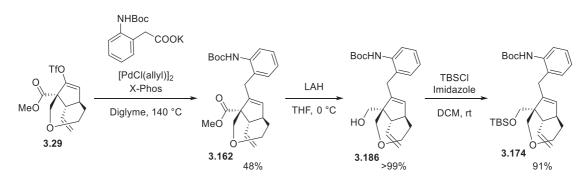


Scheme 230. Summary of the late stage of the synthesis

Palladium-catalyzed decarboxylative vinylation of potassium nitrophenyl acetate was achieved with vinyl triflate **3.29**. Any attempt for the functionalization of the terminal olefin

**3.27** failed. Reduction of the nitro group led to aniline **3.151**. The latter was used for the subsequent functionalization but only lactone **3.155** was isolated and could not be opened. Protection of the aniline afforded carbamate **3.162** but the functionalization of the alkene was unsuccessful. Hydrolysis of the ester did not allow any better reactivity of the double bond. Reduction of ester **3.151** followed by TBS-protection led to intermediate **3.171**. Neither of the two compounds was able to be further functionalized. Protection of the so-formed aniline **3.171** allowed the formation of the latest intermediate **3.174** of the synthesis so far.

Another shorter route towards the same intermediate was developed (Scheme 231).



Scheme 231. Shorter route towards latest intermediate 3.174

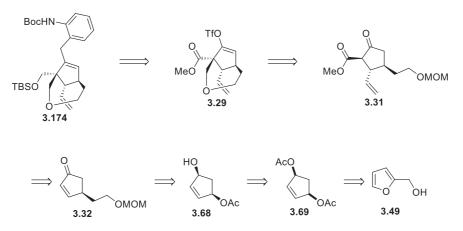
Decarboxylative coupling from vinyl triflate **3.29** did work with another potassium salt to afford directly the aryl carbamate **3.162** in moderate yield. Subsequent reduction of the ester followed by TBS-protection afforded **3.174** in excellent yield.

3.4. Conclusion and Outlook

In conclusion, we brought to the field some insights towards the first enantioselective total synthesis of unusual members of the uleine family. The synthetic studies can be highlighted by several key features:

- An enzymatic desymmetrization of a meso compound which led to an enantiopure product in good yield.
- A highly diastereoselective Michael addition on a cyclopentenone followed by quenching of the resulting enolate with Mander's ester forming two new C-C bonds.
- An unprecedented Lewis acid mediated cyclization forming the [4.2.1] bicycle with the creation of the quaternary carbon.

• An efficient palladium-catalyzed decarboxylative coupling.



Scheme 232. Summary of the key intermediates towards the total synthesis of alstilobanine C

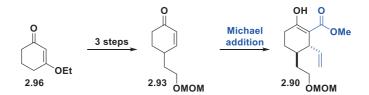
The most advanced intermediate **3.174** was obtained in 19 steps and a 2.2% overall yield from a simple starting material (Scheme 232).

## **Chapter 4 - General Conclusion**

To conclude, our interest in the synthesis of monoterpene indole alkaloids led us to study the small *Ulean* family of alkaloids containing a rare but challenging scaffold.

4.1. Racemic Synthesis

The racemic total synthesis of three natural products is presented in chapter 2. The precursor of the first key step was synthesized from the commercially available enol ether **2.96** in only 4 steps with 49% overall yield. The relative stereochemistry between the aliphatic chain and the vinyl group was controlled by a highly diastereoselective Michael addition followed by quenching of the resulting enolate with Mander's ester (Scheme 233). This one-pot reaction allowed the formation of 2 new C-C bonds.



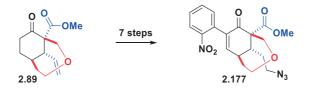
Scheme 233. Synthesis of the precursor of the first key step

The first key step of the synthesis allowed the construction of an unusual oxepane ring. Indeed, the unprecedented Lewis acid mediated cyclization of **2.90** provided the bridged [4.3.1] bicycle with concurrent creation of the quaternary carbon (Scheme 234). The reaction led to 49% yield of the desired cyclized product **2.89** and a side-product, which is the deprotected alcohol. The latter was protected and resubmitted to the reaction conditions improving the yield of **2.89** after one recycling step to 60%.



Scheme 234. First key step of the synthesis

Preparation of the precursor of the second key step was achieved in 7 steps and 32% overall yield. The hydroboration of the olefin could not be performed without protection of the ketone, adding 2 steps in the sequence. The Suzuki coupling installed the aryl moiety in excellent yield when changing the base to cesium carbonate (Scheme 235).



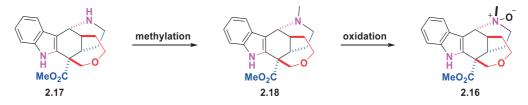
Scheme 235. Preparation of the precursor of the second key step

Finally, the last key step of the synthesis is a chemoselective reduction/cyclization/aza-Michael domino reaction, which allowed the formation of 2 new C-N bonds and the pentacyclic structure, hence (±)-alstilobanine C **2.17** (Scheme 236).



Scheme 236. Domino reaction for the synthesis of (±)-alstilobanine C

Two other members of the family, namely  $(\pm)$ -undulifoline **2.18** and  $(\pm)$ -alstilobanine B **2.16**, were obtained by methylation of the secondary amine and oxidation of the so-formed tertiary amine (Scheme 237).



Scheme 237. Synthesis of (±)-undulifoline and (±)-alstilobanine B

(±)-Alstilobanine C **2.17** was obtained in only 13 steps and a good 7.4% overall yield from a simple starting material.

This project highlighted the power of the design of unprecedented and challenging reaction as well as cascade reactions which allowed a quick access to complex polycyclic molecule from a simpler intermediate.

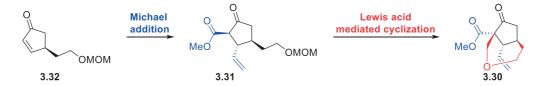
#### 4.2. Towards Enantioselective Synthesis

The synthetic studies towards the enantioselective total synthesis of alstilobanine C is presented in Chapter 3. After struggling to reach enantioenriched enone **3.32**, a scalable pathway was developed (Scheme 238).



Scheme 238. Preparation of chiral enone 3.32

Chiral enone **3.32** was synthesized from the commercially available furfural **3.49** in 13 steps and 13.2% overall yield. The enantioselective step was achieved by enzymatic desymmetrization of a meso compound. The Michael addition onto the cyclopentenone followed by quenching of the resulting enolate with Mander's ester was highly diastereoselective and allowed the formation of 2 new C-C bonds (Scheme 239). The subsequent Lewis acid-mediated cyclization of **3.31** provided the bridged [4.2.1] bicycle system **3.30** in 49% yield. Recovery of the by-product of the reaction allowed, after protection and cyclization, to increase the yield of **3.30** to 62% after one recycling operation.



Scheme 239. Diastereoselective Michael addition followed by oxepane formation

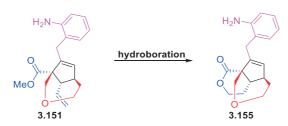
Functionalization of the olefin proved to be extremely problematic. Indeed, only vinyl triflate **3.29** could be used for the subsequent cross-coupling, as none of the other prepared substrates allowed any formation of product when submitted to the coupling conditions (Scheme 240).



Scheme 240. Decarboxylative coupling from vinyl triflate 3.29

Palladium-catalyzed decarboxylative vinylation of two different potassium salts led to the desired products **3.27** and **3.162** in good to moderate yield.

Again, the functionalization of the olefin was troublesome. Indeed, after intensive screening of reaction conditions on various intermediates, we were not able to isolate any valuable product for the synthesis besides lactone **3.155** (Scheme 241).



Scheme 241. Hydroboration followed by self-lactonization

The lactonization could not be prevented despite varying the hydroboration conditions. Efforts were made towards the opening of the  $\delta$ -lactone without any success. To avoid the formation of the lactone, we reduced the ester followed by protection of the so-formed alcohol (Scheme 242). Functionalization of the terminal alkene is ongoing but was not succeeded yet.



Scheme 242. Preparation of most advanced intermediate

The most advanced intermediate **3.174** was obtained in 19 steps and a 2.2% overall yield from a simple starting material.

For the future work, it would be interesting to investigate more on the homologation of the aldehyde formed by oxidative cleavage of the olefin. Indeed, if the desired aldehyde can be obtained, reductive amination with a protected amine would led to the precursor of the iORC. Oxidation of the alcohol to the methyl ester can be done prior or after the domino reaction.

# Chapter 5 – Experimental Section

The following chapter contains the general information, the procedures of all the reactions as well as the full characterization of all the product unknown in the literature.

## 5.1. General Information

Reagents and solvents were purchased from commercial sources (Aldrich, Acros, Merck, Fluka, TCI and VWR international) and preserved under argon. More sensitive compounds were stored in a desiccator or glove-box if required. Reagents were used without further purification unless otherwise noted.

All reactions were performed under argon (or nitrogen) unless otherwise noted. When needed, glassware was dried overnight in an oven (T > 100 °C) or *in vacuo* with a heat gun (T > 200 °C).

When solvents are indicated as dry they were either purchased as such, distilled prior to use or were dried by a pas-sage through a column of anhydrous alumina or copper using a Puresolv MD 5 from Innovative Technology Inc., based on the Grubb's design.

Flash column chromatographies were performed using Silicycle P60 silica: 230-400 mesh (40-63  $\mu$ m) silica.

Reactions were monitored using Merck Kieselgel 60F254 aluminum or glass backed plates. TLC's were visualized by UV fluorescence (254 nm) then one of the following: KMnO4, molybdenate, ninhydrine, pancaldi, *p*-anisaldehyde, phosphomolybdic acid or vanillin.

NMR spectra were recorded on a Brüker AvanceIII-400, Brüker Avance-400 or Brüker DRX-400 spectrometer at room temperature, IH frequency is at 400.13 MHz, I3C frequency is at 100.62 MHz. Chemical shifts ( $\delta$ ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 ppm for proton and 0.1 ppm for carbon (ref : CHCl3 [1H: 7.26 ppm, 13C: 77.2 ppm], MeOH [1H: 3.31 ppm, 13C: 49.0 ppm]). Coupling constants (J) were reported in Hz to the nearest 0.1 Hz. Peak multiplicity was indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Attribution of peaks was done using the multiplicities and integrals of the peaks. When needed, a COSY, HSQC and HMBC experiments were used to confirm the attribution.

IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacleTM ATR acces-sory as neat films compressed onto a Zinc Selenide window. The spectra are reported in cm-1. Abbreviations used are: w (weak), m (medium), s (strong) and br (broad).

Mass spectra were obtained by using a Waters ACQUITY H-class UPLC/MS ACQ-SQD by electron ionization (EI positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI+). The accurate masses were measured by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters.

Specific optical rotations  $[\alpha]_D$  were obtained with a Jasco P-2000 polarimeter (589 nm).

For all general procedures the order of addition of reagents has to be respected.

5.2. Procedures and their characterizations from Chapter 2

$$I \xrightarrow{O} O \xrightarrow{O} PTSOH H_2O$$

$$I \xrightarrow{OH} 2.102$$

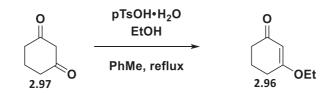
$$I \xrightarrow{O} O \longrightarrow{O} O \to{O} O \longrightarrow{O} O \to{O} O \longrightarrow{O} O \longrightarrow{O} O \longrightarrow{O} O \to{O} O \to{O} O \to{O} O \to{O} O \to O O \to O O O O \to$$

**1-iodo-2-(methoxymethoxy)ethane**: Following a reported procedure,<sup>104</sup> p-toluenesulfonic acid monohydrate (2.22 g, 11.63 mmol, 0.10 equiv) and lithium bromide (1.01 g, 11.63 mmol, 0.10 equiv) were dried under vacuum at 100 °C. 2-Iodoethanol (9.07 mL, 116.30 mmol, 1.00 equiv) and dimethoxymethane (134.00 mL, 1.51 mol, 13.00 equiv) were added. The mixture was stirred at room temperature for 16 hours and then at 40 °C for 30 minutes. After completion of the reaction, triethylamine (2.68 mL, 19.26 mmol, 0.17 equiv) was added to the solution and the excess of dimethoxymethane was distilled off. Chloroform was added and the mixture was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to afford compound **2.103** as a yellow oil, which was used in the following step without further purification. Spectroscopic properties were in agreement with those reported in the literature.

<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.67 (s, 2H), 3.81 (t, *J* = 6.6 Hz, 2H), 3.40 (s, 3H), 3.29 (t, *J* = 6.6 Hz, 2H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 96.5, 68.7, 55.8, 3.4.

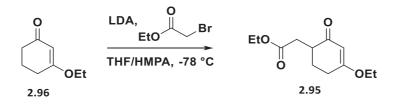
<sup>&</sup>lt;sup>104</sup> Yamazaki, T. Amine compound and use thereof. U.S. Patent 0208033 Al, Sep. 6, 2007.



**3-ethoxycyclohex-2-en-1-one**: Following a reported procedure,<sup>105</sup> p-toluenesulfonic acid monohydrate (0.40 g, 2.10 mmol, 0.02 equiv) was added to a solution of cyclohexane-1,3-dione (12.60 g, 112 mmol, 1.00 equiv) in toluene (180 mL) and ethanol (50 mL) at room temperature. The reaction mixture was heated at reflux for 12 hours. Concentration *in vacuo* gave an orange oil, which was dissolved in EtOAc (200 mL) and neutralized by addition of 1 M NaOH (50 mL). The aqueous phase was diluted with water (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a light orange oil, which was used without further purification. Spectroscopic properties were in agreement with those reported in the literature.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.34 (s, 1H), 3.89 (q, *J* = 7.0 Hz, 2H), 2.39 (t, *J* = 6.3 Hz, 2H), 2.33 (dd, *J* = 7.2, 6.0 Hz, 2H), 1.97 (quintet, *J* = 6.5 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 200.0, 178.0, 102.8, 64.3, 36.9, 29.2, 21.4, 14.3.

<sup>&</sup>lt;sup>105</sup> Findley, T. J. K.; Sucunza, D.; Miller, L. C.; Davies, D. T.; Procter, D. J. Chem. Eur. J. 2008, 14, 6862-6865.

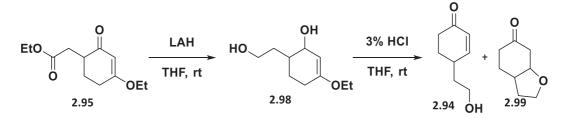


Ethyl 2-(4-ethoxy-2-oxocyclohex-3-en-1-yl)acetate: Following a reported procedure,<sup>106</sup> to a solution of DIPA (9.80 mL, 69.92 mmol, 1.40 equiv) in THF (100 mL) at 0 °C was added <sup>n</sup>BuLi (2.01 M in hexane, 32.3 mL, 64.93 mmol, 1.30 equiv) dropwise. The mixture was stirred at the same temperature for 15 minutes. The *in situ* formed solution of LDA was cooled to -78 °C and HMPA (9.38 mL, 53.94 mmol, 1.08 equiv) and **2.96** (7.00 g, 49.94 mmol, 1.00 equiv) were added dropwise. The reaction mixture was allowed to warm to -45 °C and stirred for 30 minutes. The mixture was re-cooled to -78 °C. Ethyl bromoacetate (6.15 mL, 55.44 mmol, 1.11 equiv) was added to the reaction mixture. After 5 minutes, the resulting mixture was allowed to warm to -45 °C and stirred at the same temperature for 1 hour and then quenched with saturated NH4Cl (100 mL). The solution was extracted with Et<sub>2</sub>O (3 x 100 mL) and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a brown oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 4:1) yielding the pure product **2.95** (9.95 g, 88%) as a light yellow oil. Spectroscopic properties were in agreement with those reported in the literature.

<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.35 (d, J = 1.5 Hz, 1H), 4.15 (qd, J = 7.1, 1.9 Hz, 2H), 3.94 – 3.84 (m, 2H), 2.92 (dd, J = 16.3, 5.1 Hz, 1H), 2.72 (ddt, J = 12.8, 7.8, 4.9 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.38 (ddd, J = 17.6, 5.0, 3.0 Hz, 1H), 2.27 (dd, J = 16.4, 7.8 Hz, 1H), 2.10 (dtd, J = 12.9, 4.9, 2.9 Hz, 1H), 1.78 (tdd, J = 13.0, 12.0, 5.0 Hz, 1H), 1.36 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H).

<sup>IB</sup>**C NMR** (101 MHz, CDCl<sub>3</sub>) δ 199.2, 177.2, 172.9, 102.2, 64.5, 60.6, 42.4, 34.9, 29.1, 27.3, 14.4, 14.3.

<sup>&</sup>lt;sup>106</sup> Toyota, M.; Seishi, T.; Fukumoto, K. *Tetrahedron* **1994**, *50*, 3673-3686.



**4-(2-hydroxyethyl)cyclohex-2-en-1-one** and **hexahydrobenzofuran-6(2H)-one**: Following a reported procedure,<sup>106</sup> to a stirred suspension of LAH (9.80 g, 258.23 mmol, 6.00 equiv) in THF (300 mL) at room temperature was added dropwise a solution of **2.95** (9.80 g, 43.04 mmol, 1.00 equiv) in THF (150 mL). The reaction mixture was stirred for 30 minutes before being cooled to 0 °C. After successive addition of water (9.8 mL), 15% NaOH (9.8 mL) and water (29.4 mL), the mixture was stirred for 30 minutes then filtered through Celite, washed with Et<sub>2</sub>O and evaporated. The residue was directly dissolved in THF (300 mL). To the solution was added 3% HCl (65 mL) at room temperature and stirred for 5 minutes before quenching with saturated NaHCO<sub>3</sub> at 0 °C. The mixture was extracted with EtOAc (3 x 150 mL) and the combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 2:3) yielding compound **2.94** (3.71 g, 61%) and **2.99** (1.84 g, 30%) as light yellow oils.

### Compound 2.94:

<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.90 (ddd, *J* = 10.2, 2.8, 1.4 Hz, 1H), 6.00 (dd, *J* = 10.2, 2.3 Hz, 1H), 3.86 – 3.74 (m, 2H), 2.71 – 2.60 (m, 1H), 2.51 (dt, *J* = 16.8, 4.8 Hz, 1H), 2.38 (ddd, *J* = 16.9, 12.2, 4.9 Hz, 1H), 2.16 (dqd, *J* = 13.4, 5.0, 1.4 Hz, 1H), 1.86 – 1.76 (m, 1H), 1.76 – 1.63 (m, 2H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 200.00, 154.9, 129.3, 60.3, 37.2, 37.00, 32.9, 28.7.

**IR** 3396 (w), 2930 (w), 2869 (w), 2868 (w), 2867 (w), 1662 (s), 1418 (w), 1417 (w), 1392 (w), 1256 (w), 1214 (w), 1062 (m), 1018 (w), 805 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>8</sub>H<sub>13</sub>O<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup>: 141.0910; found 141.0908.

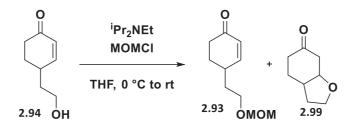
Compound **2.99**:

<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.19 (dt, *J* = 6.6, 4.4 Hz, 1H), 3.98 (dt, *J* = 8.4, 4.7 Hz, 1H), 3.65 (q, 1H), 2.63 (qd, *J* = 16.2, 4.4 Hz, 2H), 2.56 – 2.46 (m, 1H), 2.37 (ddd, *J* = 17.0, 8.1, 4.6 Hz, 1H), 2.30 – 2.16 (m, 2H), 1.97 (ddt, *J* = 13.6, 8.1, 5.2 Hz, 1H), 1.80 – 1.67 (m, 2H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 210.8, 77.6, 66.9, 43.1, 37.2, 35.9, 32.4, 26.2.

**IR** 2939 (w), 2871 (w), 2870 (w), 1714 (s), 1456 (w), 1408 (w), 1408 (w), 1408 (w), 1310 (w), 1310 (w), 1310 (w), 1237 (w), 1237 (w), 1237 (w), 1167 (w), 1142 (w), 1086 (w), 1062 (m), 999 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>8</sub>H<sub>13</sub>O<sub>2</sub> ([M+H]<sup>+</sup>): 141.0910; found 141.0907.



**4-(2-(methoxymethoxy)ethyl)cyclohex-2-en-1-one**: Following a reported procedure,<sup>107</sup> to a solution of **2.94** (2.00 g, 14.27 mmol, 1.00 equiv) in THF (14.3 mL) was added DIPEA (3.73 mL, 21.41 mmol, 1.50 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 30 minutes before being re-cooled to 0 °C. MOMCl (1.61 mL, 21.40 mmol, 1.50 equiv) was added dropwise and the mixture was allowed to slowly warm to room temperature and stirred overnight. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 4:1) yielding the pure product **2.93** (1.81 g, 68%) with as major side product **2.99** (0.27 g, 10%).

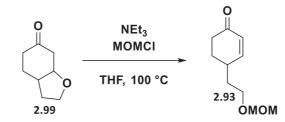
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.90 (ddd, *J* = 10.2, 2.8, 1.4 Hz, 1H), 5.99 (ddd, *J* = 10.2, 2.5, 0.8 Hz, 1H), 4.63 (s, 2H), 3.73 – 3.60 (m, 2H), 3.37 (s, 3H), 2.71 – 2.58 (m, 1H), 2.51 (dt, *J* = 16.8, 4.9 Hz, 1H), 2.38 (ddd, *J* = 16.8, 12.3, 4.9 Hz, 1H), 2.16 (dqd, *J* = 13.3, 4.9, 1.3 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.79 – 1.66 (m, 2H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 199.8, 154.7, 129.3, 96.7, 65.1, 55.5, 37.0, 34.6, 33.4, 28.8.

**IR** 2930 (w), 2930 (w), 2929 (w), 2929 (w), 2881 (w), 2880 (w), 1679 (s), 1678 (s), 1450 (w), 1417 (w), 1390 (w), 1254 (w), 1213 (w), 1148 (m), 1110 (s), 1041 (s), 918 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>10</sub>H<sub>16</sub>LiO<sub>3</sub><sup>+</sup> [M+Li]<sup>+</sup>: 191.1254; found 191.1258.

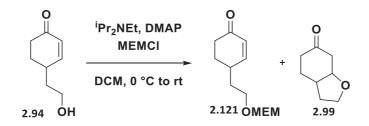
<sup>&</sup>lt;sup>107</sup> Paquette, L. A.; Peng, X.; Bondar, D. Org. Lett. 2002, 4, 937-940.



4-(2-(methoxymethoxy)ethyl)cyclohex-2-en-1-one: Following a reported procedure,<sup>108</sup> to a solution of **2.99** (100 mg, 0.71 mmol, 1.00 equiv) in THF (3 mL) was added NEt<sub>3</sub> (0.8 mL, 5.7 mmol, 8.00 equiv) and MOMCl (0.27 mL, 2.85 mmol, 4.00 equiv) at room temperature in a sealed tube.<sup>109</sup> The reaction mixture was allowed to warm to 100 °C for 4 days. After being cooled down to room temperature, the mixture was quenched by addition of saturated NH<sub>4</sub>Cl, extracted with EtOAc (3 x 10 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 4:1) yielding the pure product **2.93** (1.81 g, 89%).

<sup>&</sup>lt;sup>108</sup> Meyers, A. I.; Hanreich, R.; Wanner, K. T. J. Am. Chem. Soc. **1985**, 107, 7776-7778.

<sup>&</sup>lt;sup>109</sup> Similar results can be obtained in toluene under refluxing in a regular round bottom flask.



**4-(2-((2-methoxyethoxy)methoxy)ethyl)cyclohex-2-en-1-one**: Following a reported procedure,<sup>110</sup> to a solution of **2.94** (1.00 g, 7.13 mmol, 1.00 equiv) in DCM (23.7 mL) was added DMAP (87 mg, 0.71 mmol, 0.10 equiv) and DIPEA (1.78 mL, 10.77 mmol, 1.51 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 30 minutes before being re-cooled to 0 °C. MEMCl (1.22 mL, 10.70 mmol, 1.50 equiv) was added dropwise and the mixture was allowed to slowly warm to room temperature and stirred overnight. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 7:3) yielding the pure product **2.121** (0.57 g, 35%) with **2.99** as major side product (0.49 g, 30%).

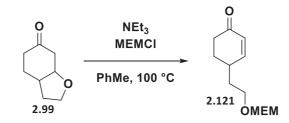
<sup>1</sup>**H** NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.90 (ddd, *J* = 10.2, 2.8, 1.4 Hz, 1H), 5.99 (dd, *J* = 10.2, 2.5 Hz, 1H), 4.73 (s, 2H), 3.75 – 3.61 (m, 4H), 3.60 – 3.52 (m, 2H), 3.40 (s, 3H), 2.68 – 2.57 (m, 1H), 2.51 (dt, *J* = 16.8, 4.8 Hz, 1H), 2.37 (ddd, *J* = 16.8, 12.3, 4.9 Hz, 1H), 2.20 – 2.10 (m, 1H), 1.89 – 1.76 (m, 1H), 1.77 – 1.65 (m, 2H).

<sup>IB</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 199.8, 154.7, 129.3, 95.7, 71.9, 67.1, 65.2, 59.2, 37.0, 34.5, 33.4, 28.8.

**IR** 2926 (m), 2878 (m), 2359 (w), 2335 (w), 1680 (s), 1454 (w), 1390 (w), 1251 (w), 1115 (m), 1097 (m), 1046 (s), 937 (w), 852 (w), 795 (w), 747 (w).

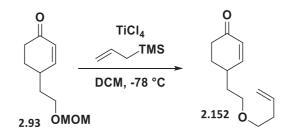
HRMS (ESI): *m*/*z* calcd for C<sub>12</sub>H<sub>20</sub>NaO<sub>4</sub><sup>+</sup> [M+Na]<sup>+</sup>: 251.1254; found 251.1256.

<sup>&</sup>lt;sup>110</sup> Heathcock, C. H.; Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. J. Org. Chem. 1988, 53, 1922-1942.



4-(2-((2-methoxyethoxy)methoxy)ethyl)cyclohex-2-en-1-one: Following a reported procedure,<sup>111</sup> to a solution of 2.99 (2.10 g, 9.20 mmol, 1.00 equiv) in toluene (75 mL) was added NEt<sub>3</sub> (8.36 mL, 36.80 mmol, 4.00 equiv) and MEMCl (3.43 mL, 18.40 mmol, 2.00 equiv) at room temperature. The reaction mixture was allowed to warm to 100 °C for 4 days. After being cooled down to room temperature, the mixture was quenched by addition of saturated NH<sub>4</sub>Cl, extracted with EtOAc (3 x 100 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 4:1) yielding the pure product 2.121 (2.58 g, 76%)

<sup>&</sup>lt;sup>111</sup> Meyers, A. I.; Hanreich, R.; Wanner, K. T. J. Am. Chem. Soc. **1985**, 107, 7776-7778.



4-(2-(but-3-en-1-yloxy)ethyl)cyclohex-2-en-1-one: Following a reported procedure,<sup>112</sup> to a solution of 2.93 (50 mg, 0.27 mmol, 1.00 equiv) in DCM (0.3 mL) was added TiCl<sub>4</sub> (1 M in DCM, 0.30 mL, 0.30 mmol, 1.10 equiv) dropwise at -78 °C and stirred for 10 minutes at the same temperature. To the mixture was added allyltrimethylsilane (52  $\mu$ L, 0.33 mmol, 1.20 equiv) dropwise at -78 °C over 2 hours. After stirring for an additional 10 minutes at the same temperature, the reaction was quenched with saturated NaHCO<sub>3</sub> (1 mL), extracted with EtOAc (3 x 10 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 4:1) yielding the pure product **2.152** (49 mg, 93%).

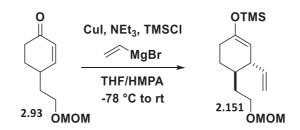
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.88 (ddd, *J* = 10.2, 2.8, 1.3 Hz, 1H), 5.95 (dd, *J* = 10.2, 2.5 Hz, 1H), 5.80 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.20 – 4.95 (m, 2H), 3.56 – 3.50 (m, 2H), 3.50 – 3.44 (m, 2H), 2.65 – 2.54 (m, 1H), 2.48 (dt, *J* = 16.7, 4.9 Hz, 1H), 2.40 – 2.34 (m, 1H), 2.34 – 2.29 (m, 2H), 2.18 – 2.07 (m, 1H), 1.87 – 1.74 (m, 1H), 1.74 – 1.60 (m, 2H).

<sup>IB</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 199.9, 155.1, 135.3, 129.1, 116.5, 70.4, 68.2, 37.0, 34.5, 34.3, 33.5, 28.8.

**IR** 2930 (w), 2861 (w), 1679 (s), 1642 (w), 1451 (w), 1434 (w), 1418 (w), 1390 (w), 1368 (w), 1354 (w), 1253 (w), 1213 (w), 1112 (s), 995 (w), 914 (m), 857 (w), 847 (w), 793 (w), 750 (w), 749 (w), 743 (w).

**HRMS** (ESI): *m*/*z* calcd for C<sub>12</sub>H<sub>19</sub>O<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup>: 195.1380; found 195.1379.

<sup>&</sup>lt;sup>112</sup> Nicolaou, K. C.; Shi, L.; Lu, M.; Pattanayak, M. R.; Shah, A. A.; Ioannidou, H. A.; Lamani, M. Angew. Chem. Int. Ed. **2014**, *53*, 10970-10974.



((4-(2-(methoxymethoxy)ethyl)-3-vinylcyclohex-1-en-1-yl)oxy)trimethylsilane:

Following a reported procedure,<sup>113</sup> to a suspension of CuI (0.53 g, 2.77 mmol, 1.02 equiv) in THF (2 mL) at -78 °C was added vinylmagnesium bromide solution (0.85 M in THF, 6.48 mL, 5.52 mmol, 2.03 equiv) followed by dropwise addition of a solution of **2.93** (0.50 g, 2.72 mmol, 1.00 equiv) in THF (3 mL) over 30 minutes and stirred for an additional 1 hour at the same temperature. HMPA (0.94 mL, 5.44 mmol, 2.00 equiv), NEt<sub>3</sub> (1.13 mL, 8.16 mmol, 3.00 equiv) and TMSCl (1.03 mL, 8.16 mmol, 3.00 equiv) were added sequentially. The reaction mixture was allowed to slowly warm to room temperature, quenched with NH<sub>4</sub>Cl/NH<sub>4</sub>OH (9:1 ratio) (15 mL), extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford **2.151** as a yellow oil (0.68 g, 88%) which was used without further purification.

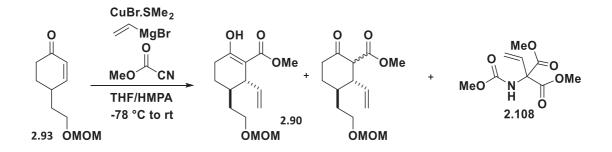
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.72 – 5.59 (m, 1H), 5.05 – 4.96 (m, 2H), 4.68 – 4.65 (m, 1H), 4.63 – 4.60 (m, 2H), 3.64 – 3.52 (m, 2H), 3.35 (s, 3H), 2.59 – 2.48 (m, 1H), 2.01 (ddt, *J* = 9.2, 6.1, 3.1 Hz, 2H), 1.90 – 1.80 (m, 2H), 1.47 – 1.23 (m, 3H), 0.18 (s, 9H).

<sup>I3</sup>**C NMR** (101 MHz, CDCl<sub>3</sub>) δ 150.8, 142.9, 114.9, 106.5, 96.5, 66.0, 55.3, 45.6, 35.0, 32.8, 28.8, 26.0, 0.5.

**IR** 2951 (w), 2950 (w), 2930 (w), 2886 (w), 2885 (w), 2880 (w), 2880 (w), 2879 (w), 1666 (w), 1373 (w), 1252 (m), 1195 (m), 1150 (m), 1112 (m), 1076 (w), 1075 (w), 1044 (s), 918 (m), 917 (m), 901 (m), 878 (m), 844 (s), 752 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>15</sub>H<sub>29</sub>O<sub>3</sub>Si<sup>+</sup> [M+H]<sup>+</sup>: 285.1880; found 285.1878.

<sup>&</sup>lt;sup>113</sup> Jones, T. K.; Denmark, S. E. J. Org. Chem. 1985, 50, 4037-4045.



**methyl 2-hydroxy-5-(2-((2-methoxyethoxy)methoxy)ethyl)-6-vinylcyclohex-1-ene-1carboxylate**: Following a reported procedure,<sup>114</sup> to a stirred suspension of copper(I) bromide-dimethyl sulfide (3.34 g, 16.25 mmol, 2.00 equiv) in THF (60 mL) at -78 °C was added vinylmagnesium bromide (0.85 M in THF, 38.3 mL, 32.50 mmol, 4.00 equiv). The mixture was stirred for 1 hour at -45 °C before being re-cooled to -78 °C and a solution of **2.93** (1.50 g, 8.13 mmol, 1.00 equiv) in THF (15 mL) was added dropwise. The reaction mixture was stirred for another hour at -45 °C. HMPA (3.9 mL, 48.75 mmol, 6.00 equiv) followed by methyl cyanoformate (13.4 mL, 77.19 mmol, 9.50 equiv) were added at -78 °C. The solution was allowed to slowly warm to room temperature and stirred overnight before being quenched with saturated NH<sub>4</sub>Cl, extracted with EtOAc (3 x 150 mL). The combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 9:1) yielding the pure product **2.90** as a mixture of diastereoisomers and tautomers (1.80 g, 82%) and **2.108** as side product.

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 12.44 (s, 1H), 5.82 (ddd, J = 16.7, 10.2, 6.0 Hz, 1H), 5.64 – 5.49 (m, 1H), 5.17 – 5.07 (m, 2H), 5.02 (dt, J = 10.2, 1.5 Hz, 1H), 4.88 (dt, J = 17.1, 1.6 Hz, 1H), 4.61 (d, J = 5.4 Hz, 4H), 3.72, 3.70 (two s, 6H), 3.63 – 3.56 (m, 4H), 3.37, 3.35 (two s, 6H), 3.29 (d, J = 11.9, 0.9 Hz, 1H), 3.08 (d, J = 6.1 Hz, 1H), 2.61 (td, J = 11.4, 9.1 Hz, 1H), 2.51 (ddd, J = 14.2, 4.3, 2.9 Hz, 1H), 2.39 (td, J = 14.1, 6.1 Hz, 1H), 2.32 – 2.14 (m, 3H), 2.10 – 1.93 (m, 1H), 1.92 – 1.76 (m, 3H), 1.72 – 1.57 (m, 2H), 1.55 – 1.42 (m, 2H), 1.39 – 1.27 (m, 1H).

<sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 205.0, 173.4, 172.9, 169.6, 142.1, 138.2, 118.5, 114.6, 97.5, 96.6, 96.6, 65.9, 65.2, 62.7, 55.4, 55.4, 52.1, 51.6, 51.6, 41.0, 40.9, 36.8, 33.4, 33.0, 31.7, 30.6, 25.3, 20.8.

**IR** 1736 (s), 1735 (s), 1650 (w), 1614 (w), 1499 (w), 1498 (w), 1440 (m), 1353 (w), 1352 (w), 1264 (s), 1221 (s), 1147 (m), 1109 (m), 1082 (m), 1046 (s), 994 (w), 917 (m), 831 (w), 779 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>14</sub>H<sub>22</sub>NaO<sub>5</sub><sup>+</sup> [M+Na]<sup>+</sup>: 293.1359; found 293.1360.

<sup>&</sup>lt;sup>114</sup> Uttaro, J. P.; Audran, G.; Monti, H. J. Org. Chem. 2005, 70, 3484–3489.

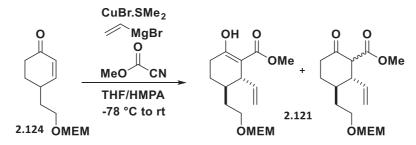
Side product 2.108

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 6.49 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.26 (s, 1H), 5.45 – 5.26 (m, 2H), 3.79 (s, 6H), 3.68 (s, 3H).

<sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 167.53 (2C), 151.72, 140.77, 116.96, 67.36, 53.94 (3C).

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 1797 (m), 1729 (s), 1516 (m), 1441 (m), 1266 (s), 1116 (m), 1197 (m), 2955 (w), 778 (w)

HRMS (ESI/QTOF) m/z: [M + H]<sup>+</sup> Calcd for C<sub>9</sub>H<sub>14</sub>NO<sub>6</sub><sup>+</sup> 232.0816; Found 232.0815.



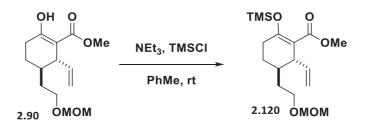
**methyl 2-hydroxy-5-(2-((2-methoxyethoxy)methoxy)ethyl)-6-vinylcyclohex-1-ene-1carboxylate**: Following a reported procedure,<sup>114</sup> to a stirred suspension of copper(I) bromide-dimethyl sulfide (1.03 g, 5.01 mmol, 2.00 equiv) in THF (23 mL) at -78 °C, was added vinylmagnesium bromide (0.8 M in THF, 12.50 mL, 10.02 mmol, 4.00 equiv). The mixture was stirred for 1 hour at -45 °C before being re-cooled to -78 °C and a solution of **2.124** (0.57 g, 2.51 mmol, 1.00 equiv) in THF (6 mL) was added dropwise. The reaction mixture was stirred for another hour at -45 °C. HMPA (2.6 mL, 15.03 mmol, 6.00 equiv) followed by methyl cyanoformate (1.88 mL, 23.80 mmol, 9.50 equiv) were added at -78 °C. The solution was allowed to slowly warm to room temperature and stirred overnight before being quenched with saturated NH<sub>4</sub>Cl, extracted with EtOAc (3 x 100 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 9:1) yielding the pure product **2.121** as a mixture of diastereoisomers and tautomers (650 mg, 83%).

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*)  $\delta$  12.43 (s, 1H), 5.81 (ddd, *J* = 17.2, 10.2, 6.0 Hz, 1H), 5.62 – 5.49 (m, 1H), 5.13 – 5.05 (m, 2H), 5.01 (dt, *J* = 10.2, 1.5 Hz, 1H), 4.88 (dt, *J* = 17.1, 1.6 Hz, 1H), 4.71 (d, *J* = 5.7 Hz, 4H), 3.72, 3.70 (two s, 6H), 3.70 – 3.66 (m, 4H), 3.64 – 3.59 (m, 4H), 3.58 – 3.53 (m, 4H), 3.40, 3.38 (two s, 6H), 3.29 (dd, *J* = 12.0, 0.9 Hz, 1H), 3.07 (d, *J* = 6.1 Hz, 1H), 2.60 (td, *J* = 11.5, 9.1 Hz, 1H), 2.50 (ddd, *J* = 14.3, 4.4, 2.9 Hz, 1H), 2.38 (td, *J* = 14.1, 6.1 Hz, 1H), 2.32 – 2.15 (m, 3H), 2.07 – 1.92 (m, 1H), 1.91 – 1.72 (m, 3H), 1.71 – 1.58 (m, 2H), 1.56 – 1.40 (m, 2H), 1.38 – 1.24 (m, 1H).

<sup>13</sup>**C NMR** (101 MHz, Chloroform-*d*) δ 205.0, 173.4, 172.9, 169.5, 142.1, 138.2, 118.5, 114.6, 97.5, 95.6, 95.6, 71.9, 67.0, 66.9, 66.1, 65.3, 62.7, 59.2, 59.2, 53.9, 52.0, 51.6, 51.55 40.9, 40.89 36.8, 33.4, 32.9, 31.6, 30.6, 25.3, 20.8.

**IR** 2931 (w), 2879 (w), 2363 (w), 1747 (s), 1716 (m), 1650 (m), 1650 (m), 1616 (w), 1440 (m), 1365 (w), 1364 (w), 1351 (w), 1350 (w), 1270 (s), 1222 (s), 1115 (s), 1114 (s), 1049 (s), 927 (w), 926 (w), 925 (w), 924 (w), 850 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>16</sub>H<sub>26</sub>NaO<sub>6</sub><sup>+</sup> [M+Na]<sup>+</sup>: 337.1622; found 337.1620.



**methyl 5-(2-(methoxymethoxy)ethyl)-2-((trimethylsilyl)oxy)-6-vinylcyclohex-1-ene-1-carboxylate**: Following a reported procedure,<sup>115</sup> to a solution of **2.90** (0.37 g, 1.37 mmol, 1.00 equiv) in toluene (5.5 mL) at room temperature was added NEt<sub>3</sub> (0.3 mL, 2.14 mmol, 1.57 equiv) followed by TMSCl (0.26 mL, 2.05 mmol, 1.50 equiv). After being stirred for 10 hours, the solution was quenched by addition of saturated NaHCO<sub>3</sub> (15 mL), extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford **2.120** as a yellow oil (355 mg, 76%) which was used without further purification.

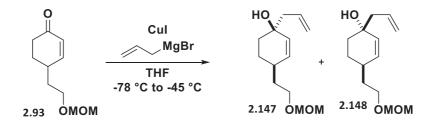
<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.77 (ddd, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.10 – 4.90 (m, 2H), 4.62 (s, 2H), 3.68 (s, 3H), 3.65 – 3.55 (m, 2H), 3.36 (s, 3H), 3.24 – 3.16 (m, 1H), 2.15 – 2.07 (m, 2H), 1.90 – 1.66 (m, 3H), 1.62 – 1.39 (m, 2H), 0.23 (s, 9H).

<sup>I3</sup>**C NMR** (101 MHz, CDCl<sub>3</sub>) δ 168.2, 158.7, 141.5, 115.4, 110.4, 96.6, 65.9, 55.3, 51.2, 44.1, 33.4, 31.9, 28.8, 22.4, 0.7.

**IR** 2934 (m), 2876 (w), 1747 (s), 1718 (m), 1652 (w), 1442 (w), 1371 (w), 1208 (s), 1150 (m), 1113 (s), 1049 (s), 1049 (s), 1048 (s), 1036 (m), 1035 (m), 920 (w), 919 (w), 851 (m).

HRMS (ESI): *m*/*z* calcd for C<sub>17</sub>H<sub>31</sub>O<sub>5</sub>Si<sup>+</sup> [M+H]<sup>+</sup>: 343.1935; found 343.1928.

<sup>&</sup>lt;sup>115</sup> Sparrow, K.; Barker, D.; Brimble, M. A. Tetrahedron 2012, 68, 1017-1028.



**1-allyl-4-(2-(methoxymethoxy)ethyl)cyclohex-2-en-1-ol**: Following a reported procedure,<sup>116</sup> to a solution of CuI (45 mg, 0.24 mmol, 2.20 equiv) in THF (0.5 mL) was added allylmagnesium bromide solution (1 M in Et<sub>2</sub>O, 0.22 mL, 0.22 mmol, 2.00 equiv) at -78 °C and the mixture was stirred for 1 hour at -45 °C. The reaction mixture was re-cooled to -78 °C and a solution of **2.93** (20 mg, 0.11 mmol, 1.00 equiv) in THF (0.5 mL) was added dropwise before warming the mixture to -45 °C and stirred for 1 hour. The reaction was quenched with saturated NH<sub>4</sub>Cl, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 4:1) yielding **2.147** and **2.148** as an inseparables mixture (22.5 mg, 92%).

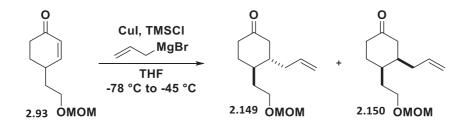
<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.88 (ddt, *J* = 17.3, 10.0, 7.2 Hz, 1H), 5.77 – 5.67 (m, 1H), 5.66 – 5.55 (m, 1H), 5.20 – 5.07 (m, 2H), 4.62 (s, 2H), 3.66 – 3.55 (m, 2H), 3.37, 3.35 (two s, 3H), 2.39 – 2.11 (m, 3H), 1.93 – 1.49 (m, 5H), 1.47 – 1.34 (m, 1H).

<sup>I3</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 135.0 , 133.7, 133.7, 133.5, 132.9, 131.8, 119.0, 118.8, 96.6, 70.1, 69.1, 65.7, 65.5, 55.4, 47.0, 46.2, 35.6, 35.1, 35.0, 34.0, 33.1, 32.1, 25.7, 25.4.

**IR** 3454 (w), 2930 (m), 2883 (w), 2869 (w), 2868 (w), 1722 (w), 1639 (w), 1441 (w), 1214 (w), 1149 (m), 1110 (s), 1037 (s), 1000 (m), 959 (w), 916 (m), 744 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>13</sub>H<sub>22</sub>NaO<sub>3</sub><sup>+</sup> [M+Na]<sup>+</sup>: 249.1461; found 249.1470.

<sup>&</sup>lt;sup>116</sup> Lipshutz, B. H.; Hackmann, C. J. Org. Chem. **1994**, 59, 7437-7444.



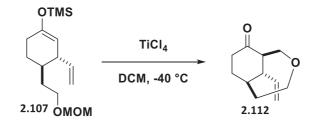
**3-allyl-4-(2-(methoxymethoxy)ethyl)cyclohexan-1-one**: Following a reported procedure,<sup>116</sup> to a solution of CuI (45 mg, 0.24 mmol, 2.20 equiv) in THF (0.5 mL) was added allylmagnesium bromide solution (1 M in Et<sub>2</sub>O, 0.22 mL, 0.22 mmol, 2.00 equiv) at -78 °C and stirred for 1 hour at -45 °C. The reaction mixture was re-cooled to -78 °C and TMSCI (30  $\mu$ L, 0.24 mmol, 2.20 equiv) followed by a solution of **2.93** (20 mg, 0.11 mmol, 1.00 equiv) in THF (0.5 mL) was added dropwise. The mixture was allowed to warm to -45 °C and stirred for 1 hour. The reaction was quenched with saturated NH<sub>4</sub>Cl, extracted with EtOAc (3 x 30 mL). The combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 9:1) yielding **2.149** and **2.150** as an inseparable mixture of two diastereoisomers (23 mg, 94%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.80 – 5.63 (m, 1H), 5.11 – 4.97 (m, 2H), 4.64, 4.62 (two s, 2H), 3.69 – 3.53 (m, 2H), 3.38, 3.36 (two s, 3H), 2.44 – 2.21 (m, 4H), 2.19 – 1.96 (m, 4H), 1.89 – 1.64 (m, 3H), 1.55 – 1.43 (m, 1H).

<sup>I3</sup>**C NMR** (101 MHz, CDCl<sub>3</sub>) δ 212.0, 211.8, 136.2, 135.1, 117.7, 117.1, 96.6, 66.0, 65.6, 55.4, 45.4, 44.6, 42.2, 40.7, 40.3, 39.5, 38.0, 36.2, 35.0, 34.0, 32.3, 30.0, 29.4, 28.1.

**IR** 2928 (w), 2927 (w), 2882 (w), 1714 (s), 1640 (w), 1441 (w), 1423 (w), 1213 (w), 1212 (w), 1150 (m), 1110 (s), 1043 (s), 1042 (s), 997 (w), 996 (w), 917 (m).

HRMS (ESI): *m*/*z* calcd for C<sub>13</sub>H<sub>22</sub>NaO<sub>3</sub><sup>+</sup> [M+Na]<sup>+</sup>: 249.1461; found 249.1469.

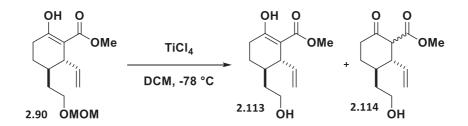


**10-vinyl-3-oxabicyclo**[**4.3.1**]**decan-9-one**: Following a reported procedure,<sup>117</sup> to a solution of TiCl<sub>4</sub> (1 M in DCM, 0.25 mL, 0.25 mmol, 3.50 equiv) in DCM (1 mL) at -40 °C was added a solution of **2.107** (20 mg, 0.07 mmol, 1.00 equiv) in DCM (0.12 mL). The reaction mixture was stirred for 1 hour before being quenched with saturated NaHCO<sub>3</sub> (10 mL) at the same temperature, The mixture was extracted with EtOAc (3 x 10 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 4:1) yielding the pure product **2.112** (7.6 mg, 53% over two steps).

<sup>1</sup>**H** NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.86 (ddd, *J* = 17.4, 10.6, 5.7 Hz, 1H), 5.14 – 4.93 (m, 2H), 4.12 (ddd, *J* = 13.0, 5.5, 2.1 Hz, 1H), 3.98 (dd, *J* = 12.3, 2.1 Hz, 1H), 3.58 (td, *J* = 12.9, 3.3 Hz, 1H), 3.50 (dd, *J* = 12.3, 3.0 Hz, 1H), 3.03 (d, *J* = 5.5 Hz, 1H), 2.73 – 2.62 (m, 1H), 2.61 – 2.57 (m, 1H), 2.38 – 2.19 (m, 2H), 2.19 – 2.02 (m, 2H), 1.94 – 1.80 (m, 1H), 1.75 – 1.60 (m, 1H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 141.6, 115.3, 75.0, 70.8, 55.7, 45.0, 38.4, 34.1, 32.8, 29.2.

<sup>&</sup>lt;sup>117</sup> Thomas, A. A.; Hunt, K. W.; Volgraf, M.; Watts, R. J.; Liu, X.; Vigers, G.; Smith, D.; Sammond, D.; Tang, T. P.; Rhodes, S. P.; Metcalf, A. T.; Brown, K. D.; Otten, J. N.; Burkard, M.; Cox, A. A.; Do, M. K. G.; Dutcher, D.; Rana, S.; Delisle, R. K.; Regal, K.; Wright, A. D.; Groneberg, R.; Scearce-Levie, K.; Siu, M.; Purkey, H. E.; Lyssikatos, J. P.; Gunawardana, I. W. *J. Med. Chem.* **2014**, *57*, 878–902.



**methyl** 2-hydroxy-5-(2-hydroxyethyl)-6-vinylcyclohex-1-ene-1-carboxylate and methyl 3-(2-hydroxyethyl)-6-oxo-2-vinylcyclohexane-1-carboxylate: Following a reported procedure,<sup>118</sup> to a solution of 2.90 (20 mg, 0.07 mmol, 1.00 equiv) in DCM (1.5 mL) was added TiCl<sub>4</sub> (1 M in DCM, 0.07 mL, 0.07 mmol, 1.00 equiv) at -78 °C. The reaction mixture was stirred for 1 hour before being quenched with saturated NaHCO<sub>3</sub> (10 mL) at the same temperature, The mixture was extracted with EtOAc (3 x 10 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 4:1) yielding the pure product 2.113 and 2.114 as an inseparable mixture (10 mg, 60%).

## **2.113**:

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 12.44 (s, 1H), 5.82 (ddd, J = 16.7, 10.2, 6.0 Hz, 1H), 5.04 – 4.84 (m, 2H), 3.81 – 3.64 (m, 2H), 3.71 (s, 3H), 3.06 (d, J = 6.0 Hz, 1H), 2.28 – 2.19 (m, 2H), 2.00 – 1.89 (m, 1H), 1.87 – 1.80 (m, 1H), 1.78 (t, J = 3.3 Hz, 1H), 1.52 – 1.45 (m, 1H), 1.32 – 1.27 (m, 1H).

<sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 173.3, 172.9, 142.0, 114.7, 97.4, 61.2, 52.1, 41.0, 34.7, 33.0, 25.4, 21.0.

## **2.114**:

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 5.56 (ddd, *J* = 16.2, 10.9, 9.0 Hz, 1H), 5.14 – 5.07 (m, 2H), 3.80 – 3.65 (m, 2H), 3.71 (s, 3H), 3.30 (d, *J* = 12.0 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.51 (ddd, *J* = 14.3, 4.4, 2.9 Hz, 1H), 2.45 – 2.34 (m, 1H), 2.27 – 2.20 (m, 1H), 1.99 – 1.90 (m, 1H), 1.87 – 1.81 (m, 1H), 1.51 – 1.45 (m, 1H), 1.36 – 1.29 (m, 1H).

<sup>13</sup>**C NMR** (101 MHz, Chloroform-*d*) δ 205.0, 169.6, 138.2, 118.5, 62.7, 60.4, 52.1, 51.6, 40.8, 36.4, 35.9, 30.7.

**IR** 3429 (w), 2947 (m), 2946 (m), 2934 (m), 2933 (m), 2932 (m), 2920 (m), 2880 (w), 2873 (w), 2872 (w), 2366 (w), 1736 (s), 1715 (s), 1652 (w), 1438 (m), 1268 (s), 1222 (s), 1222 (s), 1110 (m), 1109 (m), 1065 (m), 1064 (m), 1054 (m), 1053 (m), 1045 (m), 1037 (m), 1036 (m).

HRMS (ESI): *m*/*z* calcd for C<sub>12</sub>H<sub>19</sub>O<sub>4</sub><sup>+</sup> [M+H]<sup>+</sup>: 227.1278; found 227.1272.

<sup>&</sup>lt;sup>118</sup> Thomas, A. A.; Hunt, K. W.; Volgraf, M.; Watts, R. J.; Liu, X.; Vigers, G.; Smith, D.; Sammond, D.; Tang, T. P.; Rhodes, S. P.; Metcalf, A. T.; Brown, K. D.; Otten, J. N.; Burkard, M.; Cox, A. a.; Do, M. K. G.; Dutcher, D.; Rana, S.; Delisle, R. K.; Regal, K.; Wright, A. D.; Groneberg, R.; Scearce-Levie, K.; Siu, M.; Purkey, H. E.; Lyssikatos, J. P.; Gunawardana, I. W. *J. Med. Chem.* **2014**, *57*, 878–902.



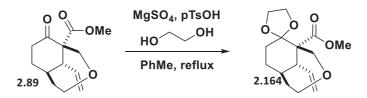
**methyl 9-oxo-10-vinyl-3-oxabicyclo**[**4.3.1**]**decane-1-carboxylate**: To a suspension of MgBr<sub>2</sub> (1.77 g, 9.61 mmol, 2.00 equiv) in DCM (50 mL) at room temperature was added a solution of **2.90** (1.30 g, 4.81 mmol, 1.00 equiv) in DCM (50 mL) dropwise. The reaction mixture was allowed to stir for 12 hours before being quenched by addition of brine (100 mL), extracted with EtOAc (3 x 100 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/DCM/EA 3.5:1:0.5) yielding the pure product **2.89** (0.55 g, 48%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.05 (dt, *J* = 16.7, 10.0 Hz, 1H), 5.11 – 4.93 (m, 2H), 4.15 (d, *J* = 12.0 Hz, 1H), 4.03 (ddd, *J* = 13.0, 5.6, 4.1 Hz, 1H), 3.89 (d, *J* = 12.1 Hz, 1H), 3.70 (ddd, *J* = 13.1, 10.4, 4.0 Hz, 1H), 3.59 (s, 3H), 3.09 (d, *J* = 9.9 Hz, 1H), 2.64 – 2.55 (m, 2H), 2.44 – 2.33 (m, 1H), 2.33 – 2.23 (m, 1H), 2.15 – 2.05 (m, 1H), 1.85 – 1.72 (m, 1H), 1.72 – 1.62 (m, 1H).

<sup>IB</sup>**C NMR** (101 MHz, CDCl<sub>3</sub>) δ 209.3, 170.4, 139.5, 115.7, 78.8, 70.5, 65.4, 51.8, 50.5, 37.1, 34.6, 34.3, 26.2.

**IR** 2950 (w), 2362 (w), 1728 (s), 1709 (s), 1434 (w), 1249 (s), 1111 (m), 1040 (m), 995 (w), 994 (w), 923 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>13</sub>H<sub>19</sub>O<sub>4</sub><sup>+</sup> [M+H]<sup>+</sup>: 239.1278; found 239.1281.



**methyl 10-vinyl-4-oxaspiro[bicyclo[4.3.1]decane-7,2'-[1,3]dioxolane]-6-carboxylate**: Following a reported procedure,<sup>119</sup> to a suspension of **2.89** (1,5 g, 6.00 mmol, 1.00 equiv) and MgSO<sub>4</sub> (500 mg) in toluene (42 mL), was added ethylene glycol (1,2 mL, 21.00 mmol, 3.40 equiv) followed by p-toluenesulfonic acid monohydrate (60 mg, 0.3 mmol, 0.05 equiv). The mixture was allowed to warm to 110 °C and stirred for 2 days before being quenched by addition of NaHCO<sub>3</sub> (50 mL) at 0 °C. The solution was extracted with EtOAc (3 x 100 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 9:1) yielding the pure product **2.164** (1,4 g, 79%).

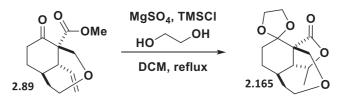
<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>) δ 6.35 (dt, J = 17.0, 9.9 Hz, 1H), 5.03 – 4.89 (m, 2H), 4.28 (d, J = 12.6 Hz, 1H), 4.24 – 4.18 (m, 1H), 4.13 – 4.06 (m, 1H), 4.05 – 3.94 (m, 3H), 3.76 – 3.61 (m, 2H), 3.57 (s, 3H), 3.14 (d, J = 9.7 Hz, 1H), 2.15 – 1.97 (m, 4H), 1.68 (ddd, J = 15.7, 10.9, 5.8 Hz, 1H), 1.55 – 1.52 (m, 1H), 1.36 – 1.18 (m, 1H).

<sup>IB</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 171.4, 141.4, 114.6, 110.7, 77.4, 71.8, 65.4, 64.6, 59.7, 51.4, 48.4, 35.9, 35.9, 30.6, 27.2.

**IR** 2929 (w), 2928 (w), 2921 (w), 2906 (w), 2905 (w), 2873 (w), 2872 (w), 2360 (w), 2343 (w), 2337 (w), 2328 (w), 2327 (w), 1745 (s), 1717 (w), 1267 (w), 1234 (m), 1194 (m), 1193 (m), 1170 (m), 1101 (m), 1087 (m), 1062 (m), 1051 (s), 999 (w), 957 (w), 956 (w), 955 (w), 950 (w), 949 (w), 916 (w), 915 (w), 861 (w), 860 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>15</sub>H<sub>23</sub>O<sub>5</sub><sup>+</sup> [M+H]<sup>+</sup>: 283.1540; found 283.1541.

<sup>&</sup>lt;sup>119</sup> Aburel, P. S.; Rømming, C.; Ma, K.; Undheim, K. J. Chem. Soc. Perkin Trans. 1 2001, 1458–1472.



**I'-methyltetrahydro-I'H,3'H,4'H-spiro**[[**1,3**]**dioxolane-2,1I'-**[**3a,8**]**propanofuro**[**3,4c**]**oxepin**]-**3'-one**: Following a reported procedure,<sup>120</sup> to a suspension of **2.89** (15 mg, 0.06 mmol, 1.00 equiv) and MgSO<sub>4</sub> (5 mg) in DCM (0.13 mL), was added ethylene glycol (17.5  $\mu$ L, 0.31 mmol, 5.00 equiv) followed by TMSCl (32.2  $\mu$ L, 0.25 mmol, 4.00 equiv). The mixture was stirred at 40 °C for 2 days before being quenched with saturated NaHCO<sub>3</sub> (5 mL) at 0 °C. The solution was extracted with EtOAc (3 x 10 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 9:1) yielding the pure product **2.165** (15 mg, 89%).

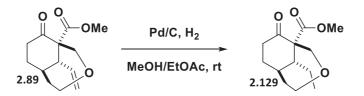
<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.71 (dq, *J* = 10.6, 6.1 Hz, 1H), 4.60 (d, *J* = 12.1 Hz, 1H), 4.12 – 4.00 (m, 2H), 4.00 – 3.85 (m, 3H), 3.53 (dt, *J* = 12.8, 3.8 Hz, 1H), 3.26 (d, *J* = 12.1 Hz, 1H), 2.41 (d, *J* = 10.6 Hz, 1H), 2.15 – 2.14 (m, 1H), 2.09 (td, *J* = 13.9, 3.9 Hz, 1H), 2.02 – 1.88 (m, 2H), 1.79 – 1.66 (m, 1H), 1.59 – 1.52 (m, 1H), 1.39 (d, *J* = 6.1 Hz, 3H), 1.28 – 1.20 (m, 1H).

<sup>I3</sup>**C NMR** (101 MHz, CDCl<sub>3</sub>) δ 167.4, 109.3, 76.3, 74.9, 70.9, 65.2, 56.3, 52.1, 42.5, 34.7, 29.6, 27.3, 25.9, 19.0.

**IR** 2977 (w), 2976 (w), 2967 (w), 2966 (w), 2932 (w), 2895 (w), 2359 (w), 2342 (w), 2336 (w), 1763 (s), 1762 (s), 1458 (w), 1328 (w), 1262 (w), 1230 (m), 1189 (m), 1172 (m), 1098 (s), 1088 (m), 1050 (w), 1023 (m), 1008 (w), 949 (w), 934 (w), 934 (w), 854 (w), 668 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>14</sub>H<sub>21</sub>O<sub>5</sub><sup>+</sup> [M+H]<sup>+</sup>: 269.1384; found 269.1388.

<sup>&</sup>lt;sup>120</sup> Suzuki, H.; Aoyagi, S. Chem. Commun. 2011, 47, 7878-7879.



**methyl 10-ethyl-9-oxo-3-oxabicyclo**[**4.3.1**]**decane-1-carboxylate**: Following a reported procedure,<sup>121</sup> palladium on carbon (5 mg, 0.05 mmol, 2.50 equiv) was added to a solution of **2.89** (5 mg, 0.02 mmol, 1.00 equiv) in a mixture of MeOH (0.1 mL) and EtOAc (0.1 mL). The system was purged with a hydrogen balloon and the reaction mixture was allowed to stir for 12 hours at room temperature. The reaction mixture was filtered through Celite and the solution was concentrated *in vacuo* to afford **2.129** (4.9 mg, 97%) as a yellow oil.

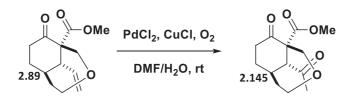
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.16 (d, *J* = 12.0 Hz, 1H), 3.97 (dt, *J* = 12.9, 5.1 Hz, 1H), 3.83 (d, *J* = 12.0 Hz, 1H), 3.73 – 3.64 (m, 4H), 2.58 – 2.51 (m, 2H), 2.51 – 2.42 (m, 1H), 2.34 – 2.25 (m, 1H), 2.23 – 2.11 (m, 1H), 2.09 – 1.96 (m, 1H), 1.82 – 1.69 (m, 1H), 1.69 – 1.56 (m, 1H), 1.55 – 1.37 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

<sup>IB</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 209.7, 171.3, 78.4, 69.9, 65.7, 52.0, 46.4, 36.7, 34.6, 29.4, 25.6, 25.0, 12.9.

**IR** 2956 (m), 2890 (w), 1736 (s), 1704 (s), 1458 (w), 1431 (w), 1263 (w), 1222 (s), 1165 (w), 1094 (w), 1026 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>13</sub>H<sub>20</sub>NaO<sub>4</sub><sup>+</sup> [M+Na]<sup>+</sup>: 263.1254; found 263.1252.

<sup>&</sup>lt;sup>121</sup> Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombroskit, M. A. *J. Am. Chem. Soc.* **1992**, *113*, 6607–6617.



**methyl 10-acetyl-9-oxo-3-oxabicyclo**[**4.3.1**]**decane-1-carboxylate**: Following a reported procedure,<sup>122</sup> to a solution of **2.89** (10 mg, 0.04 mmol, 1.00 equiv) in a mixture of DMF (0.37 mL) and water (0.05 mL), was added PdCl<sub>2</sub> (7.5 mg, 0.04 mmol, 1.00 equiv) and CuCl (4.2 mg, 0.04 mmol, 1.00 equiv). The flask was then purged with an oxygen balloon and the reaction mixture was allowed to stir at room temperature for 12 hours before being quenched by addition of brine (3 mL). The mixture was extracted with EtOAc (3 x 10 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/DCM/EA 2.5:1:1.5) yielding the pure product **2.145** (9.3 mg, 87%).

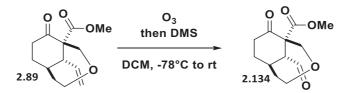
<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.21 (d, *J* = 12.7 Hz, 1H), 4.11 (ddd, *J* = 13.0, 6.1, 3.6 Hz, 1H), 3.73 (s, 3H), 3.65 – 3.53 (m, 3H), 2.76 (ddd, *J* = 15.5, 11.8, 7.1 Hz, 1H), 2.53 (ddd, *J* = 15.6, 6.1, 3.4 Hz, 1H), 2.44 – 2.36 (m, 1H), 2.33 (s, 3H), 2.24 – 2.07 (m, 2H), 2.03 – 1.88 (m, 1H), 1.72 – 1.60 (m, 1H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 208.6, 204.7, 170.7, 76.5, 70.3, 65.2, 56.9, 53.0, 37.8, 35.5, 29.3, 29.0, 28.6.

**IR** 2952 (w), 2951 (w), 1715 (s), 1435 (w), 1363 (w), 1362 (w), 1252 (m), 1169 (w), 1147 (w), 1121 (w), 1104 (w), 1049 (w), 943 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>13</sub>H<sub>19</sub>O<sub>5</sub><sup>+</sup> [M+H]<sup>+</sup>: 255.1227; found 255.1227.

<sup>&</sup>lt;sup>122</sup> Dong, J. J.; Browne, W. R.; Feringa, B. L. Angew. Chem. Int. Ed. 2015, 54, 734-744.



**methyl 10-formyl-9-oxo-3-oxabicyclo**[**4.3.1**]**decane-1-carboxylate**: Following a reported procedure,<sup>123</sup> ozone was bubbled through a solution of **2.89** (10 mg, 0.04 mmol, 1.00 equiv) in DCM (1 mL) at -78 °C until its color changed from colorless to blue. Dimethyl sulfide (0.3 mL) was added and the reaction mixture was allowed to slowly warm to room temperature and stirred overnight. The solution was concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 3:2) yielding the pure product **2.134** (9 mg, 94%).

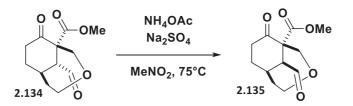
<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.78 (d, *J* = 2.8 Hz, 1H), 4.29 (d, *J* = 12.7 Hz, 1H), 4.10 (ddd, *J* = 13.1, 6.0, 3.6 Hz, 1H), 3.75 (s, 3H), 3.70 (d, *J* = 12.8 Hz, 1H), 3.59 (ddd, *J* = 13.0, 10.5, 4.5 Hz, 1H), 3.38 – 3.34 (m, 1H), 2.87 (ddd, *J* = 15.1, 11.2, 6.5 Hz, 1H), 2.69 – 2.58 (m, 1H), 2.50 (dt, *J* = 15.1, 5.4 Hz, 1H), 2.26 – 2.11 (m, 2H), 2.01 – 1.85 (m, 1H), 1.81 – 1.70 (m, 1H).

<sup>I3</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 206.3, 200.2, 170.2, 76.6, 70.5, 64.0, 56.5, 53.1, 38.1, 35.4, 29.1, 29.0.

IR 2966 (w), 2385 (w), 1753 (s), 1697 (s), 1423 (w), 1275 (s), 1135 (m), 1082 (m), 1033 (m).

HRMS (ESI): *m*/*z* calcd for C<sub>12</sub>H<sub>16</sub>NaO<sub>5</sub><sup>+</sup> [M+Na]<sup>+</sup>: 263.0890; found 263.0894.

<sup>&</sup>lt;sup>123</sup> Liu, L.; Floreancig, P. E. Org. Lett. 2009, 11, 3152–3155.



**methyl 10-epi-formyl-9-oxo-3-oxabicyclo**[4.3.1]decane-1-carboxylate: Following a reported procedure,<sup>124</sup> to a solution of **2.134** (10 mg, 0.04 mmol, 1.00 equiv) in MeNO<sub>2</sub> (2 mL), was added NH<sub>4</sub>OAc (6.4 mg. 0.08 mmol, 2.00 equiv) and Na<sub>2</sub>SO<sub>4</sub> (10 mg) and the reaction mixture was warmed to 75 °C for 12 hours before being quenched by addition of a buffer pH=7 (NaH<sub>2</sub>PO<sub>4</sub>/NaOH). The mixture was extracted with EtOAc (3 x 10 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 3:2) yielding the pure product **2.135** (9.5 mg, 95%).

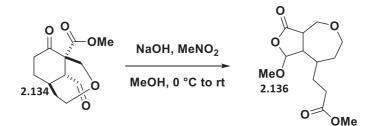
<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.77 (s, 1H), 4.23 – 4.06 (m, 2H), 3.91 (ddd, *J* = 13.4, 5.8, 4.0 Hz, 1H), 3.76 (s, 3H), 3.67 (d, *J* = 4.7 Hz, 1H), 3.35 (ddd, *J* = 13.4, 10.6, 4.4 Hz, 1H), 3.18 – 3.05 (m, 1H), 2.84 (ddd, *J* = 15.4, 12.1, 6.4 Hz, 1H), 2.60 – 2.50 (m, 1H), 2.27 – 2.11 (m, 2H), 1.97 – 1.81 (m, 2H).

<sup>IB</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 207.9, 200.8, 169.9, 72.1, 69.9, 64.0, 56.7, 53.0, 37.6, 33.3, 31.5, 28.0.

**IR** 2951 (w), 2924 (w), 2886 (w), 2874 (w), 2873 (w), 2853 (w), 1738 (s), 1707 (s), 1551 (w), 1459 (w), 1436 (w), 1261 (m), 1235 (s), 1166 (w), 1133 (m), 1114 (w), 1097 (w), 1049 (m), 858 (w), 767 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>12</sub>H<sub>16</sub>NaO<sub>5</sub><sup>+</sup> [M+Na]<sup>+</sup>: 263.0890; found 263.0895.

<sup>&</sup>lt;sup>124</sup> Weiss, M. E.; Carreira, E. M. Angew. Chem. Int. Ed. 2011, 50, 11501–11505.



**methyl 3-(1-methoxy-3-oxohexahydro-1H,3H-furo[3,4-c]oxepin-8-yl)propanoate**: Following a reported procedure,<sup>125</sup> to a solution of **2.134** (10 mg, 0.04 mmol, 1.00 equiv) in MeOH (0.19 mL) was added NaOH (1.75 mg, 0.04 mmol, 1.05 equiv) in water (8.6  $\mu$ L) at 0 °C. Nitromethane (2.25  $\mu$ L, 0.04 mmol, 1.00 equiv) was then added and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated NH<sub>4</sub>Cl, extracted with EtOAc (3 x 10 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 3:2) yielding the pure product **2.136** (9 mg, 79%).

<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.28 (d, *J* = 3.1 Hz, 1H), 4.40 (dd, *J* = 13.1, 3.2 Hz, 1H), 3.99 (dt, *J* = 12.4, 3.5 Hz, 1H), 3.69 (s, 3H), 3.57 (dd, *J* = 13.1, 2.5 Hz, 1H), 3.51 (s, 3H), 3.34 – 3.22 (m, 1H), 3.00 (dt, *J* = 11.2, 2.9 Hz, 1H), 2.68 (dt, *J* = 11.2, 3.4 Hz, 1H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.07 – 1.89 (m, 1H), 1.84 – 1.67 (m, 2H), 1.67 – 1.58 (m, 2H).

<sup>B</sup>**C NMR** (101 MHz, CDCl<sub>3</sub>) δ 177.1, 173.6, 105.4, 73.0, 69.9, 57.2, 51.9, 46.6, 45.4, 37.9, 34.4, 31.9, 29.5.

**IR** 2951 (w), 2950 (w), 2942 (w), 2941 (w), 2870 (w), 2869 (w), 2868 (w), 2364 (w), 2343 (w), 1780 (s), 1733 (s), 1559 (w), 1457 (w), 1449 (w), 1438 (w), 1259 (w), 1241 (w), 1176 (m), 1126 (s), 999 (w), 960 (m), 916 (m), 915 (m), 732 (m).

HRMS (ESI): *m*/*z* calcd for C<sub>13</sub>H<sub>20</sub>NaO<sub>6</sub><sup>+</sup> [M+Na]<sup>+</sup>: 295.1152; found 295.1153.

<sup>&</sup>lt;sup>125</sup> Cantrell, A. S.; Engelhardt, P.; Högberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kangasmetsä, J.; Kinnick, M. D.; Lind, P.; Morin, J. M.; Muesing, M. A.; Noreén, R.; Oberg, B.; Pranc, P.; Sahlberg, C.; Ternansky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H. *J. Med. Chem.* **1996**, *39*, 4261–4274.



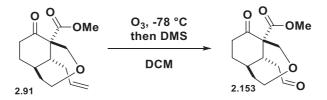
**methyl 10-allyl-9-oxo-3-oxabicyclo[4.3.1]decane-1-carboxylate**: To a suspension of MgBr<sub>2</sub> (97 mg, 0.53 mmol, 3.00 equiv) in DCM (1.75 mL) at room temperature was added a solution of **2.146** (50 mg, 0.18 mmol, 1.00 equiv) in DCM (1.75 mL) dropwise. The reaction mixture was allowed to stir for 12 hours before being quenched by addition of brine (10 mL), extracted with EtOAc (3 x 20 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/DCM/EA 3.5:1:0.5) yielding the pure product **2.91** (4.5 mg, 10%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.76 – 5.57 (m, 1H), 5.15 – 5.01 (m, 2H), 4.17 (d, *J* = 12.0 Hz, 1H), 3.99 (ddd, *J* = 12.7, 5.3, 4.4 Hz, 1H), 3.84 (d, *J* = 12.0 Hz, 1H), 3.72 – 3.59 (m, 1H), 3.70 (s, 3H), 2.60 – 2.49 (m, 3H), 2.49 – 2.40 (m, 1H), 2.23 – 2.12 (m, 3H), 2.06 – 1.96 (m, 1H), 1.80 – 1.69 (m, 1H), 1.66 – 1.57 (m, 1H).

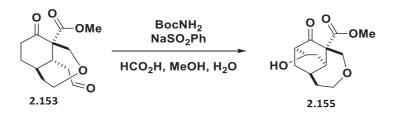
<sup>IB</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 209.4, 171.0, 136.4, 117.3, 78.6, 70.1, 65.2, 52.1, 44.0, 37.3, 36.7, 34.4, 29.7, 24.9.

**IR** 2940 (w), 2933 (w), 2921 (w), 2879 (w), 2878 (w), 2872 (w), 2365 (w), 2355 (w), 2336 (w), 2324 (w), 1727 (s), 1726 (s), 1708 (s), 1458 (w), 1437 (w), 1436 (w), 1242 (s), 1155 (w), 1114 (w), 1045 (m), 1001 (w), 917 (w).

HRMS (ESI): *m*/*z* calcd for C<sub>14</sub>H<sub>20</sub>NaO<sub>4</sub><sup>+</sup> [M+Na]<sup>+</sup>: 275.1254; found 275.1252.\$



**methyl** (**IS,6R,10R)-9-oxo-10-(2-oxoethyl)-3-oxabicyclo**[**4.3.1**]**decane-1-carboxylate**: To a solution of methyl 10-allyl-9-oxo-3-oxabicyclo[**4.3.1**]**decane-1-carboxylate 2.91** (150 mg, 0.59 mmol, 1 equiv) in DCM (3 mL) at -78 °C was bubbled ozone until the color of the solvent turned blue (~3 min). The excess of ozone was removed by purging the solvent with argon and SMe<sub>2</sub> (4.4 mL, 59.5 mmol, 100 equiv) was added and the mixture was allowed to warm slowly to room temperature over 2 h. The solvent was distilled under reduced pressure and the crude **2.153** was used directly for the next step without further purification.



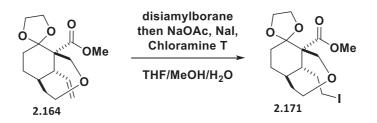
methyl (5R,5aR,7S,8R,9aS)-7-hydroxy-9-oxooctahydro-5,8methanobenzo[c]oxepane-9a(1H)-carboxylate: To a stirred solution of methyl (1S,6R,10R)-9-oxo-10-(2-oxoethyl)-3-oxabicyclo[4.3.1]decane-1-carboxylate 2.153 (151 mg, 0.59 mmol, 1 equiv) in a mixture of H<sub>2</sub>O, MeOH, HCO<sub>2</sub>H (1.5 mL, 0.75 mL, 0.05 mL) was added NaSO<sub>2</sub>Ph (97.5 mg, 0.59 mmol, 1 equiv) and BocNH<sub>2</sub> (70 mg, 0.59 mmol, 1 equiv) sequentially. After 24 h, NaSO<sub>2</sub>Ph (97.5 mg, 0.59 mmol, 1 equiv) and BocNH<sub>2</sub> (70 mg, 0.59 mmol, 1 equiv) were added. NaHCO<sub>3</sub> (~10 mL) was added and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (PE/EtOAc, 1:1) afforded 2.155 (105 mg, 70%) as a yellowish oil.

<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>) δ 4.39 (d, J = 12.3 Hz, 1H), 4.19 (dt, J = 10.1, 3.3 Hz, 1H), 3.93 (ddd, J = 12.5, 8.7, 7.3 Hz, 1H), 3.74 (d, J = 9.5 Hz, 5H), 2.65 (q, J = 3.2 Hz, 1H), 2.38 (q, J = 2.7 Hz, 1H), 2.28 (ddd, J = 15.1, 10.0, 2.9 Hz, 1H), 2.20 – 2.09 (m, 1H), 2.05 – 1.88 (m, 3H), 1.83 (ddd, J = 14.1, 6.9, 2.9 Hz, 1H), 1.71 (dt, J = 15.1, 3.1 Hz, 1H).

<sup>I3</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 210.17, 171.60, 73.05, 68.67, 68.09, 64.51, 53.00, 51.99, 42.31, 37.49, 32.95, 32.28, 25.58.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2942 (m), 2867 (w), 1716 (s), 1447 (m), 1234 (s), 1128 (m), 1097 (m), 1053 (s), 759 (m)

HRMS (ESI/QTOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>18</sub>NaO<sub>5</sub><sup>+</sup> 277.1046; Found 277.1055



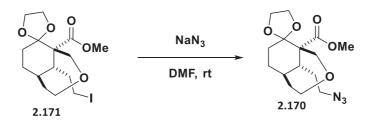
methyl (IR,6S,10R)-10-(2-iodoethyl)-4-oxaspiro[bicyclo[4.3.1]decane-7,2'-**[1,3]dioxolane]-6-carboxylate**: To a stirred solution of BH<sub>3</sub>·THF (1.0 M in THF, 50.0 mL, 50 mmol, 10 equiv) at 0 °C was added 2-methyl-2-butene (11.6 mL, 110 mmol, 22 equiv)dropwise, and the resulting mixture was stirred at the same temperature for 2 h. To a stirred solution of methyl 10-vinyl-4-oxaspiro[bicyclo[4.3.1]decane-7,2'-[1,3]dioxolane]-6carboxylate (2.164, 1.4 g, 5 mmol, 1.0 equiv) in THF (2.0 mL) at 0 °C was added dropwise the in situ prepared solution of disiamyl borane. The reaction mixture was stirred at room temperature for 8 h. To the stirred reaction mixture at 0 °C was added a solution of NaOAc (3.3 g, 40.2 mmol, 8.0 equiv) in MeOH (40.0 mL), a solution of NaI (899 mg, 30.2 mmol, 6 equiv) in water (28 mL) and a solution of chloramine T (1.69 g, 30.2 mmol, 6 equiv) in MeOH (55 mL) sequentially. The resulting reaction mixture was stirred at room temperature for 10 min and quenched by addition of sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>(~50 mL) and 1N HCl (~50 mL). The reaction mixture was diluted with water (50 mL) and extracted with EtOAc  $(3 \times 200 \text{ mL})$ . The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was absorbed on silica gel and purified by FCC (PE/EtOAc, 9:1) to give methyl (IR,6S,1OR)-10-(2-iodoethyl)-4-oxaspiro[bicyclo[4.3.1]decane-7,2'-[1,3]dioxolane]-6carboxylate (2.171, 1.73 g, 85%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.25 (d, *J* = 12.6 Hz, 1H), 4.17 – 4.09 (m, 2H), 4.03 – 3.91 (m, 3H), 3.70 – 3.56 (m, 5H), 3.28 (ddd, *J* = 9.6, 8.2, 5.1 Hz, 1H), 3.14 (ddd, *J* = 9.6, 8.3, 7.4 Hz, 1H), 2.47 (dd, *J* = 9.5, 1.9 Hz, 1H), 2.20 – 2.05 (m, 3H), 2.05 – 1.90 (m, 2H), 1.80 – 1.65 (m, 2H), 1.53 – 1.47 (m, 1H), 1.35 – 1.27 (m, 1H).

<sup>I3</sup>C NMR (**101 MHz, CDCl**<sub>3</sub>) δ 171.77, 110.62, 77.36, 71.57, 65.40, 64.58, 60.42, 51.61, 44.04, 36.54, 35.51, 31.67, 30.73, 26.86, 6.73.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2923 (s), 2360 (m), 2041 (m), 2016 (m), 1741 (s), 1710 (m), 1460 (m), 1428 (m), 1241 (s), 1234 (s), 1197 (s), 1166 (s), 1090 (s), 1047 (s).

HRMS (ESI/QTOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>23</sub>INaO<sub>5</sub><sup>+</sup> 433.0482; Found 433.0482.



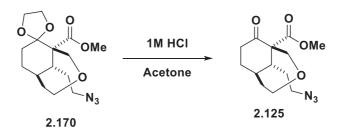
methyl (IR,6S,10R)-10-(2-azidoethyl)-4-oxaspiro[bicyclo[4.3.1]decane-7,2'-[1,3]dioxolane]-6-carboxylate : To a stirred solution of methyl (1R,6S,10R)-10-(2iodoethyl)-4-oxaspiro[bicyclo[4.3.1]decane-7,2'-[1,3]dioxolane]-6-carboxylate (2.171, 1.7 g, 4.1 mmol, 1.0 equiv) in DMF (17 mL) at room temperature was added NaN<sub>3</sub> (2.66 g, 41.0 mmol, 10 equiv), and the resulting mixture was stirred at the same temperature for 12 h. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (PE/EtOAc, 10:1) afforded methyl (1R,6S,10R)-10-(2-azidoethyl)-4oxaspiro[bicyclo[4.3.1]decane-7,2'-[1,3]dioxolane]-6-carboxylate (2.170, 1.21 g, 90%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.26 (d, *J* = 12.6 Hz, 1H), 4.19 – 4.08 (m, 2H), 3.98 (m, 3H), 3.71 – 3.55 (m, 5H), 3.32 (ddd, *J* = 12.8, 7.8, 5.4 Hz, 1H), 3.22 (dt, *J* = 12.3, 7.5 Hz, 1H), 2.54 – 2.46 (m, 1H), 2.21 – 1.81 (m, 6H), 1.78 – 1.66 (m, 1H), 1.54 – 1.49 (m, 1H), 1.34 – 1.28 (m, 1H).

<sup>I3</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 171.90, 110.69, 77.37, 71.55, 65.44, 64.54, 60.52, 51.71, 51.40, 40.08, 35.55, 32.49, 32.17, 30.73, 26.77.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2936 (m), 2911 (m), 2880 (m), 2360 (m), 2098 (s), 1741 (s), 1460 (m), 1097 (s), 1053 (s).

HRMS m/z: [M + Na]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>23</sub>N<sub>3</sub>NaO<sub>5</sub><sup>+</sup> 348.1530; Found 348.1533.



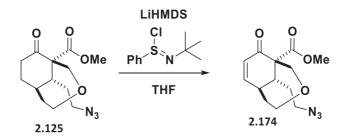
**methyl (IS,6R,10R)-10-(2-azidoethyl)-9-oxo-3-oxabicyclo[4.3.1]decane-1-carboxylate**: To a stirred solution of methyl (IR,6S,10R)-10-(2-azidoethyl)-4-oxaspiro[bicyclo[4.3.1]-decane-7,2'-[1,3]dioxolane]-6-carboxylate (**2.170**, 1.3 g, 4.0 mmol, 1.0 equiv) in acetone (20 mL) at room temperature was added a solution of HCl (1.0 M in H<sub>2</sub>O, 20.0 mL, 20 mmol, 5 equiv), and the resulting mixture was stirred at the same temperature for 3 h. The reaction mixture was cooled to 0 °C, and aq. sat. NaHCO<sub>3</sub> (~20 mL) was added and extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (PE/EtOAc, 4:1) afforded methyl (IS,6R,10R)-10-(2-azidoethyl)-9-oxo-3-oxabicyclo[4.3.1]decane-1-carboxylate (**2.125**, 1.01 g, 90%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.16 (d, *J* = 12.2 Hz, 1H), 3.99 (dt, *J* = 12.9, 5.4 Hz, 1H), 3.85 (d, *J* = 12.2 Hz, 1H), 3.78 – 3.66 (m, 4H), 3.41 – 3.27 (m, 2H), 2.68 – 2.48 (m, 3H), 2.42 – 2.33 (m, 1H), 2.19 (ddt, *J* = 14.1, 9.2, 7.1 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.84 – 1.67 (m, 4H).

<sup>IB</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 208.71, 170.88, 77.98, 69.89, 65.38, 52.34, 50.09, 42.07, 36.88, 34.50, 32.30, 31.42, 25.42.

 $IR \; (\nu_{max}, \; cm^{\text{-1}}) \; 2928 \; (m), \; 2871 \; (w), \; 2852 \; (w), \; 2162 \; (s), \; 2099 \; (m), \; 1802 \; (m), \; 1726 \; (m), \; 1441 \; (m), \; 1245 \; (m), \; 720 \; (s).$ 

HRMS m/z: [M + H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>20</sub>N<sub>3</sub>O<sub>4</sub><sup>+</sup> 282.1448; Found 282.1447.



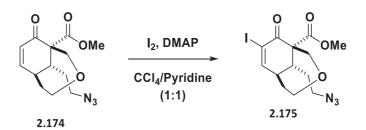
methyl (1S,6S,10R)-10-(2-azidoethyl)-9-oxo-3-oxabicyclo[4.3.1]dec-7-ene-1-То a solution of methyl (1S,6R,10R)-10-(2-azidoethyl)-9-oxo-3carboxylate: oxabicyclo[4.3.1]decane-1-carboxylate (2.125, 1.00 g, 3.55 mmol, 1 equiv) in THF (10 mL) was added LiHMDS solution (1 M in THF, 3.9 mL, 3.90 mmol, 1.1 equiv) at -78 °C. The mixture was stirred for 30 min. A solution of N-tert-Butylbenzenesulfinimidoyl chloride (919 mg, 4.26 mmol, 1.2 equiv) in THF (4 Ml) was added at the same temperature and the mixture was stirred for another 30 min then warmed to room temperature for 15 min. The reaction was quenched by addition of 1% HCl (20mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (PE/EtOAc, 7:3) afforded methyl (1S,6S,10R)-10-(2-azidoethyl)-9-oxo-3oxabicyclo[4.3.1]dec-7-ene-1-carboxylate (2.174, 803 mg, 81%) as a colorless oil.

<sup>1</sup>**H NMR** (**400 MHz**, **CDCl**<sub>3</sub>)  $\delta$  6.81 (ddd, J = 10.1, 5.9, 1.7 Hz, 1H), 6.21 (dd, J = 10.1, 1.5 Hz, 1H), 4.29 (d, J = 12.7 Hz, 1H), 4.00 (d, J = 12.7 Hz, 1H), 3.92 (dt, J = 12.8, 5.3 Hz, 1H), 3.76 (s, 3H), 3.64 (ddd, J = 12.8, 9.0, 4.9 Hz, 1H), 3.38 (ddd, J = 12.6, 6.9, 5.8 Hz, 1H), 3.29 (ddd, J = 12.5, 7.8, 6.6 Hz, 1H), 2.82 (dddt, J = 5.6, 4.0, 2.5, 1.3 Hz, 1H), 2.66 (ddt, J = 8.7, 3.1, 1.4 Hz, 1H), 2.15 (ddt, J = 14.9, 9.0, 5.9 Hz, 1H), 1.96 (dtd, J = 14.7, 4.9, 3.0 Hz, 1H), 1.77 – 1.62 (m, 2H).

<sup>I3</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 195.76, 171.52, 149.86, 130.46, 78.98, 70.50, 63.88, 52.68, 50.30, 40.75, 37.68, 34.45, 31.92.

**IR** (v<sub>max</sub>, cm<sup>-1</sup>) 2949 (m), 2936 (m), 2880 (m), 2348 (m), 2091 (s), 1729 (s), 1672 (s), 1234 (s), 1047 (s), 1397 (m), 1453 (m).

HRMS (ESI/QTOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>NaO<sub>4</sub><sup>+</sup> 302.1111; Found 302.1116.



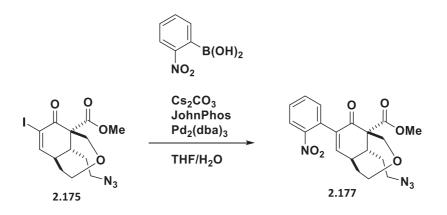
methyl (1S,6R,10R)-10-(2-azidoethyl)-8-iodo-9-oxo-3-oxabicyclo[4.3.1]dec-7-ene-1carboxylate: To a stirred solution of methyl (1S,6S,1OR)-10-(2-azidoethyl)-9-oxo-3oxabicyclo[4.3.1]dec-7-ene-1-carboxylate (2.174, 387 mg, 1.38 mmol, 1.0 equiv) in CCl<sub>4</sub> (2.1 mL) and pyridine (2.1 mL) was added DMAP (33.9 mg, 0.28 mmol, 0.2 equiv) and I<sub>2</sub> (1.06 g, 4.16 mmol, 3.0 equiv). The resulting reaction mixture was stirred at 45 °C in the dark for 30 min. The reaction mixture was allowed to cool to room temperature, and diluted with EtOAc (10 mL). The resulting solution was washed with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2×25 mL). The aqueous phase was separated, and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was purified by FCC (PE/EtOAc, 7:3) give methyl (1S,6R,10R)-10-(2-azidoethyl)-8-iodo-9-oxo-3to oxabicyclo[4.3.1]dec-7-ene-1-carboxylate (2.175, 494 mg, 88%) as a yellowish oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.57 (dd, *J* = 6.4, 1.5 Hz, 1H), 4.19 (d, *J* = 12.7 Hz, 1H), 3.99 (d, *J* = 12.7 Hz, 1H), 3.87 (dt, *J* = 12.8, 5.6 Hz, 1H), 3.77 – 3.63 (m, 4H), 3.36 (ddd, *J* = 12.5, 6.7, 5.8 Hz, 1H), 3.27 (ddd, *J* = 12.5, 7.9, 6.4 Hz, 1H), 2.87 – 2.79 (m, 1H), 2.63 (ddt, *J* = 8.9, 3.7, 1.4 Hz, 1H), 2.13 – 1.97 (m, 2H), 1.75 – 1.55 (m, 2H).

<sup>I3</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 189.12, 170.72, 158.74, 103.01, 79.02, 70.40, 63.73, 52.76, 50.01, 41.76, 41.16, 33.93, 31.77.

IR  $(v_{max}, cm^{-1})$  IR  $(v_{max}, cm^{-1})$  2953 (m), 2871 (m), 2270 (m), 2162 (m), 2093 (s), 1732 (s), 1682 (s), 1232 (s), 1137 (m), 1049 (m), 1441 (m), 1599 (m), 1517 (m).

HRMS (ESI/QTOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>16</sub>IN<sub>3</sub>NaO<sub>4</sub><sup>+</sup> 428.0078; Found 428.0084.



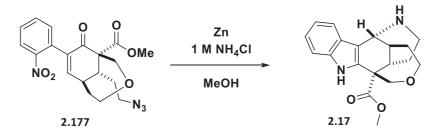
methyl (1S,6S,10R)-10-(2-azidoethyl)-8-(2-nitrophenyl)-9-oxo-3-oxabicyclo[4.3.1]dec -7-ene-1-carboxylate: A flask was charged with methyl (1S,6R,10R)-10-(2-azidoethyl)-8iodo-9-oxo-3-oxabicyclo[4.3.1]dec-7-ene-1-carboxylate 2.175 (270 mg, 0.67 mmol, 1.0 equiv), 2-nitrophenyl boronic acid(122.3 mg, 0.73 mmol, 1.1 equiv), Pd<sub>2</sub>(dba)<sub>3</sub> (30.5 mg, 0.03 mmol, 0.05 equiv), 2-(di-tert-butylphosphino)-biphenyl (JohnPhos, 39.8 mg, 0.13 mmol, 0.2 equiv), and cesium carbonate (651.4 mg, 2.00 mmol, 3.0 equiv). THF (11 mL) and water (2.2 mL) were added sequentially to the flask, and the resulting reaction mixture was heated to 40 °C under argon atmosphere for 2.5 h. The reaction mixture was allowed to cool to room temperature, and quenched by addition of sat. NH<sub>4</sub>Cl (10 mL). The mixture was diluted with water, extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was purified by FCC (PE/EtOAc, 3:2) to give methyl (1S,6S,10R)-10-(2-azidoethyl)-8-(2-nitrophenyl)-9-oxo-3oxabicyclo[4.3.1]dec-7-ene-1-carboxylate (2.177, 250 mg, 93%) as a yellowish oil.

<sup>1</sup>**H** NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.04 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.62 (td, *J* = 7.5, 1.3 Hz, 1H), 7.51 (td, *J* = 7.8, 1.5 Hz, 1H), 7.30 – 7.27 (m, 1H), 6.94 – 6.81 (m, 1H), 4.34 (d, *J* = 12.9 Hz, 1H), 4.00 (dt, *J* = 12.7, 5.3 Hz, 1H), 3.82 (ddd, *J* = 13.2, 9.0, 4.9 Hz, 1H), 3.75 (s, 3H), 3.52 – 3.33 (m, 2H), 3.03 (td, *J* = 6.2, 3.0 Hz, 1H), 2.75 (dd, *J* = 8.8, 3.6 Hz, 1H), 2.25 (ddt, *J* = 14.8, 8.7, 5.9 Hz, 1H), 2.14 – 2.03 (m, 1H), 1.90 (td, *J* = 13.9, 7.5 Hz, 2H).

<sup>IB</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 192.89, 171.38, 146.57, 139.93, 135.27, 133.44, 132.19, 131.32, 129.42, 124.53, 78.62, 70.62, 63.84, 52.65, 50.30, 40.87, 37.92, 34.75, 31.77.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2944 (m), 2922 (m), 2371 (m), 2336 (m), 2274 (m), 2126 (m), 2095 (s), 2016 (m), 1898 (m), 1732 (s), 1679 (m), 1526 (s), 1355 (s), 1263 (s), 1237 (m), 1136 (m), 1049 (m), 760 (s).

HRMS (ESI/QTOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>NaO<sub>6</sub><sup>+</sup> 423.1275; Found 423.1278.



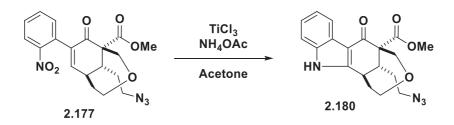
Alstilobanine C: To a stirred solution of methyl (IS,6S,10R)-10-(2-azidoethyl)-8-(2-nitrophenyl)-9-oxo-3-oxabicyclo[4.3.1]dec-7-ene-1-carboxylate (**2.177**, 24 mg, 0.06 mmol, 1 equiv) in MeOH (6 mL) was added a solution of NH<sub>4</sub>Cl (1 M in H<sub>2</sub>O, 0.6 mL, 0.60 mmol, 10 equiv) and zinc (388 mg, 6.00 mmol, 100 equiv). The mixture was stirred for 5 min and aq. sat. NaHCO<sub>3</sub> (~5 mL) was added then filtered over Celite. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (DCM/MeOH/NEt<sub>3</sub>, 90:5:5) afforded alstilobanine C (**2.17**, 17 mg, 87%) as an amorphous white solid.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  7.63 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.41 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.20 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 4.75 (d, *J* = 2.8 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.02 (d, *J* = 12.0 Hz, 1H), 3.80 (s, 3H), 3.77 – 3.68 (m, 1H), 3.66 – 3.53 (m, 3H), 2.99 (dt, *J* = 9.0, 2.8 Hz, 3H), 2.81 (ddt, *J* = 10.8, 5.3, 2.9 Hz, 1H), 2.20 – 2.07 (m, 2H), 1.76 (dd, *J* = 15.4, 2.9 Hz, 1H), 1.34 – 1.31 (m, 2H).

<sup>I3</sup>C NMR (101 MHz, CD<sub>3</sub>OD) δ 173.05, 138.79, 138.65, 127.12, 123.56, 120.84, 118.82, 112.45, 104.33, 78.91, 69.87, 56.02, 53.03, 51.85, 38.65, 38.59, 37.22, 33.65, 29.14.

IR (v<sub>max</sub>, cm<sup>-1</sup>) 3422 (m), 2364 (s), 2341 (m), 2190 (w), 1720 (s), 1345 (w), 1278 (s)

HRMS (ESI/QTOF) m/z: [M + H]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup> 327.1703; Found 327.1702.



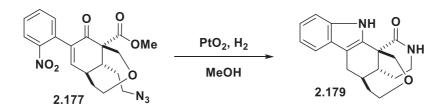
methyl (2S,7R,13R)-13-(2-azidoethyl)-1-oxo-5,6,7,8-tetrahydro-1H-2,7methanooxonino[5,6-b]indole-2(3H)-carboxylate: To a stirred solution of NH<sub>4</sub>OAc (2.5 M in H<sub>2</sub>O, 0.4 mL, 0.99 mmol, 33 equiv) was added TiCl<sub>3</sub> (1.6M in HCl, 0.19 mL, 0.30 mmol, 10 equiv) at room temperature. A solution of methyl (1S,6S,10R)-10-(2-azidoethyl)-8-(2-nitrophenyl)-9-oxo-3-oxabicyclo[4.3.1]dec-7-ene-1-carboxylate (2.177, 12 mg, 0.03 mmol, 1 equiv) in acetone (0.15 mL) was added. The mixture was stirred for 8 h and aq. sat. NaHCO<sub>3</sub> (~5 mL) was added and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (DCM/MeOH/NEt<sub>3</sub>, 90:5:5) afforded methyl (2S,7R,13R)-13-(2-azidoethyl)-1-oxo-5,6,7,8-tetrahydro-1H-2,7-methanooxonino [5,6-b]indole-2(3H)-carboxylate (2.180, 7.5 mg, 68%) as a yellowish oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.57 (s, 1H), 8.25 (dd, *J* = 6.3, 2.8 Hz, 1H), 7.38 (ddd, *J* = 7.4, 3.6, 2.2 Hz, 1H), 7.31 – 7.27 (m, 2H), 4.41 (d, *J* = 12.7 Hz, 1H), 4.17 (d, *J* = 12.8 Hz, 1H), 3.88 (dt, *J* = 12.9, 5.4 Hz, 1H), 3.80 (s, 3H), 3.58 (ddd, *J* = 13.1, 8.5, 4.8 Hz, 1H), 3.51 (ddd, *J* = 5.9, 3.2, 1.2 Hz, 1H), 3.38 (dt, *J* = 12.7, 6.4 Hz, 1H), 3.27 (ddd, *J* = 12.5, 7.7, 6.3 Hz, 1H), 2.88 (ddd, *J* = 8.9, 3.2, 1.2 Hz, 1H), 2.38 (ddt, *J* = 14.3, 8.6, 5.6 Hz, 1H), 2.23 – 2.13 (m, 1H), 1.86 (dtd, *J* = 14.6, 7.2, 3.2 Hz, 1H), 1.70 (ddt, *J* = 14.9, 8.9, 6.2 Hz, 1H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 190.04, 172.14, 150.39, 136.38, 124.80, 124.16, 123.12, 122.17, 113.58, 111.19, 79.34, 70.10, 64.84, 52.60, 50.25, 42.85, 36.39, 35.93, 32.33.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2360 (s), 2335 (s), 2091 (m), 1797 (w), 1729 (w), 1616 (w), 1472 (w), 1253 (w), 2936 (s), 1078 (w), 759 (w), 1948 (w), 2160 (w), 2523 (m)

HRMS (ESI/QTOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>NaO<sub>4</sub><sup>+</sup> 391.1377; Found 391.1373.



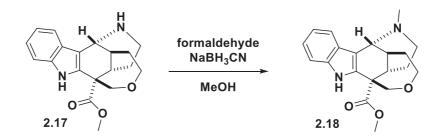
(4aR,5R,1lbR)-3,4,4a,5,6,1l-hexahydro-5,1lb-(ethanooxymethano)pyrido[3,4a]carbazol-1(2H)-one: To a stirred solution of methyl (IS,6S,10R)-10-(2-azidoethyl)-8-(2nitrophenyl)-9-oxo-3-oxabicyclo[4.3.1]dec-7-ene-1-carboxylate (2.177, 14 mg, 0.04 mmol, 1 equiv) in MeOH (0.7 mL) was added PtO<sub>2</sub> (9.8 mg, 0.04 mmol, 1 equiv). A balloon was used to bubble hydrogen for 5 min in the mixture. The mixture was stirred for 5 min and aq. sat. NaHCO<sub>3</sub> (~3 mL) was added then filtered over Celite. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (DCM/MeOH/NEt<sub>3</sub>, 90:5:5) afforded (4aR,5R,1lbR)-3,4,4a,5,6,1l-hexahydro-5,1lb-(ethanooxymethano)pyrido[3,4-a]carbazol-1(2H)-one (2.179, 9.5 mg, 92%) as a yellowish oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.05 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.19 – 7.10 (m, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 5.83 (s, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 3.87 (d, *J* = 11.9 Hz, 1H), 3.60 (dd, *J* = 6.7, 3.9 Hz, 2H), 3.48 (td, *J* = 12.1, 3.5 Hz, 1H), 3.30 (d, *J* = 11.9 Hz, 1H), 3.05 (dd, *J* = 16.3, 6.2 Hz, 1H), 2.72 (dt, *J* = 12.9, 2.8 Hz, 1H), 2.63 (d, *J* = 16.3 Hz, 1H), 2.51 (s, 1H), 2.25 – 2.10 (m, 1H), 1.98 (td, *J* = 12.8, 4.9 Hz, 1H), 1.86 – 1.78 (m, 1H), 1.71 – 1.62 (m, 1H).

<sup>I3</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 136.53, 131.62, 127.55, 121.93, 119.14, 118.23, 111.38, 108.39, 78.61, 67.94, 42.26, 39.20, 38.01, 35.07, 27.42, 25.46.

IR  $(v_{max}, cm^{-1})$  2924 (s), 2360 (s), 2342 (m), 2198 (w), 1797 (w), 1710 (w), 1647 (m), 1460 (w), 1341 (w), 1078 (w)

HRMS (ESI/QTOF) m/z: [M + H]<sup>+</sup> Calcd for C<sub>18</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub><sup>+</sup> 297.1598; Found 297.1598.

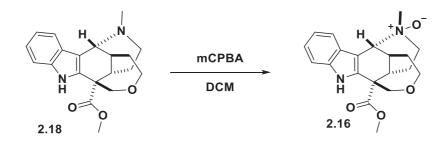


**Undulifoline**: To a solution of alstilobanine C **2.17** (15 mg, 0.04 mmol, 1 equiv) and 37 % aqueous formaldehyde (0.02 mL, 0.40 mmol, 10 equiv) in MeOH (0.5 mL) was added sodium cyanoborohydride (6.0 mg, 0.16 mmol, 4 equiv) at room temperature. After the reaction mixture was stirred for 5 min, saturated aqueous NH<sub>4</sub>Cl solution was added, and the resulting mixture was extracted with EtOAc (3×5 mL). The organic layers were combined, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (DCM/MeOH/NEt<sub>3</sub>, 94:4:2) afforded undulifoline **2.18** (15 mg, 96%) as an amorphous white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.43 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.22 – 7.13 (m, 1H), 7.11 (td, *J* = 7.6, 1.1 Hz, 1H), 4.18 (d, *J* = 11.9 Hz, 1H), 3.99 (d, *J* = 2.7 Hz, 1H), 3.90 (d, *J* = 11.8 Hz, 1H), 3.79 (s, 3H), 3.73 (dt, *J* = 12.7, 3.5 Hz, 1H), 3.50 (ddd, *J* = 13.4, 12.3, 1.5 Hz, 1H), 2.79 (t, *J* = 3.4 Hz, 1H), 2.77 – 2.72 (m, 1H), 2.53 – 2.44 (m, 1H), 2.32 (s, 3H), 2.18 – 1.96 (m, 3H), 1.64 (dq, *J* = 14.3, 2.5 Hz, 1H), 1.39 – 1.29 (m, 1H).

<sup>I3</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 172.70, 136.99, 135.00, 128.94, 122.20, 119.94, 118.96, 111.48, 107.01, 79.22, 69.76, 58.77, 55.60, 52.54, 46.20, 43.97, 40.18, 37.90, 33.19, 30.57.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 3344 (m), 2321 (s), 2336 (m), 2165 (w), 1719 (s), 1445 (w), 1258 (s), 875 (w) HRMS (ESI/QTOF) m/z: [M + H]<sup>+</sup> Calcd for C<sub>20</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup> 341.1860; Found 341.1862.

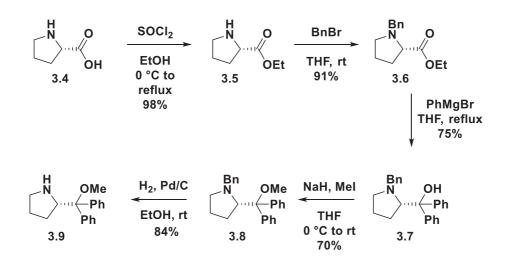


**Alstilobanine B**: To a stirred solution of undulifoline **2.18** (10 mg, 0.03 mmol, 1 equiv) in DCM (0.1 mL) at 0 °C was added mCPBA (5.4 mg, 0.03 mmol, 1.05 equiv) in DCM (0.3 mL). The mixture was stirred for 30 min at the same temperature then 1.5 h at room temperature and aq. sat. NaHCO<sub>3</sub> (~5 mL) was added and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (DCM/MeOH/NEt<sub>3</sub>, 90:5:5) afforded alstilobanine B **2.16** (7.5 mg, 68%) as an amorphous white solid.

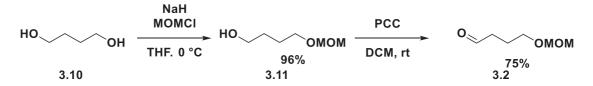
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  7.63 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.41 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.20 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 4.75 (d, *J* = 2.8 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.02 (d, *J* = 12.0 Hz, 1H), 3.80 (s, 3H), 3.77 – 3.68 (m, 1H), 3.66 – 3.53 (m, 3H), 2.99 (dt, *J* = 9.0, 2.8 Hz, 3H), 2.81 (ddt, *J* = 10.8, 5.3, 2.9 Hz, 1H), 2.20 – 2.07 (m, 2H), 1.76 (dd, *J* = 15.4, 2.9 Hz, 1H), 1.34 – 1.31 (m, 2H).

<sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD) δ 173.05, 138.79, 138.65, 127.12, 123.56, 120.84, 118.82, 112.45, 104.33, 78.91, 69.87, 56.02, 53.03, 51.85, 38.65, 38.59, 37.22, 33.65, 29.14.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 3429 (m), 2911 (m), 2356 (s), 2361 (m), 2177 (w), 1745 (s), 1344 (w), 1251 (s) HRMS (ESI/QTOF) m/z: [M + H]<sup>+</sup> Calcd for C<sub>20</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub><sup>+</sup> 357.1809; Found 357.1809. 5.3. Procedures and their characterizations from Chapter 3

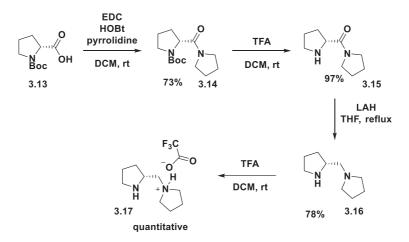


It was prepared according to a literature procedure.<sup>69</sup>

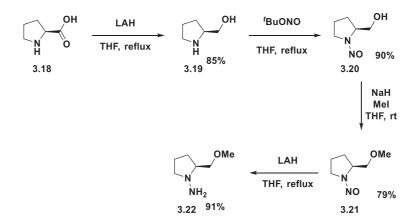


It was prepared according to a literature procedure. <sup>126</sup>

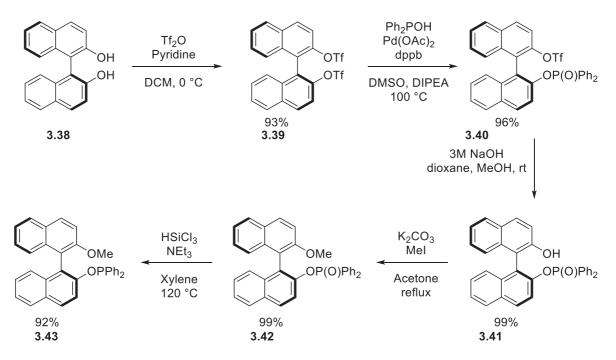
<sup>&</sup>lt;sup>126</sup> Wilson, N. S.; Keay, B. A. J. Org. Chem. **1996**, 61, 2918–2919.



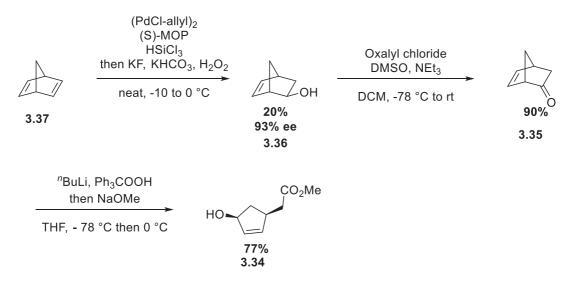
It was prepared according to a literature procedure.<sup>71</sup>



It was prepared according to a literature procedure.<sup>74</sup>

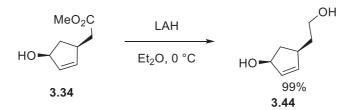


It was prepared according to a literature procedure.<sup>127</sup>

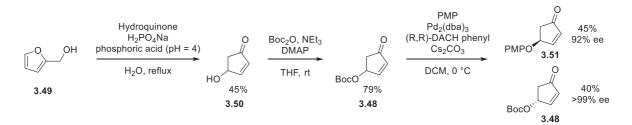


It was prepared according to a literature procedure.<sup>77</sup>

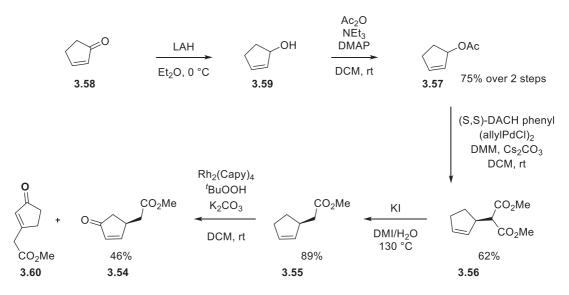
<sup>&</sup>lt;sup>127</sup> Uozumi, Y.; Tanahashi, A.; Lee, S. Y.; Hayashi, T. J. Org. Chem. 1993, 58, 1945–1948.



It was prepared according to a literature procedure.<sup>128</sup>

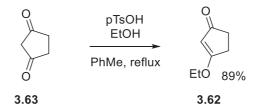


It was prepared according to a literature procedure.<sup>82</sup>

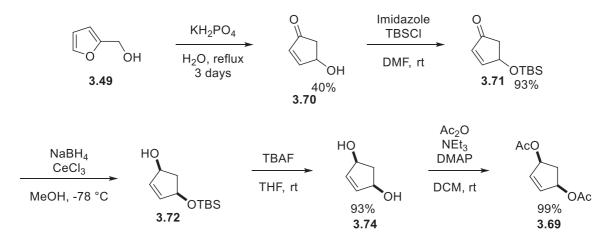


It was prepared according to a literature procedure.<sup>84</sup>

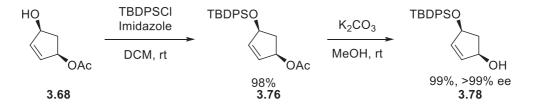
<sup>&</sup>lt;sup>128</sup> Marschner, C.; Baumgartner, J.; Griengl, H. J. Org. Chem. **1995**, 60, 5224–5235.



It was prepared according to a literature procedure.<sup>129</sup>



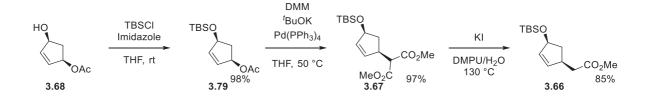
It was prepared according to a literature procedure.<sup>87</sup>



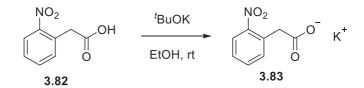
It was prepared according to a literature procedure.<sup>130</sup>

<sup>&</sup>lt;sup>129</sup> Kikani, B. B.; Mckee, J. R.; Zanger, M. Synthesis **1991**, 176.

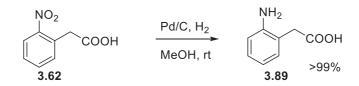
<sup>&</sup>lt;sup>130</sup> Wang, Q.; Kobayashi, Y. Org. Lett. **2011**, 13, 6252–6255.



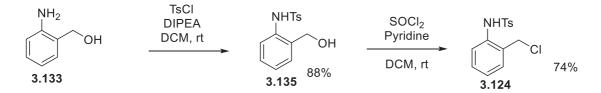
It was prepared according to a literature procedure.<sup>131</sup>



It was prepared according to a literature procedure.<sup>76</sup>



It was prepared according to a literature procedure.<sup>132</sup>



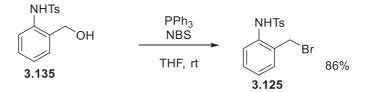
It was prepared according to a literature procedure.<sup>133,134</sup>

<sup>&</sup>lt;sup>131</sup> Acharya, H. P.; Kobayashi, Y. *Tetrahedron* **2006**, *62*, 3329–3343.

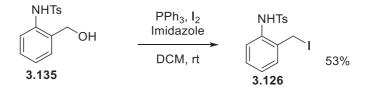
<sup>&</sup>lt;sup>132</sup> Hutchings, M. G.; Devonald, D. P. *Tetrahedron Lett.* **1989**, *28*, 3715-3718.

<sup>&</sup>lt;sup>133</sup> Chwastek, M.; Pieczykolan, M.; Stecko, S. J. Org. Chem. 2016, 81, 9046–9074.

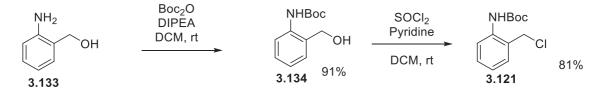
<sup>&</sup>lt;sup>134</sup> Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. Tetrahedron **2010**, *66*, 4687–4695.



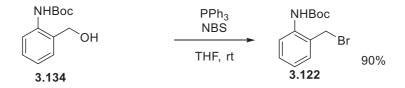
It was prepared according to a literature procedure.<sup>135</sup>



It was prepared according to a literature procedure.<sup>136</sup>



It was prepared according to a literature procedure.<sup>137,138</sup>



It was prepared according to a literature procedure.<sup>139</sup>

<sup>&</sup>lt;sup>135</sup> Sriramurthy, V.; Kwon, O. Org. Lett. **2010**, *12*, 1084–1087.

<sup>&</sup>lt;sup>136</sup> Han, S. J.; Vogt, F.; May, J. A.; Krishnan, S.; Gatti, M.; Virgil, S. C.; Stoltz, B. M. *J. Org. Chem.* **2015**, 80, 528–547.

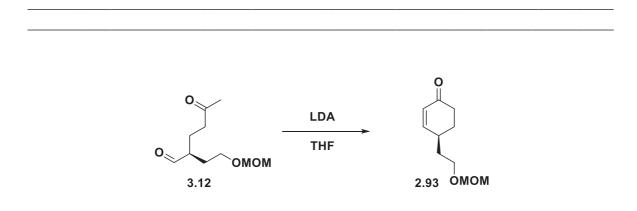
<sup>&</sup>lt;sup>137</sup> Popp, T. A.; Uhl, E.; Ong, D. N.; Dittrich, S.; Bracher, F. *Tetrahedron* **2016**, *72*, 1668–1674.

<sup>&</sup>lt;sup>138</sup> Hovey, M. T.; Check, C. T.; Sipher, A. F.; Scheidt, K. A. Angew. Chemie - Int. Ed. 2014, 53, 9603–9607.

<sup>&</sup>lt;sup>139</sup> Borrero, N. V.; Deratt, L. G.; Ferreira Barbosa, L.; Abboud, K. A.; Aponick, A. Org. Lett. 2015, 17, 1754–1757.



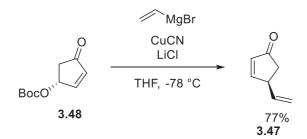
It was prepared according to a literature procedure.<sup>140</sup>



(S)-4-(2-(methoxymethoxy)ethyl)cyclohex-2-en-1-one: To a solution of DIPA (0.02 mL, 0.17 mmol, 1.40 equiv) in THF (0.25 mL) at 0 °C was added "BuLi (2.01 M in hexane, 0.08 mL, 0.16 mmol, 1.30 equiv) dropwise. The mixture was stirred at the same temperature for 15 minutes. The *in situ* formed solution of LDA was cooled to -78 °C and **3.12** (25 mg, 0.12 mmol, 1.00 equiv) was added dropwise. The reaction mixture was allowed to warm to -45 °C and stirred for 30 minutes and then quenched with saturated NH<sub>4</sub>Cl (1 mL). The solution was extracted with Et<sub>2</sub>O (3 x 1 mL) and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a brown oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 4:1) yielding the pure product **2.93** in traces amount.

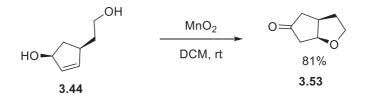
The spectroscopic data of this compound are in accord with these in Chapter 5.2.

<sup>&</sup>lt;sup>140</sup> Crich, D.; Rahaman, M. Y. J. Org. Chem. 2009, 74, 6792-6796.



(S)-4-vinylcyclopent-2-en-1-one: To a stirred solution of CuCN (102 mg, 1.14 mmol, 3.0 equiv) and anhydrous LiCl (96 mg, 2.28 mmol, 6.0 equiv) in THF (4 mL) was added the Grignard reagent (1.14 mmol, 3.0 equiv) dropwise at -40 °C. The reaction mixture was cooled to -78 °C upon which a solution of (R)-*tert*-butyl (4-oxocyclopent-2-en-1-yl) carbonate (75 mg, 0.38 mmol, 1.0 equiv) in THF (1 mL) was added. After the starting material had disappeared (ca. 1 h, monitored by TLC), saturated NH<sub>4</sub>Cl (5 mL) was added and the reaction mixture was extracted with Et<sub>2</sub>O (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 9:1) yielding the pure product **3.47** (32 mg, 77%) as a light yellow oil.

The spectroscopic data of this compound are in accord with these reported in the literature.<sup>141</sup>

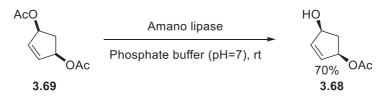


(**3R,6S**)-hexahydro-5H-cyclopenta[b]furan-5-one: MnO<sub>2</sub> (1.6 g, 18.0 mmol, 20.0 equiv) was added to a solution of **3.44** (115 mg, 0.90 mmol, 1.00 equiv) in DCM (9.2 mL). The reaction mixture was allowed to stir for 2 hours at room temperature. The reaction mixture was filtered through Celite and the solution was concentrated *in vacuo* to afford **3.53** (90 mg, 81%) as a yellow oil.

The spectroscopic data of this compound are in accord with these reported in the literature.<sup>142</sup>

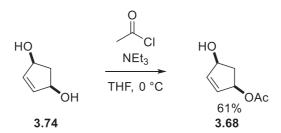
<sup>&</sup>lt;sup>141</sup> Habermas, K. L.; Denmark, S. E.; Jones, T. K. Organic Reactions 1994, 45, 130.

<sup>142</sup> Mihara, H.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. Chem. - An Asian J. 2008, 3, 359-366.



(**IR**,**4S**)-**4**-**hydroxycyclopent-2-en-1-yl acetate:** To a stirred solution of **3.69** (10.6 g, 57.5 mmol, 1 equiv) in a NaH<sub>2</sub>PO<sub>4</sub>/NaOH buffer (250 mL), was added amano lipase from Pseudomonas fluorescens (1.6 g, > 20,000 U/g). The reaction mixture was stirred for 12 h, during which the pH had to be kept around pH=7 by addition of 1 M NaOH. The reaction mixture was filtered then water (50 mL) was added and extracted with EtOAc (2 x 300 mL). The combined organic extracts were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 3:1) yielding the pure product **3.68** (5.7 g, 70%) as a light yellow oil.

The spectroscopic data of this compound are in accord with the commercially available reference.



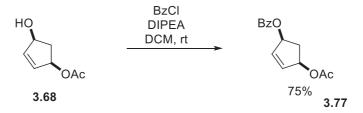
**4-hydroxycyclopent-2-en-1-yl acetate:** To a stirred solution of **3.74** (10.0 mg, 0.1 mmol, 1 equiv) in THF (1 mL), was added NEt<sub>3</sub> (14  $\mu$ L, 0.1 mmol, 1 equiv) and acetyl chloride (5  $\mu$ L, 0.08 mmol, 0.8 equiv) at 0 °C. The reaction mixture was stirred for 1 h and then quenched with saturated NH<sub>4</sub>Cl (1 mL). The solution was extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 3:1) yielding the pure product **3.68** (4.7 mg, 61%) as a light yellow oil.

The spectroscopic data of this compound are in accord with the commercially available reference.



(IR,4S)-4-(benzyloxy)cyclopent-2-en-1-yl acetate: To a stirred solution of 3.68 (3.3 mg, 0.02 mmol, 1 equiv) in DCM (0.2 mL), was added DIPEA (8  $\mu$ L, 0.04 mmol, 2 equiv) and benzyl chloride (4  $\mu$ L, 0.03 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred overnight at room temperature and then quenched with saturated NH<sub>4</sub>Cl (1 mL). The solution was extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 8:1) yielding the pure product **3.75** (3.2 mg, 60%) as a light yellow oil.

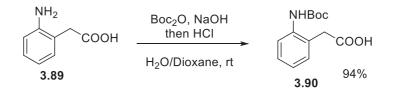
The spectroscopic data of this compound are in accord with these reported in the literature.<sup>143</sup>



(**IS,4R)-4-acetoxycyclopent-2-en-1-yl benzoate**: To a stirred solution of **3.68** (3.3 mg, 0.02 mmol, 1 equiv) in DCM (0.2 mL), was added DIPEA (8  $\mu$ L, 0.04 mmol, 2 equiv) and benzoyl chloride (4  $\mu$ L, 0.03 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred overnight at room temperature and then quenched with saturated NH<sub>4</sub>Cl (1 mL). The solution was extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 8:1) yielding the pure product **3.77** (4.0 mg, 75%) as a light yellow oil.

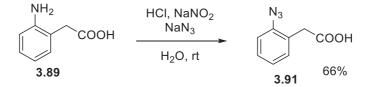
The spectroscopic data of this compound are in accord with these reported in the literature. $143^{143}$ 

<sup>&</sup>lt;sup>143</sup> Wang, Q.; Kobayashi, Y. Org. Lett. 2011, 13, 6252–6255.



**2-(2-((tert-butoxycarbonyl)amino)phenyl)acetic acid**: To a stirred solution of **3.89** (1 g, 6.6 mmol, 1 equiv) in a mixture of water (15 mL) and dioxane (15 mL), was added NaOH (0.58 g, 14.52 mmol, 2.2 equiv) and Boc<sub>2</sub>O (4.32 g, 19.80 mmol, 3 equiv) at 0 °C. The reaction mixture was stirred for 2 h at room temperature and then quenched with 1 M HCl until pH=2. The solution was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 3:2) yielding the pure product **3.90** (1.55 g, 94%) as a light yellow oil.

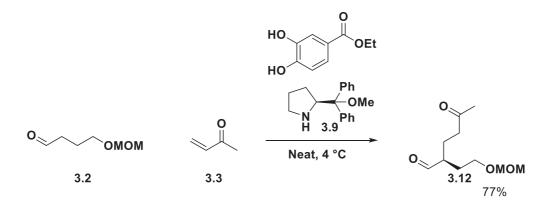
The spectroscopic data of this compound are in accord with the commercially available reference.



**2-(2-azidophenyl)acetic acid**: To a stirred solution of **3.89** (1 g, 6.6 mmol, 1 equiv) in water (7.5 mL), was added fuming HCl (10 mL) at 0 °C. NaNO<sub>2</sub> (0.46 g, 6.6 mmol, 1.05 equiv) in water (35 mL) was added dropwise over 15 min. The reaction mixture was stirred for 20 min at the same temperature then NaN<sub>3</sub> (4.3 g, 66.6 mmol, 10 equiv) in water (100 mL) was added dropwise over 15min. The reaction mixture was allowed to warm to room temperature and stirred for 15 min. The solution was extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 3:2) yielding the pure product **3.91** (0.77 g, 66%) as a light yellow oil.

The spectroscopic data of this compound are in accord with these reported in the literature.<sup>144</sup>

<sup>&</sup>lt;sup>144</sup> Schwarzer, D. D.; Gritsch, P. J.; Gaich, T. Angew. Chemie - Int. Ed. 2012, 51, 11514–11516.

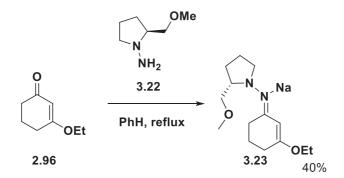


(S)-2-(2-(methoxymethoxy)ethyl)-5-oxohexanal: Aldehyde 3.2 (50 mg, 0.38 mmol, 1 equiv), MVK 3.3 (46  $\mu$ L, 0.57 mmol, 1.5 equiv), catechol (5 mg, 0.02 mmol, 0.05 equiv) and prolinol 3.9 (13 mg, 0.08 mmol, 0.2 equiv) were stirred at 4 °C for 2 days. The crude was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 5:1) yielding the pure product 3.12 (43 mg, 77%) as a light yellow oil.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 9.58 (d, *J* = 2.6 Hz, 1H), 4.57 (s, 2H), 3.62 – 3.52 (m, 2H), 3.33 (s, 3H), 2.62 – 2.47 (m, 2H), 2.45 – 3.38 (m, 1H), 2.14 (s, 3H), 2.07 – 1.95 (m, 1H), 1.95 – 1.86 (m, 1H), 1.82 – 1.71 (m, 2H).

<sup>B</sup>C NMR (101 MHz, Chloroform-*d*) δ 207.8, 204.1, 96.5, 65.9, 55.4, 48.6, 40.8, 30.0, 28.7, 20.9.

HRMS (ESI): *m*/*z* calcd for C<sub>10</sub>H<sub>18</sub>LiO<sub>4</sub><sup>+</sup> [M+Li]<sup>+</sup>: 209.1360; found 209.1362.

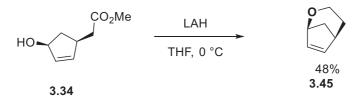


(S)-3-ethoxy-N-(2-(methoxymethyl)pyrrolidin-1-yl)cyclohex-2-en-1-imine: To a stirred solution of 2.96 (0.5 g, 3.57 mmol, 1 equiv) in PhH (4 mL), was hydrazine 3.22 (0.49 mL, 3.68 mmol, 1.03 equiv) then then mixture was heated to reflux with a Dean-Stark for 1 day then concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 3:2 with 1% NEt<sub>3</sub>) yielding the pure product 3.23 (360 mg, 40%) as a light yellow oil.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  5.41 (d, *J* = 1.4 Hz, 1H), 3.92 – 3.79 (m, 2H), 3.44 (dd, *J* = 9.2, 3.7 Hz, 1H), 3.34 (s, 3H), 3.24 (dd, *J* = 9.2, 7.1 Hz, 1H), 3.21 – 3.08 (m, 2H), 2.88 (dt, *J* = 16.2, 4.7 Hz, 1H), 2.41 (q, *J* = 8.7 Hz, 1H), 2.35 – 2.26 (m, 1H), 2.24 – 2.10 (m, 2H), 2.05 – 1.95 (m, 1H), 1.89 – 1.78 (m, 3H), 1.76 – 1.63 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H).

<sup>I3</sup>C NMR (101 MHz, Chloroform-*d*) δ 165.29, 164.95, 99.16, 75.60, 66.60, 63.14, 59.35, 54.66, 28.89, 26.79, 26.44, 22.27, 21.59, 14.64.

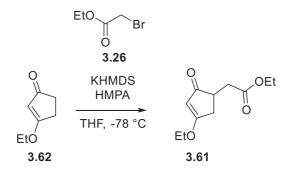
HRMS (ESI): *m*/*z* calcd for C<sub>14</sub>H<sub>24</sub>N<sub>2</sub>NaO<sub>2</sub><sup>+</sup> [M+Na]<sup>+</sup>: 275.1730; found 275.1729.



(**IS,5R**)-**2-oxabicyclo**[**3.2.1**]**oct-6-ene**: to a stirred suspension of LAH (160 mg, 4.3 mmol, 6.00 equiv) in THF (5 mL) at 0 °C was added dropwise a solution of **3.34** (220 mg, 0.72 mmol, 1.00 equiv) in THF (2 mL). The reaction mixture was stirred for 30 minutes at room temperature before being cooled to 0 °C. After successive addition of water (0.16 mL), 15% NaOH (0.16 mL) and water (0.49 mL), the mixture was stirred for 30 minutes then filtered through Celite, washed with Et<sub>2</sub>O and evaporated. The crude was not further purified.

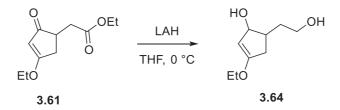
<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*)  $\delta$  5.86 – 5.80 (m, 1H), 5.63 – 5.57 (m, 1H), 5.04 (dd, *J* = 7.1, 2.5 Hz, 1H), 3.70 (ddd, *J* = 8.4, 6.9, 4.2 Hz, 1H), 3.51 (td, *J* = 8.6, 5.8 Hz, 1H), 2.86 – 2.76 (m, 1H), 2.62 – 2.51 (m, 1H), 2.13 – 2.05 (m, 1H), 2.02 – 1.91 (m, 1H), 1.50 (ddt, *J* = 12.2, 5.7, 4.0 Hz, 1H).

HRMS (ESI): *m*/*z* calcd for C<sub>7</sub>H<sub>11</sub>O<sup>+</sup> [M+H]<sup>+</sup>: 111.0804; found 111.0804.

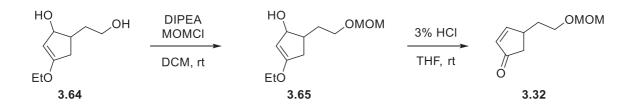


ethyl 2-(4-ethoxy-2-oxocyclopent-3-en-1-yl)acetate: To a stirred solution of 3.62 (1.00 g, 7.93 mmol, 1.00 equiv) in THF (80 mL) at -78 °C was added KHMDS (0.5 M, 20.4 mL, 10.3 mmol, 1.3 equiv). The reaction was stirred 15 min then HMPA (1.87 mL, 11.1 mmol, 1.4 equiv) followed by ethyl bromoacetate 3.26 (1.4 mL, 15.8 mmol, 2.0 equiv) were added to the reaction mixture sequentially. After 5 minutes, the resulting mixture was allowed to warm to -45 °C and stirred at the same temperature for 1 hour and then quenched with saturated NH<sub>4</sub>Cl (100 mL). The solution was extracted with Et<sub>2</sub>O (3 x 100 mL) and the combined organic layers were washed with brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellowish oil which was used without purification for the next step.

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*)  $\delta$  5.27 (d, *J* = 1.1 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.07 – 4.00 (m, 2H), 3.29 – 3.20 (m, 1H), 2.79 (dd, *J* = 15.9, 4.7 Hz, 1H), 2.71 (dd, *J* = 18.1, 7.3 Hz, 1H), 2.35 (dd, *J* = 15.9, 9.5 Hz, 1H), 2.16 (dd, *J* = 18.2, 2.8 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H).



**3-ethoxy-5-(2-hydroxyethyl)cyclopent-2-en-1-ol**: to a stirred suspension of LAH (900 mg, 23.7 mmol, 6.00 equiv) in THF (28 mL) at 0 °C was added dropwise a solution of **3.61** (900 mg, 3.95 mmol, 1.00 equiv) in THF (11 mL). The reaction mixture was stirred for 30 minutes at room temperature before being cooled to 0 °C. After successive addition of water (0.90 mL), 15% NaOH (0.90 mL) and water (2.7 mL), the mixture was stirred for 30 minutes then filtered through Celite, washed with Et<sub>2</sub>O and evaporated. The crude was used for the next step without further purification.

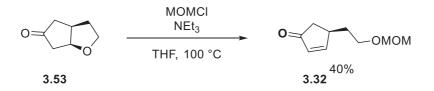


4-(2-(methoxymethoxy)ethyl)cyclopent-2-en-1-one: To a stirred solution of 3.64 (720 mg, 4.19 mmol, 1 equiv) in DCM (21 mL), was added DIPEA (1.46 mL, 8.38 mmol, 2 equiv) and MOMCl (0.48 mL, 6.29 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred overnight at room temperature and then quenched with saturated NH<sub>4</sub>Cl (20 mL). The solution was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was directly dissolved in THF (30 mL). To the solution was added 3% HCl (6.5 mL) at room temperature and stirred for 1 h before quenching with saturated NaHCO<sub>3</sub> at 0 °C. The mixture was extracted with EtOAc (3 x 20 mL) and the combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/Et<sub>2</sub>O 1:1) yielding compound **3.32** (430 mg, 33% over 4 steps) as a light yellow oil.

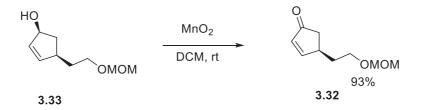
<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 7.68 (dt, *J* = 5.6, 2.7 Hz, 1H), 6.19 (dt, *J* = 5.8, 2.1 Hz, 1H), 4.62 (d, *J* = 1.1 Hz, 2H), 3.72 – 3.60 (m, 2H), 3.36 (s, 3H), 2.91 (ddt, *J* = 19.5, 6.9, 2.4 Hz, 1H), 2.50 – 2.41 (m, 2H), 2.22 – 2.07 (m, 2H).

<sup>I3</sup>**C NMR** (101 MHz, Chloroform-*d*) δ 212.08, 163.45, 133.87, 96.54, 65.96, 55.38, 42.42, 36.01, 31.37.

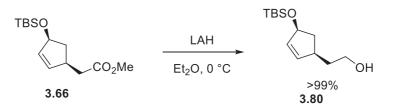
**IR** (ν<sub>max</sub>, cm<sup>-1</sup>) 2936 (w), 2886 (w), 2360 (w), 1710 (s), 1147 (m), 1109 (m), 1040 (s), 922 (w) **HRMS** (ESI): *m*/*z* calcd for C<sub>9</sub>H<sub>15</sub>O<sub>3</sub><sup>+</sup> [M+H]<sup>+</sup>: 171.1016; found 171.1017.



(R)-4-(2-(methoxymethoxy)ethyl)cyclopent-2-en-1-one: to a solution of 3.53 (10 mg, 0.07 mmol, 1.00 equiv) in THF (0.3 mL) was added NEt<sub>3</sub> (0.08 mL, 0.57 mmol, 8.00 equiv) and MOMCl (0.03 mL, 0.29 mmol, 4.00 equiv) at room temperature in a sealed tube. The reaction mixture was allowed to warm to 100 °C for 4 days. After being cooled down to room temperature, the mixture was quenched by addition of saturated NH<sub>4</sub>Cl, extracted with EtOAc (3 x 1 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/Et<sub>2</sub>O 1:1) yielding the pure product **3.32** (5.4 mg, 40%).

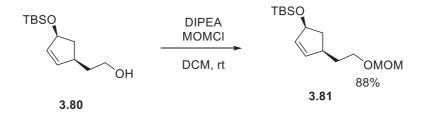


(R)-4-(2-(methoxymethoxy)ethyl)cyclopent-2-en-1-one: MnO<sub>2</sub> (7.3 g, 83.6 mmol, 20.0 equiv) was added to a solution of **3.33** (720 mg, 4.18 mmol, 1.00 equiv) in DCM (30 mL). The reaction mixture was allowed to stir for 2 hours at room temperature. The reaction mixture was filtered through Celite and the solution was concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/Et<sub>2</sub>O 1:1) yielding the pure product **3.32** (662 mg, 93%).



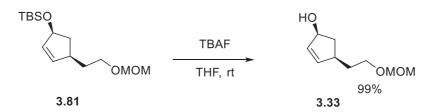
**2-((1R,4S)-4-((***tert***-butyldimethylsilyl)oxy)cyclopent-2-en-1-yl)ethan-1-ol**: to a stirred suspension of LAH (1.15 g, 30.3 mmol, 6.00 equiv) in Et<sub>2</sub>O (45 mL) at 0 °C was added dropwise a solution of **3.66** (1.37 g, 5.06 mmol, 1.00 equiv) in Et<sub>2</sub>O (5 mL). The reaction mixture was stirred for 30 minutes at room temperature before being cooled to 0 °C. After successive addition of water (1.15 mL), 15% NaOH (1.15 mL) and water (3.45 mL), the mixture was stirred for 30 minutes then filtered through Celite, washed with Et<sub>2</sub>O and evaporated. The crude was used for the next step without further purification.

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 5.89 – 5.80 (m, 1H), 5.79 – 5.70 (m, 1H), 4.85 – 4.78 (m, 1H), 3.77 – 3.64 (m, 2H), 2.79 – 2.68 (m, 1H), 2.38 (dt, *J* = 13.5, 7.8 Hz, 1H), 2.25 – 2.17 (m, 1H), 1.85 – 1.75 (m, 1H), 1.70 – 1.61 (m, 1H), 1.50 (dt, *J* = 13.6, 4.4 Hz, 1H), 0.93 – 0.87 (m, 9H), 0.09 (s, 6H).



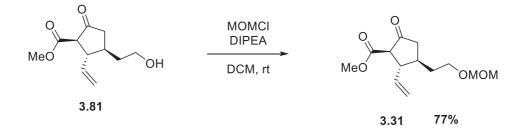
*tert*-butyl(((1S,4R)-4-(2-(methoxymethoxy)ethyl)cyclopent-2-en-1-yl)oxy)dimethyl silane: To a stirred solution of **3.80** (1.3 g, 5.36 mmol, 1 equiv) in DCM (35 mL), was added DIPEA (8.41 mL, 48.24 mmol, 9 equiv) and MOMCl (2.44 mL, 32.16 mmol, 6 equiv) at 0 °C. The reaction mixture was stirred overnight at room temperature and then quenched with saturated NH<sub>4</sub>Cl (100 mL). The solution was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was used for the next step without further purification.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  5.84 – 5.77 (m, 1H), 5.73 – 5.65 (m, 1H), 4.88 – 4.78 (m, 1H), 4.62 (s, 2H), 3.58 (td, *J* = 6.7, 3.5 Hz, 2H), 3.36 (s, 3H), 2.70 – 2.58 (m, 1H), 2.41 (dt, *J* = 12.9, 7.5 Hz, 1H), 1.87 – 1.75 (m, 1H), 1.68 – 1.58 (m, 1H), 1.35 – 1.20 (m, 1H), 0.89 (s, 9H), 0.07 (s, 6H).

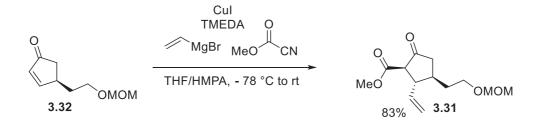


(**IS,4R**)-**4**-(**2**-(**methoxymethoxy**)**ethyl**)**cyclopent-2-en-1-ol**: To a stirred solution of **3.81** (1.2 g, 4.19 mmol, 1 equiv) in THF (40 mL) at 0 °C was added TBAF (1 M in THF, 7.2 mL, 7.12 mmol, 1.7 equiv). The solution was allowed to warm to room temperature and was stirred for 2 h before being quenched by addition of water (30 mL). The solution was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was used for the next step without further purification.

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 5.95 – 5.86 (m, 1H), 5.86 – 5.77 (m, 1H), 4.81 (s, 1H), 4.62 (s, 2H), 3.63 – 3.55 (m, 2H), 3.36 (s, 3H), 2.77 – 2.66 (m, 1H), 2.53 (dt, *J* = 13.4, 7.7 Hz, 1H), 1.87 – 1.77 (m, 1H), 1.73 – 1.60 (m, 2H), 1.32 (dt, *J* = 13.6, 5.1 Hz, 1H).



**methyl** (IR,2S,3R)-3-(2-(methoxymethoxy)ethyl)-5-oxo-2-vinylcyclopentane-1carboxylate: To a stirred solution of 3.81 (720 mg, 3.39 mmol, 1 equiv) in DCM (20 mL), was added DIPEA (1.18 mL, 8.38 mmol, 2 equiv) and MOMCl (0.17 mL, 2.26 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred overnight at room temperature and then quenched with saturated NH<sub>4</sub>Cl (20 mL). The solution was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 4.25:0.75) yielding the pure product 3.31 (669 mg, 77%).



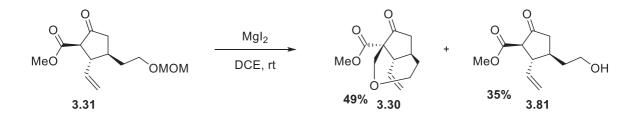
methyl (IR,2S,3R)-3-(2-(methoxymethoxy)ethyl)-5-oxo-2-vinylcyclopentane-1carboxylate: to a stirred suspension of copper(I) iodide (394 mg, 2.07 mmol, 0.10 equiv) in THF (190 mL) at rt was added TMEDA (5.62 mL, 37.22 mmol, 1.80 equiv) and the mixture was stirred for 5 min at the same temperature. To the resulting mixture was added at – 78 °C vinylmagnesium bromide (0.85 M in THF, 45 mL, 39.29 mmol, 1.90 equiv). The mixture was stirred for 15 min at -78 °C and a solution of enone **3.32** (3.52 g, 20.68 mmol, 1.00 equiv) in THF (15 mL) was added dropwise. The reaction mixture was stirred for 2 hour at - 78 °C, then HMPA (5.4 mL, 31.02 mmol, 1.50 equiv) followed by methyl cyanoformate (4.76 mL, 59.97 mmol, 2.90 equiv) were added at -78 °C. The solution was allowed to slowly warm to room temperature and stirred overnight before being quenched with saturated NH4Cl, extracted with EtOAc (3 x 150 mL). The combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 4.25:0.75) yielding the pure product **3.31** as a single diastereoisomer (4.40 g, 83%).

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 5.72 (ddd, *J* = 17.1, 10.2, 8.2 Hz, 1H), 5.26 – 5.12 (m, 2H), 4.59 (s, 2H), 3.74 (s, 3H), 3.62 – 3.50 (m, 2H), 3.34 (s, 3H), 3.11 (dd, *J* = 12.0, 1.0 Hz, 1H), 2.91 – 2.79 (m, 1H), 2.72 – 2.58 (m, 1H), 2.13 – 2.00 (m, 3H), 1.56 – 1.45 (m, 1H).

<sup>IB</sup>C NMR (101 MHz, Chloroform-*d*) δ 209.50, 169.00, 137.15, 118.38, 96.60, 66.29, 61.90, 55.43, 52.62, 51.52, 44.52, 37.65, 33.19.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2949 (m), 2880 (m), 2360 (m), 1754 (s), 1729 (s), 1666 (m), 1441 (m), 1259 (m), 1222 (m), 1147 (m), 1109 (s), 1047 (s), 922 (m)

HRMS (ESI/QTOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>20</sub>NaO<sub>5</sub><sup>+</sup> 279.1203; Found 279.1205.



**methyl** (**IR**,**6R**,**9S**)-**8**-**oxo**-**9**-**vinyl**-**3**-**oxabicyclo**[**4**.**2**.**1**]**nonane**-**1**-**carboxylate**: to a stirred suspension of MgI<sub>2</sub> (8.15 g, 29.26 mmol, 3.00 equiv) in DCE (485 mL) at rt was added **3.31** (2.50 g, 9.75 mmol, 1.00 equiv). The mixture was stirred overnight at the same temperature before being quenched with water (300 mL), extracted with EtOAc (3 x 300 mL). The combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 9:1) yielding the pure product **3.30** (1.71 g, 49%) and the side product **3.81** (724 mg, 35%).

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*)  $\delta$  5.87 (dt, *J* = 16.8, 10.0 Hz, 1H), 5.18 – 4.98 (m, 2H), 4.30 (d, *J* = 11.6 Hz, 1H), 3.93 (d, *J* = 11.7 Hz, 1H), 3.90 – 3.85 (m, 1H), 3.61 (s, 3H), 3.40 – 3.34 (m, 1H), 3.19 (ddd, *J* = 13.7, 11.1, 2.6 Hz, 1H), 2.86 (dd, *J* = 18.5, 8.5 Hz, 1H), 2.55 – 2.46 (m, 1H), 2.16 (dd, *J* = 18.6, 1.6 Hz, 1H), 2.11 – 1.99 (m, 1H), 1.54 – 1.44 (m, 1H).

<sup>IB</sup>C NMR (101 MHz, Chloroform-*d*) δ 217.24, 169.37, 137.05, 116.59, 74.90, 67.13, 66.80, 52.28, 51.32, 43.50, 37.43, 35.25.

**3.3** (v<sub>max</sub>, cm<sup>-1</sup>) 2955 (m), 2917 (m), 2360 (m), 1729 (s), 1234 (s), 1109 (w), 1078 (w), 1047 (w), 997 (w), 928 (w), 1435 (w)

HRMS (ESI/QTOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>16</sub>NaO<sub>4</sub><sup>+</sup> 247.0941; Found 247.0946.

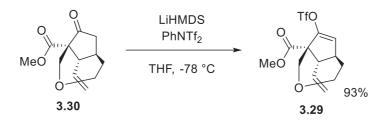
## Alcohol 3.81

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 5.73 (ddd, *J* = 17.0, 10.2, 8.3 Hz, 1H), 5.27 – 5.14 (m, 2H), 3.75 (s, 3H), 3.73 – 3.64 (m, 2H), 3.12 (dd, *J* = 12.0, 1.0 Hz, 1H), 2.93 – 2.82 (m, 1H), 2.74 – 2.62 (m, 1H), 2.12 – 1.99 (m, 3H), 1.52 – 1.44 (m, 2H).

<sup>I3</sup>C NMR (101 MHz, Chloroform-*d*) δ 209.38, 168.88, 137.24, 118.45, 61.94, 61.51, 52.65, 51.51, 44.54, 37.24, 36.07.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2936 (m), 2886 (m), 2360 (m), 1754 (s), 1729 (s), 1435 (m), 1272 (m), 1128 (s), 1040 (s), 928 (m)

HRMS (ESI/QTOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>11</sub>H<sub>16</sub>NaO<sub>4</sub><sup>+</sup> 235.0941; Found 235.0939.



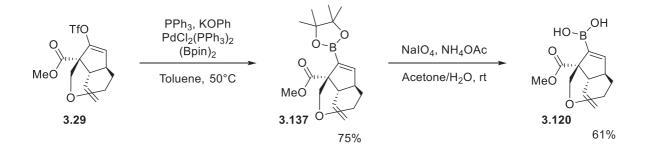
**methyl** (**IR**,**6S**,**9S**)-**8**-(((**trifluoromethyl**)**sulfonyl**)**oxy**)-**9**-**vinyl**-**3**-**oxabicyclo**[**4.2.1**]-**non-7-ene-1-carboxylate**: To a stirred solution of **3.30** (895 mg, 3.99 mmol, 1.00 equiv) in THF (15 mL), was added LiHMDS (1 M in THF, 6.09 mL, 5.99 mmol, 1.50 equiv) at -78 °C. The reaction mixture was stirred 1 h at the same temperature and PhNTf<sub>2</sub> (2.84 g, 7.98 mmol, 2.00 equiv) in THF (15 mL) was added dropwise. The reaction mixture was stirred another hour at the same temperature. The mixture was then allowed to warm slowly to room temperature. After addition of saturated NH<sub>4</sub>Cl (50 mL), the solution was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (150 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/Et<sub>2</sub>O 4.6:0.4 + 1% NEt<sub>3</sub>) yielding the pure product **3.29** (1.32 g, 93%).

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*)  $\delta$  5.83 (dt, *J* = 17.0, 10.0 Hz, 1H), 5.77 (d, *J* = 3.3 Hz, 1H), 5.17 – 4.98 (m, 2H), 4.23 (d, *J* = 12.3 Hz, 1H), 3.90 – 3.82 (m, 2H), 3.80 – 3.71 (m, 1H), 3.66 (s, 3H), 3.14 (d, *J* = 9.9 Hz, 1H), 2.78 – 2.71 (m, 1H), 2.11 – 1.98 (m, 1H), 1.78 – 1.67 (m, 1H).

<sup>IB</sup>C NMR (101 MHz, Chloroform-*d*) δ 169.39, 147.94, 136.99, 119.38, 117.18, 72.67, 68.57, 52.77, 52.12, 48.30, 44.29, 41.47, 34.60.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2929 (m), 2868 (w), 2363 (w), 1736 (m), 1650 (w), 1422 (m), 1213 (s), 1139 (s), 1071 (m), 1022 (m), 899 (m), 838 (m)

HRMS (ESI/QTOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>15</sub>F<sub>3</sub>NaO<sub>6</sub>S<sup>+</sup> 379.0434; Found 379.0435.



((1S,6R,9S)-1-(methoxycarbonyl)-9-vinyl-3-oxabicyclo[4.2.1]non-7-en-8-yl)boronic

acid: PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (21 mg, 0.03 mmol, 0.03 equiv), Ph<sub>3</sub>P (16 mg, 0.06 mmol, 0.06 equiv), bis(pinacolato) diboron (279 mg, 1.1 mmol, 1.10 equiv), and KOPh (198 mg, 1.5 mmol, 1.50 equiv) were added to a flask then flushed with nitrogen and then charged with **3.29** (356 mg, 1.0 mmol, 1.00 equiv) in toluene (6 mL). The mixture was then stirred at 50 °C for 1 h. The reaction mixture was treated with water (5 mL) at room temperature, filtered over Celite, extracted with toluene, washed with brine, and dried over MgSO<sub>4</sub>. The crude was directly used for the next step without further purification.

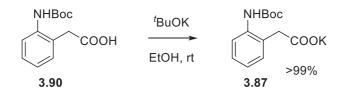
The crude **3.137** (250 mg, 0.75 mmol, 1 equiv), NaIO<sub>4</sub> (481 mg, 2.25 mmol, 3 equiv), and NH<sub>4</sub>OAc (173 mg, 2.25 mmol, 3 equiv). These reagents were then diluted with a mixture of acetone (9 mL) and water (9 mL). The resulting slurry was allowed to stir vigorously for 2 d. The slurry was then filtered over Celite and diluted with water and extracted with ethyl acetate. The organic layer was then dried with brine and MgSO<sub>4</sub> and concentrated under reduced pressure to give **3.120** (115 mg, 61%).

<sup>1</sup>**H** NMR (400 MHz, Chloroform-*d*) δ 6.57 (d, J = 2.9 Hz, 1H), 5.68 (dt, J = 16.3, 9.8 Hz, 1H), 5.14 – 4.88 (m, 2H), 4.03 (d, J = 11.8 Hz, 1H), 3.76 (t, J = 5.9 Hz, 2H), 3.71 – 3.60 (m, 4H), 3.11 (d, J = 9.7 Hz, 1H), 2.75 – 2.68 (m, 1H), 1.95 – 1.82 (m, 1H), 1.74 – 1.63 (m, 1H).

<sup>B</sup>C NMR (101 MHz, Chloroform-*d*) δ 176.38, 150.58, 138.99, 129.84, 115.90, 76.54, 69.69, 54.85, 52.43, 49.34, 32.59, 29.84.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2924 (s), 2855 (m), 2360 (m), 1722 (s), 1616 (m), 1347 (s), 1253 (s), 1103 (m), 1065 (s)

HRMS (APCI/QTOF) m/z: [M + H]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>18</sub>BO<sub>5</sub><sup>+</sup> 253.1242; Found 253.1250.



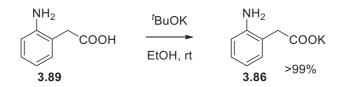
**potassium 2-(2-((tert-butoxycarbonyl)amino)phenyl)acetate**: To a solution of 2-(2-((tert-butoxycarbonyl)amino)phenyl)acetic acid **3.90** (3.0 g, 11.9 mmol, 1.0 equiv) in EtOH (24 mL, 0.5 M) at rt was added dropwise a solution of <sup>t</sup>BuOK (1.34 g, 11.9 mmol, 1.0 equiv) in EtOH (24 mL, 0.5 M). The resulting mixture was stirred at rt for 1 h and volatiles were then removed under reduced pressure. The resulting solid was washed several times with Et<sub>2</sub>O and dried under vacuum to afford 3.44 g (quantitative yield) of potassium carboxylate **3.87** as a yellowish amorphous solid.

<sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 7.28 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 3.40 (s, 2H), 1.51 (d, *J* = 1.4 Hz, 9H).

<sup>I3</sup>C NMR (101 MHz, Methanol-*d*<sub>4</sub>) δ 180.49, 155.76, 155.51, 140.72, 133.80, 130.41, 119.65, 118.80, 80.58, 45.76, 28.73 (3C).

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2360 (m), 2335 (m), 1697 (s), 1572 (s), 1522 (s), 1378 (s), 1322 (s), 1247 (m), 1159 (s), 1053 (m)

HRMS (ESI/QTOF) m/z: [M + K-1]<sup>-</sup> Calcd for C<sub>13</sub>H<sub>16</sub>K<sub>0</sub>NO<sub>4</sub><sup>-</sup> 250.1085; Found 250.1084.



**potassium 2-(2-aminophenyl)acetate**: To a solution of 2-(2-aminophenyl)acetic acid **3.89** (3.0 g, 19.8 mmol, 1.0 equiv) in EtOH (39 mL, 0.5 M) at rt was added dropwise a solution of 'BuOK (2.22 g, 19.8 mmol, 1.0 equiv) in EtOH (39 mL, 0.5 M). The resulting mixture was stirred at rt for 1 h and volatiles were then removed under reduced pressure. The resulting solid was washed several times with Et<sub>2</sub>O and dried under vacuum to afford 3.74 g (quantitative yield) of potassium carboxylate **3.86** as a yellowish amorphous solid.

<sup>1</sup>**H NMR** (400 MHz, Methanol-*d*<sub>4</sub>) δ 7.07 (d, *J* = 7.5 Hz, 1H), 6.97 (t, *J* = 7.7 Hz, 1H), 6.80 – 6.71 (m, 1H), 6.66 (t, *J* = 7.4 Hz, 1H), 3.42 (s, 2H).

<sup>IB</sup>C NMR (101 MHz, Methanol-*d*<sub>4</sub>) δ 180.22, 147.04, 131.70, 128.10, 125.44, 119.80, 117.55, 43.53.

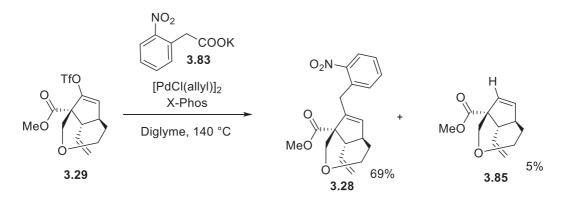
IR (v<sub>max</sub>, cm<sup>-1</sup>) 2367 (w), 3343 (m), 1560 (s), 1497 (m), 1378 (s), 1334 (s), 1103 (m)

HRMS (ESI/QTOF) m/z: [M + K-1]<sup>-</sup> Calcd for C<sub>8</sub>H<sub>8</sub>K<sub>0</sub>NO<sub>2</sub><sup>-</sup> 150.0561; Found 150.0560.



**potassium 2-(2-azidophenyl)acetate**: To a solution of 2-(2-azidophenyl)acetic acid **3.91** (3.0 g, 16.9 mmol, 1.0 equiv) in EtOH (34 mL, 0.5 M) at rt was added dropwise a solution of <sup>t</sup>BuOK (1.89 g, 16.9 mmol, 1.0 equiv) in EtOH (34 mL, 0.5 M). The resulting mixture was stirred at rt for 1 h and volatiles were then removed under reduced pressure. The resulting solid was washed several times with Et<sub>2</sub>O and dried under vacuum to afford 3.64 g (quantitative yield) of potassium carboxylate **3.88** as a redish amorphous solid.

<sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 7.36 – 7.26 (m, 2H), 7.02 – 6.80 (m, 2H), 3.45 (s, 2H). <sup>13</sup>C NMR (101 MHz, Methanol-*d*<sub>4</sub>) δ 179.89, 138.97, 136.56, 131.72 (2C), 119.67 (2C), 45.70. IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2360 (m), 2329 (m), 2123 (s), 1572 (s), 1510 (m), 1385 (m), 1291 (m), 1015 (w) HRMS (ESI/QTOF) m/z: [M + K-1]<sup>-</sup> Calcd for C<sub>8</sub>H<sub>6</sub>K<sub>0</sub>N<sub>3</sub>O<sub>2</sub><sup>-</sup> 176.0466; Found 176.0465.



**methyl (IS,6R,9S)-8-(2-nitrobenzyl)-9-vinyl-3-oxabicyclo[4.2.1]non-7-ene-1-carboxylate**: A dried flask under Ar was charged with potassium carboxylate **3.83** (1.58 g, 7.20 mmol, 2.5 equiv), [PdCl(allyl)]<sub>2</sub> (105 mg, 0.29 mmol, 0.1 equiv) and X-Phos (410 mg, 0.86 mmol, 0.3 equiv) and was then evacuated for 10 min. The flask was refilled with Ar and a solution of vinyl triflate **3.29** (1.02 g, 2.86 mmol, 1.0 equiv) in degassed diglyme (29 mL, 0.1 M) was added. The resulting suspension was purged 3 times (vacuum-Ar) and quickly warmed to 140 °C. The mixture was stirred for 2 h while the solution turned to black and CO<sub>2</sub> evolution was observed. The mixture was cooled to rt, diluted with water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (once), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered through a pad of Celite and concentrated under reduced pressure (water bath at 60 °C). Purification by FCC (PE/EA: 4.1/0.9) afforded **3.28** (677 mg, 69%) and **3.85** (29 mg, 5%).

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 7.91 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.55 (td, *J* = 7.5, 1.4 Hz, 1H), 7.47 – 7.34 (m, 2H), 5.76 (dt, *J* = 17.1, 10.0 Hz, 1H), 5.08 – 4.84 (m, 3H), 4.19 (d, *J* = 12.0 Hz, 1H), 4.07 – 3.98 (m, 1H), 3.79 – 3.70 (m, 2H), 3.68 (d, *J* = 12.1 Hz, 1H), 3.63 (s, 3H), 3.58 (ddd, *J* = 12.7, 8.9, 3.8 Hz, 1H), 3.08 (d, *J* = 9.9 Hz, 1H), 2.53 – 2.46 (m, 1H), 1.85 (ddt, *J* = 13.8, 9.3, 4.8 Hz, 1H), 1.51 – 1.41 (m, 1H).

<sup>IB</sup>C NMR (101 MHz, Chloroform-*d*) δ 172.59, 149.85, 143.27, 139.33, 134.47, 133.43, 132.97, 131.35, 127.66, 124.80, 115.30, 73.53, 68.83, 67.46, 55.30, 51.66, 47.52, 34.50, 32.03.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2921 (s), 2023 (s), 1732 (s), 1529 (s), 1517 (s), 758 (s), 1068 (s), 1264 (s), 1352 (m), 2858 (m)

HRMS m/z: [M + H]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>22</sub>NO<sub>5</sub><sup>+</sup> 344.1492; Found 344.1493.

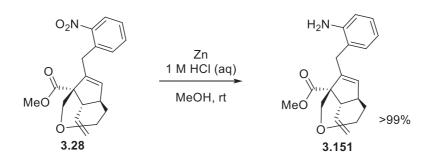
## **Deprotopalladation 3.85**

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  5.92 (d, *J* = 5.7 Hz, 1H), 5.86 – 5.82 (m, 1H), 5.73 (dt, *J* = 17.1, 9.9 Hz, 1H), 5.07 (ddd, *J* = 17.1, 2.0, 0.7 Hz, 1H), 4.92 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.12 (d, *J* = 11.8 Hz, 1H), 3.79 (ddd, *J* = 12.7, 5.5, 4.7 Hz, 1H), 3.70 (ddd, *J* = 12.2, 8.0, 3.7 Hz, 1H), 3.62 (s, 3H), 3.56 (d, *J* = 11.8 Hz, 1H), 3.09 (d, *J* = 9.7 Hz, 1H), 2.72 (dt, *J* = 5.3, 2.8 Hz, 1H), 1.92 (ddt, *J* = 14.3, 8.2, 4.9 Hz, 1H), 1.63 – 1.54 (m, 1H).

<sup>I3</sup>**C NMR** (101 MHz, Chloroform-*d*) δ 169.39, I36.99, I34.54, 129.51, 117.18, 68.57, 52.77, 52.12, 48.30, 44.29, 41.47, 34.60.

IR (v<sub>max</sub>, cm<sup>-1</sup>) 2930 (s), 2855 (s), 2360 (s), 2329 (s), 1804 (s), 1735 (s), 1234 (s)

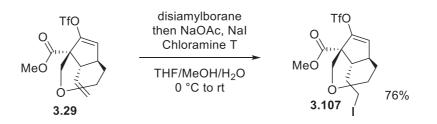
HRMS (APCI/QTOF) m/z: [M + H]<sup>+</sup> Calcd for C<sub>12</sub>H<sub>17</sub>O<sub>3</sub><sup>+</sup> 209.1172; Found 209.1171.



methyl (1S,6R,9S)-8-(2-aminobenzyl)-9-vinyl-3-oxabicyclo[4.2.1]non-7-ene-1carboxylate: To a stirred solution of 3.28 (480 mg, 1.40 mmol, 1.00 equiv) in MeOH (140 mL) was added a solution of HCl (1 M in H<sub>2</sub>O, 14 mL, 14.0 mmol, 10 equiv) and zinc (2.73 g, 42 mmol, 30 equiv). The mixture was stirred for 5 min and aq. sat. NaHCO<sub>3</sub> (~100 mL) was added then filtered over Celite. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (PE/EA, 4.1:0.9) afforded 3.151 (439 mg, 99%) as a yellowish oil.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.16 – 7.08 (m, 2H), 6.90 – 6.82 (m, 2H), 5.80 (dt, J = 17.0, 9.8 Hz, 1H), 5.36 (d, J = 2.3 Hz, 1H), 5.09 – 4.88 (m, 2H), 4.03 – 3.97 (m, 1H), 3.97 (d, J = 12.2 Hz, 1H), 3.83 (d, J = 12.3 Hz, 1H), 3.74 – 3.68 (m, 1H), 3.66 (s, 3H), 3.63 – 3.57 (m, 1H), 3.26 (dt, J = 17.2, 1.8 Hz, 1H), 3.02 (d, J = 9.7 Hz, 1H), 2.57 – 2.49 (m, 1H), 1.76 – 1.66 (m, 2H). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 172.31, 142.15, 139.72, 139.22, 134.32, 131.50, 127.88, 126.22, 120.88, 118.00, 115.39, 75.09, 71.15, 67.78, 55.67, 51.76, 46.44, 32.82, 31.50. **IR** ( $v_{max}$ , cm<sup>-1</sup>) 2927 (m), 2877 (m), 2358 (s), 1726 (s), 1498 (m), 1460 (m), 1441 (m), 1264 (s)

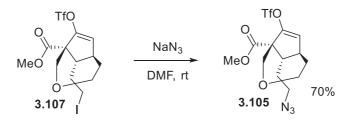
HRMS m/z: [M + H]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>24</sub>NO<sub>3</sub><sup>+</sup> 314.1751; Found 314.1756.



**methyl** (**IR**,6**S**,9**S**)-9-(2-iodoethyl)-8-(((trifluoromethyl)sulfonyl)oxy)-3-oxabicyclo-[4.2.1]non-7-ene-1-carboxylate: To a stirred solution of BH<sub>3</sub>·THF (1.0 M in THF, 26.0 mL, 26 mmol, 10 equiv) at 0 °C was added 2-methyl-2-butene (6.07 mL, 57.5 mmol, 22 equiv) dropwise, and the resulting mixture was stirred at the same temperature for 2 h. To a stirred solution of 3.29 (932 mg, 2.61 mmol, 1.0 equiv) in THF (1.0 mL) at 0 °C was added dropwise the *in-situ* prepared solution of disiamyl borane. The reaction mixture was stirred at room temperature for 8 h. To the stirred reaction mixture at 0 °C was added a solution of NaOAc (1.7 g, 21.0 mmol, 8.0 equiv) in MeOH (21.0 mL), a solution of NaI (470 mg, 15.8 mmol, 6 equiv) in MeOH (29 mL) sequentially. The resulting reaction mixture was stirred at room temperature for 10 min and quenched by addition of sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>(~25 mL) and IN HCl (~25 mL). The reaction mixture was diluted with water (25 mL) and extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (PE/Et<sub>2</sub>O, 4.3:0.7) afforded **3.107** (960 mg, 76%) as a yellowish oil.

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 5.72 (d, *J* = 3.0 Hz, 1H), 4.18 (d, *J* = 12.3 Hz, 1H), 3.88 – 3.74 (m, 2H), 3.84 (d, *J* = 12.3 Hz, 1H), 3.77 (s, 3H), 3.29 (ddd, *J* = 10.0, 7.9, 4.4 Hz, 1H), 3.08 (ddd, *J* = 10.0, 9.0, 7.3 Hz, 1H), 2.78 – 2.69 (m, 2H), 2.05 – 1.86 (m, 2H), 1.81 – 1.66 (m, 2H).

Further characterizations could not be performed as the intermediate is highly unstable.



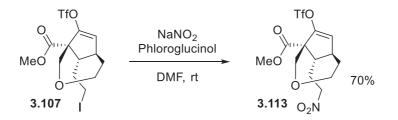
**methyl (IR,6S,9S)-9-(2-azidoethyl)-8-(((trifluoromethyl)sulfonyl)oxy)-3-oxabicyclo-**[**4.2.1**]**non-7-ene-1-carboxylate**: To a stirred solution of **3.107** (100 mg, 0.2 mmol, 1.0 equiv) in DMF (2 mL) at room temperature was added NaN<sub>3</sub> (130 mg, 2.0 mmol, 10 equiv), and the resulting mixture was stirred at the same temperature for 12 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (PE/Et<sub>2</sub>O, 4:1) afforded **3.105** (56 mg, 70%) as a colorless oil.

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 5.72 (d, J = 2.3 Hz, 1H), 4.17 (d, J = 12.4 Hz, 1H), 3.84 (d, J = 12.3 Hz, 1H), 3.82 – 3.77 (m, 2H), 3.77 (s, 3H), 3.41 (ddd, J = 12.3, 7.2, 5.0 Hz, 1H), 3.30 (ddd, J = 12.5, 8.5, 6.4 Hz, 1H), 2.82 – 2.76 (m, 1H), 2.70 (ddd, J = 10.7, 3.5, 1.1 Hz, 1H), 2.03 – 1.90 (m, 1H), 1.80 – 1.62 (m, 2H), 1.52 – 1.44 (m, 1H).

<sup>IB</sup>C NMR (101 MHz, Chloroform-*d*) δ 169.96, 147.79, 119.49, 73.13, 68.71, 63.99, 52.45, 49.37, 44.71, 42.07, 34.63, 30.33.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2922 (m), 2196 (m), 1737 (m), 1551 (s), 1543 (s), 1456 (m), 1369 (s), 1342 (s), 1160 (s), 1209 (m), 1073 (m), 833 (m), 744 (m)

HRMS m/z: [M + H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>17</sub>F<sub>3</sub>N<sub>3</sub>O<sub>6</sub>S<sup>+</sup> 400.0785; Found 400.0786.



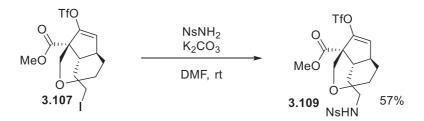
**methyl** (**IR**,**6S**,**9S**)-**9**-(**2**-**nitroethyl**)-**8**-(((**trifluoromethyl**)**sulfonyl**)**oxy**)-**3**-**oxabicyclo**-[**4.2.1**]**non-7-ene-1-carboxylate**: To a stirred solution of **3.107** (100 mg, 0.2 mmol, 1.0 equiv) in DMF (2 mL) at room temperature was added NaN<sub>3</sub> (130 mg, 2.0 mmol, 10 equiv) and phloroglucinol (62 mg, 0.48 mmol, 2.4 equiv). The resulting mixture was stirred at the same temperature for 12 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (PE/Et<sub>2</sub>O, 3.5:0.5) afforded **3.113** (57 mg, 70%) as a yellowish oil.

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 5.74 (d, *J* = 2.3 Hz, 1H), 4.53 – 4.37 (m, 2H), 4.17 (d, *J* = 12.5 Hz, 1H), 3.84 (d, *J* = 12.3 Hz, 1H), 3.84 – 3.75 (m, 2H), 3.80 (s, 3H), 2.76 (ddd, *J* = 5.3, 3.3, 2.4 Hz, 1H), 2.69 – 2.64 (m, 1H), 2.12 – 2.02 (m, 2H), 2.01 – 1.92 (m, 1H), 1.81 – 1.72 (m, 1H).

<sup>IB</sup>C NMR (101 MHz, Chloroform-*d*) δ 169.64, 147.73, 119.29, 73.56, 73.02, 68.56, 63.77, 52.71, 44.32, 42.44, 34.64, 29.15.

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2939 (m), 2358 (s), 2195 (m), 1736 (m), 1550 (s), 1546 (s), 1422 (m), 1369 (s), 1347 (s), 1168 (s), 833 (m), 1209 (m), 1073 (m), 744 (m)

HRMS m/z: [M + H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>17</sub>F<sub>3</sub>NSO<sub>8</sub>S<sup>+</sup> 404.0621; Found 404.0622.



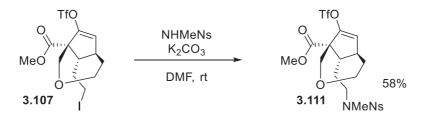
**methyl** (IR,6S,9S)-9-(2-((4-nitrophenyl)sulfonamido)ethyl)-8-(((trifluoromethyl)sulfonyl)oxy)-3-oxabicyclo[4.2.1]non-7-ene-1-carboxylate: To a stirred solution of 3.107 (50 mg, 0.1 mmol, 1.0 equiv) in DMF (1 mL) at room temperature was added NsNH<sub>2</sub> (42 mg, 0.2 mmol, 2.0 equiv) and K<sub>2</sub>CO<sub>3</sub> (34 mg, 0.25 mmol, 2.5 equiv). The resulting mixture was stirred at the same temperature for 12 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (DCM/MeOH, 98:2) afforded 3.109 (32 mg, 57%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.07 (m, 1H), 7.93 – 7.84 (m, 1H), 7.81 – 7.68 (m, 2H), 5.70 (d, J = 3.3 Hz, 1H), 5.29 (t, J = 6.3 Hz, 1H), 4.09 (d, J = 12.3 Hz, 1H), 3.82 (d, J = 12.5 Hz, 1H), 3.79 – 3.74 (m, 2H), 3.72 (s, 3H), 3.21 – 3.10 (m, 2H), 2.81 – 2.73 (m, 1H), 2.69 (dd, J = 10.6, 3.5 Hz, 1H), 2.00 – 1.89 (m, 1H), 1.80 – 1.61 (m, 2H), 1.51 – 1.38 (m, 1H).

<sup>IB</sup>C NMR (101 MHz, Chloroform-*d*) δ 171.30, 148.45, 133.90, 133.79, 132.64, 132.42, 131.73, 131.04, 124.68, 120.83, 73.56, 69.34, 64.09, 53.57, 47.76, 44.03, 42.32, 34.17, 24.43.

IR  $(v_{max}, cm^{-1})$  2987 (s), 2359 (s), 1737 (m), 1541 (s), 1423 (m), 1369 (s), 1178 (s), 833 (m), 1209 (m), 1074 (m), 2195 (m), 2940 (m), 740 (m)

HRMS(ESI/QTOF) m/z: [M+Na]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>NaO<sub>10</sub>S<sub>2</sub><sup>+</sup> 581.0482; Found 581.0484.



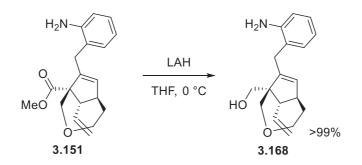
**methyl** (**IR**,**6S**,**9S**)-**9**-(**2**-((**N**-**methyl**-**4**-**nitrophenyl**)**sulfonamido**)**ethyl**)-**8**-(((**trifluoro methyl**)**sulfonyl**)**oxy**)-**3**-**oxabicyclo**[**4.2.1**]**non**-**7**-**ene**-**1**-**carboxylate**: To a stirred solution of **3.107** (50 mg, 0.1 mmol, 1.0 equiv) in DMF (1 mL) at room temperature was added NHMeNs (43 mg, 0.2 mmol, 2.0 equiv) and K<sub>2</sub>CO<sub>3</sub> (48 mg, 0.35 mmol, 3.5 equiv). The resulting mixture was stirred at the same temperature for 12 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by FCC (PE/EA, 3:2) afforded **3.111** (33 mg, 58%) as a colorless oil.

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 8.02 – 7.95 (m, 1H), 7.76 – 7.66 (m, 2H), 7.66 – 7.57 (m, 1H), 5.75 (d, *J* = 2.9 Hz, 1H), 4.10 (d, *J* = 12.2 Hz, 1H), 3.87 (d, *J* = 12.3 Hz, 1H), 3.84 – 3.78 (m, 2H), 3.75 (s, 3H), 3.53 (ddd, *J* = 14.7, 9.1, 6.6 Hz, 1H), 3.11 (ddd, *J* = 14.1, 7.0, 3.8 Hz, 1H), 2.86 – 2.81 (m, 4H), 2.68 (dd, *J* = 10.9, 3.0 Hz, 1H), 2.11 – 1.98 (m, 1H), 1.80 – 1.71 (m, 1H), 1.70 – 1.59 (m, 1H), 1.53 – 1.47 (m, 1H).

<sup>IB</sup>C NMR (101 MHz, Chloroform-*d*) δ 171.30, 148.45, 135.36, 133.79, 132.64, 132.42, 131.73, 131.04, 124.68, 120.83, 73.56, 69.34, 64.09, 53.57, 52.32, 47.76, 44.03, 41.76, 34.17, 28.53.

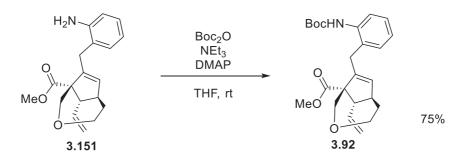
IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2360 (s), 1735 (m), 1547 (s), 1422 (m), 1372 (s), 1172 (s), 834 (m), 1209 (m), 1078 (m), 2198 (m), 2942 (m), 740 (m)

HRMS(ESI/QTOF) m/z: [M+Na]<sup>+</sup> Calcd for C<sub>20</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>NaO<sub>10</sub>S<sub>2</sub><sup>+</sup> 595.0638; Found 595.0640.



((**IR,6R,9S**)-**8**-(**2-aminobenzyl**)-**9-vinyl-3-oxabicyclo**[**4.2.1**]**non-7-en-1-yl**)**methanol**: to a stirred suspension of LAH (73 mg, 1.92 mmol, 6.00 equiv) in THF (2.5 mL) at 0 °C was added dropwise a solution of **3.151** (100 mg, 0.32 mmol, 1.00 equiv) in THF (0.7 mL). The reaction mixture was stirred for 30 minutes at room temperature before being cooled to 0 °C. After successive addition of water (0.07 mL), 15% NaOH (0.07 mL) and water (0.22 mL), the mixture was stirred for 30 minutes then filtered through Celite, washed with Et<sub>2</sub>O and evaporated. The crude was used for the next step without further purification.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.16 – 7.08 (m, 2H), 6.90 – 6.82 (m, 2H), 5.80 (dt, J = 17.0, 9.8 Hz, 1H), 5.36 (d, J = 2.3 Hz, 1H), 5.09 – 4.88 (m, 2H), 4.03 – 3.97 (m, 1H), 3.97 (d, J = 12.2 Hz, 1H), 3.93 – 3.87 (m, 1H), 3.83 (d, J = 12.3 Hz, 1H), 3.74 – 3.68 (m, 1H), 3.63 – 3.57 (m, 1H), 3.55 – 3.45 (m, 1H), 3.26 (dt, J = 17.2, 1.8 Hz, 1H), 3.02 (d, J = 9.7 Hz, 1H), 2.57 – 2.49 (m, 1H), 1.76 – 1.66 (m, 2H).



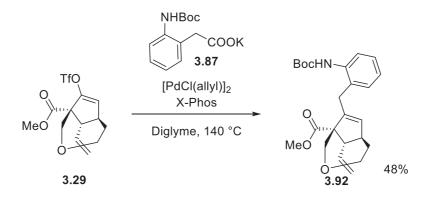
**methyl** (**IS,6R,9S**)-**8**-(**2**-((**tert-butoxycarbonyl**)**amino**)**benzyl**)-**9**-**vinyl**-**3**-**oxabicyclo**-[**4.2.1**]**non-7-ene-1-carboxylate**: to a solution of **3.151** (233 mg, 0.74 mmol, 1.00 equiv) in THF (7.4 mL) was added NEt<sub>3</sub> (0.15 mL, 1.11 mmol, 1.5 equiv), DMAP (87 mg, 0.07 mmol, 0.10 equiv) and Boc<sub>2</sub>O (210 mg, 0.96 mmol, 1.3 equiv) at 0 °C. The mixture was allowed to slowly warm to room temperature and stirred overnight. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl, extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 4.8:0.2) yielding the pure product **3.92** (230 mg, 75%).

<sup>1</sup>**H NMR** (400 MHz, Chloroform-*d*) δ 8.02 (d, J = 8.2 Hz, 1H), 7.45 (s, 1H), 7.28 – 7.23 (m, 1H), 7.17 (dd, J = 7.5, 1.6 Hz, 1H), 6.99 (td, J = 7.4, 1.2 Hz, 1H), 5.83 (dt, J = 16.9, 9.9 Hz, 1H), 5.20 (s, 1H), 5.12 – 4.87 (m, 2H), 4.09 (d, J = 12.2 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.83 (d, J = 12.0 Hz, 1H), 3.78 – 3.71 (m, 1H), 3.70 (s, 3H), 3.56 (dt, J = 17.2, 1.7 Hz, 1H), 3.16 (dt, J = 17.3, 1.9 Hz, 1H), 3.07 (d, J = 9.9 Hz, 1H), 2.52 (dt, J = 4.9, 2.0 Hz, 1H), 1.85 – 1.73 (m, 1H), 1.67 – 1.59 (m, 1H), 1.51 (s, 9H).

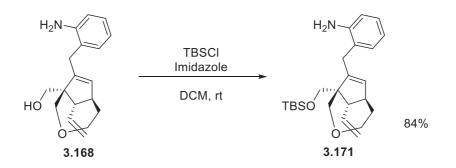
<sup>B</sup>C NMR (101 MHz, Chloroform-*d*) δ 172.43, 153.52, 140.66, 139.11, 137.28, 133.99, 130.86, 127.89, 127.56, 122.88, 120.62, 115.32, 79.74, 74.13, 70.15, 67.68, 55.62, 51.78, 46.76, 33.36, 31.29, 28.45 (3C).

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2360 (w), 2930 (w), 1722 (s), 1591 (w), 1535 (m), 1453 (m), 1241 (s), 1159 (s), 1047 (m), 909 (m), 734 (s)

HRMS (ESI/QTOF) m/z: [M + Na]<sup>+</sup> Calcd for C<sub>24</sub>H<sub>31</sub>NNaO<sub>5</sub><sup>+</sup> 436.2094; Found 436.2091.

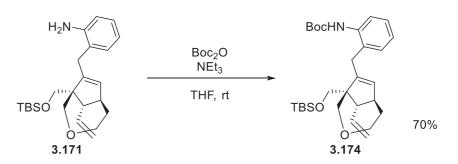


**methyl** (**IS**,6**R**,9**S**)-**8**-(**2**-((**tert-butoxycarbonyl**)**amino**)**benzyl**)-**9**-**vinyl**-**3**-**oxabicyclo**-[**4.2.1**]**non-7-ene-1-carboxylate**: A dried flask under Ar was charged with potassium carboxylate **3.87** (318 mg, 1.10 mmol, 2.5 equiv), [PdCl(allyl)]<sub>2</sub> (16 mg, 0.04 mmol, 0.1 equiv) and X-Phos (63 mg, 0.13 mmol, 0.3 equiv) and was then evacuated for 10 min. The flask was refilled with Ar and a solution of vinyl triflate **3.29** (155 mg, 0.44 mmol, 1.0 equiv) in degassed diglyme (4.4 mL, 0.1 M) was added. The resulting suspension was purged 3 times (vacuum-Ar) and quickly warmed to 140 °C. The mixture was stirred for 2 h while the solution turned to black and CO<sub>2</sub> evolution was observed. The mixture was cooled to rt, diluted with water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (once), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered through a pad of Celite and concentrated under reduced pressure (water bath at 60 °C). Purification by FCC (PE/EA: 4.8/0.2) afforded **3.92** (87 mg, 48%)



2-(((**IS**,6**R**,9**S**)-**I**-(((**tert-butyldimethylsilyl**)**oxy**)**methyl**)-**9**-**vinyl**-**3**-**oxabicyclo**[**4.2.1**]-**non-7-en-8-yl**)**methyl**)**aniline**: To a stirred solution of **3.168** (60 mg, 0.21 mmol, 1 equiv) in DCM (2 mL), was added imidazole (36 mg, 0.53 mmol, 2.50 equiv) and TBSCl (38 mg, 0.25 mmol, 1.2 equiv) at 0 °C. The reaction mixture was stirred overnight at room temperature and then quenched with saturated NH<sub>4</sub>Cl (5 mL). The solution was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/EA 4.25:0.75) yielding the pure product **3.171** (669 mg, 84%). The crude was used for the next step without further purification.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.16 – 7.08 (m, 2H), 6.90 – 6.82 (m, 2H), 5.85 (dt, *J* = 17.1, 9.8 Hz, 1H), 5.09 – 4.88 (m, 3H), 3.83 (d, *J* = 12.2 Hz, 1H), 3.80 – 3.54 (m, 5H), 3.30 – 3.14 (m, 2H), 2.87 (d, *J* = 9.6 Hz, 1H), 2.49 – 2.38 (m, 1H), 1.83 – 1.72 (m, 1H), 1.41 – 1.31 (m, 1H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).



*tert*-butyl (2-(((1S,6R,9S)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-9-vinyl-3-oxabicyclo[4.2.1]non-7-en-8-yl)methyl)phenyl)carbamate: To a solution of 3.171 (55 mg, 0.14 mmol, 1.00 equiv) in THF (1.4 mL) was added NEt<sub>3</sub> (29 μL, 0.21 mmol, 1.5 equiv) and Boc<sub>2</sub>O (40 mg, 0.18 mmol, 1.3 equiv) at 0 °C. The mixture was allowed to slowly warm to room temperature and stirred overnight. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl, extracted with EtOAc (3 x 10 mL), washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>, PE/Et<sub>2</sub>O 4.8:0.2) yielding the pure product 3.174 (49 mg, 75%).

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.84 (d, J = 8.1 Hz, 1H), 7.27 – 7.20 (m, 1H), 7.14 (dd, J = 7.5, 1.6 Hz, 1H), 7.02 (td, J = 7.4, 1.3 Hz, 1H), 6.91 (s, 1H), 5.85 (dt, J = 17.1, 9.8 Hz, 1H), 5.09 – 4.88 (m, 3H), 3.83 (d, J = 12.2 Hz, 1H), 3.80 – 3.54 (m, 5H), 3.30 – 3.21 (m, 2H), 2.87 (d, J = 9.6 Hz, 1H), 2.49 – 2.38 (m, 1H), 1.83 – 1.72 (m, 1H), 1.50 (s, 9H), 1.41 – 1.31 (m, 1H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

<sup>I3</sup>C NMR (101 MHz, Chloroform-*d*) δ 162.72, 153.31, 145.27, 141.29, 137.22, 130.69, 130.39, 127.61, 122.73, 115.71, 79.87, 72.86, 68.04, 65.95, 62.54, 59.74, 54.59, 46.84, 34.89, 30.63, 28.51 (2C), 25.78 (3C), 18.11, 15.36, -3.47 (2C).

IR ( $\nu_{max}$ , cm<sup>-1</sup>) 2930 (m), 2360 (m), 1729 (s), 1591 (m), 1522 (m), 1453 (m), 1241 (m), 1159 (s), 1047 (m)

HRMS (ESI/QTOF) m/z: [M + H]<sup>+</sup> Calcd for C<sub>29</sub>H<sub>46</sub>NO<sub>4</sub>Si<sup>+</sup> 500.3191; Found 500.3193.

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# Curriculum vitae

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- Specialized in organic chemistry
- Enthusiastic, motivated and innovative
- Sociable and work willingly in teams

## Education

2014 - 2018	PhD in Organic Chemistry in the Laboratory of Prof. Jieping Zhu <b>Swiss Federal Institute of Technology (EPFL)</b> , Lausanne, Switzerland
	Total Synthesis of Alstilobanine C, Undulifoline and Alstilobanine B
	Co-responsible of the safety in the laboratory
	More than 600 hours of teaching given (theoretical and practical)
2013 - 2014	Master Project in the Laboratory of Prof. Barry M. Trost
	Stanford University, California, United States of America
	Development of Substituted Donors for the Palladium-Catalyzed Trimethylenemethane
	Asymmetric [3+2] Cycloaddition Involving Nitrogen, Oxygen and Sulfur Functional Groups
2012 - 2014	Master of Science in Molecular and Biological Chemistry
	Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland
2008 - 2012	Bachelor of Science in Chemistry and Chemical Engineering
	Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland
2005 - 2008	Federal Maturity in Chemistry and Biology
	High school of Burier, La Tour-de-Peilz, Switzerland
	Graduation project in chemistry, summa cum laude

# Leadership and Professional Experiences

Summer 2014	Temporary employee at Roche in Research and Early Development (5 months)
	Discovery, inspiring, challenging
Spring 2013	Teaching assistant for a chemistry practical course for first year chemistry students
	Supervision, responsibility
Autumn 2012	Teaching assistant for "General chemistry" (Prof. Rainer Beck) and "Organic chemistry"
	(Prof. Luc Patiny) courses
	Supervision, involvement
Summer 2012	Internship in the Laboratory of Asymmetric Catalysis and Synthesis (LCSA) (8 weeks)
	"Enantioselective Rhodium-Catalyzed C-C bond Activation for the Construction of
	Quaternary Stereogenic Centers"
	Optimization of the starting material synthetic route for the rhodium-catalyzed reaction

Spring 2012	Project in the Laboratory for Computational Molecular Design (LCMD)
	"Physical Origin of the Selectivity of Molecular Receptors towards Caffeine"
	Calculations of a caffeine/receptor complex
May 2011/12	Chemistry show for school children, Open House EPFL (more than 1500 spectators)
	Popularization of chemical experiments, sociability
Autumn 2012	Teaching assistant for "Structural analysis" course (Prof. Luc Patiny)
	Supervision, involvement
Summer 2011	Internship in the Laboratory of Catalysis and Organic Synthesis (LCSO) (7 weeks)
	"Catalytic Diastereoselective Formal [3+2] Cycloaddition of Aminocyclopropane with Indole"
	Optimization of a transition metal catalyzed reaction
May 2010	Substitute teacher in sciences, secondary school
	Leadership, sociability
2008 - 2013	Private tuition in sciences for high school and Bachelor students
	Supervision, involvement

## **Publications**

Gaeng, N.; Wang, Q.; Zhu, J. Manuscript in preparation

Bartels, B.; Bolas, C. G.; Cueni, P.; Fantasia, S.; Gaeng, N.; Trita, A. S. J. Org. Chem. 2015, 80, 1249.

Luisier, N.; Ruggi, A.; Steinmann, S. N.; Favre, L.; Gaeng, N.; Corminboeuf, C.; Severin, K. Org. Biomol. Chem. 2012, 10, 7487.

### Scholarship

### 2013 Fondation Zdenek et Michaela Bakala, Geneva, Switzerland Excellence scholarship

### Skills

Chemical synthesis and analytics

Organic and organometallics synthesis, design and performance of multi-step syntheses of target molecules, asymmetric transition metals catalysis, laboratory safety, nuclear magnetic resonance, infrared spectroscopy, mass spectrometry, gas chromatography, chiral HPLC, UV-Vis

Informatics

Gaussian, Molden, VMD, TINKER, Bash, AMBER

#### Languages

French	Native language
English	Fluent (level C1)
German	Basic knowledge (level B1)
Italian	Basic communication (level A2)

## **Extra-Curricular Activities**

2008 - 2010	Aperto employee, store Leadership, flexibility, personal management
Summers 2006- 2017	Volunteer for the Montreux Jazz Festival Responsible of the disabled people accessibility team Responsibility, communication skills, personal management

## References

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