Total Synthesis of Aspidosperma Family Indole Alkaloids through the iORC Domino Process

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PAR

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Il faut toujours connaître les limites du possible. Pas pour s'arrêter, mais pour tenter l'impossible dans les meilleurs conditions
— Roman Gary
I feel the need to write this section in a comprehensive more than succinct way, as it is the best opportunity for me to express my gratitude, in writing, to all the people who supported me and helped me during my graduate career.

First of all, I would like to thank my PhD supervisor Jieping for accepting me to his group and having the confidence in me to be a good chemist. It was a fascinating experience to work on these challenging projects with his support and supervision. I am also inspired and impressed by Jieping, by his enthusiasm for chemistry, his spirit to challenge some of the hardest problems, his sharing of great ideas, and his hard-working attitude. I wish I would be an excellent chemist as him in the future. I appreciate his patience with me, his advices and his constant support for me.

Next, I want to express my gratitude to Professor Reissig, Professor Gaich, Professor Cramer and Professor Waser for taking time to review my PhD work and for serving on my graduate committee.

I would also like to thank Qian for her valuable guidance of my work, her kindness to help me under any circumstances and her rigor in the attention to detail. Her positive attitude and professional dedication set up a model for us to follow.

I certainly could not accomplish my PhD work without the assistance of my wonderful colleagues. First goes to JB, with whom I started my academic studies ten years ago in EPFL. He is a generous friend and great companion with a dark humor but shining personality. We have gone though so many great moments together, from our Bachelor, while playing video games, to our PhD defence, with all the great lunches and coffee breaks and the mutual support during the tough days where nothing was working. I will always keep with me part of his wisdom, as his famous quote "Si tu penses que la violence ne résout rien, c’est que tu n’as pas frappé assez fort". I am also grateful for his patience and help in proofreading my papers and correcting my English. And now I am lucky enough to have him as my best man on my most important day.

I have to thank Thomas, who has been an amazing colleague to me. I enjoyed discussing with him about chemistry as well as life, his silly jokes and optimistic vision could
I want to express my appreciation to Solène, from the neighboring lab, for her support through my entire PhD work. I have known her since our master studies in EPFL and always admire her positive outlook and her ability to smile despite the situation. She is always a great friend to me and I think fondly of time having lunch with her, discussing and gossiping, or having a drink in the Great Escape.

I am always thankful to my former colleague but forever mate Nick, for his unique humor and his wisdom. We not only go out together for the music festival and brunches, but also have insightful discussions about chemistry and support each other though the darkest times. He also contributes significantly to my PhD thesis as proofreader and later on to my wedding as my best man.

The following person I would express my appreciation is Claire, who brought fresh air to the lab even though she only stayed with us for nine months. She is so friendly and cheerful, and could always light up our days by her particular “Good Morning” greetings along with her smile. Besides, she is amongst few people who truly understand my silly jokes and always give me a great laughter instead of a pity look. I believe short times are gone, but more fun times will come.

Next, I would like to thank Dylan and Antonin, who are talented chemists and very cool guys. I had as much fun in the lab with them as in the bars drinking and dancing. They have been so supportive to me and share their insights about chemistry and life with me.

I am also grateful to Viktoria, a smart and interesting girl with who I always love to talk. She has her special philosophy of life and she taught me not to let the stress take the best of me. We shared great laugh in the lab during the past four years, and hopefully in the future too.

I would like to dedicate a special thanks to Zhengren and Shuo, the two excellent post-docs who had fundamental influence on me. Zhengren who is currently doing another post-doc in the United States inspired me with his efficiency, professional, enthusiastic, and his dedication to chemistry work. He is my primary resource to solve scientific confusions and was helping me though my PhD time. Besides, Zhengren was my Chinese teacher who always kindly corrects my Chinese. Shuo who worked next to me motivated me with her support, her kindness and sweetness. She had always been there for me when I had questions and tried to help me out.

Certainly, I owe my thanks to all my remarkable co-workers. It is a great pleasure for me to work with Cyril, Tu and Nico, who I valued all the lovely discussions and enjoyed sharing
great afternoon coffee time; Weiwu and Yang, who I appreciate their help and nice discussions; Xu, who is always been friendly to me; and Bo, who shared his good ideas with us.

There are more colleagues in my PhD time I would like to thank to, who are not only great helpers for my PhD work but also lovely friends in my life: Ioulia, for her constant support, her insightful advice, and the greatest tricks of all as the “emergency chocolate”; Giulia, for her smile and her encouragement to my work; Stephan, for his “keep calm, work hard and party harder” spirit which inspired me to enjoy life; Hugo, for his classic humor that always brought me smiles; Yann, for his generous sharing of his own experience; Martina, for her kindness and friendliness; and Ala, for the unique spirit she passed on us which brought a brand new perspective in our lives. And lastly, a special thanks to all the young promising chemists in our lab who I had the pleasure to work with: Marion, Mathias, Samuel, Raphael, Sjaak, David, Balázs and Johan.

Particularly, I would like to express my gratitude to Monique, our secretary, for her kindness and patience, as well as all the administration work she did for us.

In the past four years, I was honoured to meet and work with some brilliant scientists who inspired and motivated me all the time. Sandrine, my Mentor, who was a role model as a researcher and teacher; Davide, who I admire his fashion style as well as his time management skills and multitasking capability; Francoise, who I cherish her laughter and her free spirit; Slavo, who I adore his working attitude; Francois, who I like his living style; and Pascal, who always surprises me with his wide knowledge. There are also so many other awesome scientists from the LCSA and LCSO, with whom I have the luck to share great moments during Barbecues and Aperos and got to know them.

My PhD work could certainly not have gone well without the assistance of the technical teams of ISIC. I would thank the NMR service (Anto, Pascal and Martial), for their effort to maintain the machines; the Mass Service (Laure, Daniel and Francisco), for their fast, efficient and accurate analysis of our samples; Luc, for his hard work in developing all the fantastic informatics tools to help us; the Magasin (Giovanni, Annelise, Gladys, and Benjamin), for their efficiency in providing us requested new chemicals and equipments; the Mechanical workshop, for designing personalized spare parts for our machines; and finally Patrick, for his patience in solving our various hardware problems.

Besides my work, family and friends are the best part of my life. I could not successfully finish my PhD work without their continuous support. I would express my greatest appreciation to my beloved family: my parents, Philippe and Dominique, who taught me to be a gentleman and always support my decisions; my dear brother Raphaël, who is the coolest and best brother everyone wishes to have. Also, I would like to thank my life-long friends who grew up with me and mean so much to me, especially Simon, Marc, Laurence, Laura,
Acknowledgements

Valentine and Amaniel, for always cheering me up and giving me a hand when I needed the most. I cherish the love and friendship you constantly give to me.

The best outcome in the past four years is not only finish my PhD, but more importantly find my lifelong soul mate Huiwen. She has been a true and great supporter since we are together and always has faith in me. She cheered me up in the depressing time, worked along with me in the lab until 3am, and shared life responsibilities with me in tough period and happy days. I am the luckiest man to have her on my side and will love her from now and forever.

Lausanne, June 8, 2015

O. W.
Abstract

This thesis describes a unified strategy for the synthesis of monoterpenoid indole alkaloids of the *Aspidosperma* family. These syntheses feature two key steps: (1) a palladium-catalyzed decarboxylative vinylation that provides quick access to cyclopentene intermediates containing all of the carbons present in the natural products and (2) an integrated oxidation/reduction/cyclization (iORC) sequence for skeletal reorganization that converts the cyclopentenes to the corresponding pentacyclic structures of the natural products. By incorporation of a geometric constraint to the iORC substrates, both the chemoselectivity (*C7 versus N1* cyclization) and the stereoselectivity (*trans*- versus *cis*-fused ring system) of the cyclization process can be controlled. Using this method, we achieved the total synthesis of racemic aspidospermidine and dehydroaspidospermidine in seven steps; both of which feature a *cis*-fused ring system. We then accomplished a ten-steps synthesis of kopsihainanine A featuring a *trans*-fused ring system. The work towards the total synthesis of aspidolbidine and kopsinitarine E using the same two key steps was attempted, but was not completed in the time provided. This PhD will also cover our synthetic efforts towards the alkaloid minfiensine, featuring a domino reduction/cyclization sequence performed prior to the development of the iORC process.

**Keywords:** natural product, indole alkaloids, domino reaction, iORC, total synthesis, minfiensine, aspidospermidine, dehydroaspidospermidine, vincadiformine, aspidolbidine, kopsihainanine A, kopsinitarine E.
Résumé

Cette thèse décrit une stratégie unifiée pour la synthèse d’alcaloïdes indoliques monoterpeniques de la famille des *Aspidosperma*. Ces synthèses présentent deux étapes clés : (1) une vinylation décarboxylante catalysée au palladium, qui fournit un accès rapide aux intermédiaires cyclopenténiques contenant tous les carbones présents dans les produits naturels ciblés et (2) une séquence domino d’oxydation/réduction/cyclisation intégrée (ORCi) permettant une réorganisation du squelette des cyclopentènes en leurs structures pentacycliques équivalentes. Par incorporation d’une contrainte géométrique aux substrats de l’ORCi, tant la chimiosélectivité (cyclisation en C7 ou N1) que la stéréosélectivité (systèmes cycliques fusionnés en *trans* ou en *cis*) du procédé de cyclisation peuvent être contrôlées. En utilisant cette méthode, nous avons achevé la synthèse totale racémique de l’aspidospermidine et de la déhydroaspidospermidine en sept étapes ; les deux présentant un système cyclique fusionné en *cis*. Nous avons ensuite accompli la synthèse totale racémique de la kopsihainanine A en dix étapes et présentant un système cyclique fusionné en *trans*. Le travail vers la synthèse totale de l’aspidoalbidine et la kopsinitarine E utilisant ces deux étapes clés ont été tentées, mais ne furent pas complétées dans le temps imparti. Ce doctorat couvre aussi nos efforts de synthèse de la minfiensine, utilisant une séquence domino de réduction/cyclisation antérieure au développement du procédé ORCi.

**Mots-Clés :** produit naturel, alcaloïde indolique, réaction domino, ORCi, synthèse totale, minfiensine, aspidospermidine, dehydroaspidospermidine, vincadifformine, aspidoalbidine, kopsihainanine A, kopsinitarine E.
List of Abbreviations

Ac       Acetyl
AIBN     Azobisisobutyronitrile
Boc      Tert-butyloxycarbonyl
Bn       Benzyl
Bp       Boiling Point
BRSM     Based on Recovered Starting Material
Bu       Butyl
Bz       Benzoyl
Cbz      Carboxybenzyl
CMPI     2-Chloro-1-methylpyridinium iodide
COSY     Correlation Spectroscopy
DABCO    1,4-Diazabicyclo[2.2.2]octane
dba      Dibenzylideneacetone
DBU      1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC      Dicyclohexyl Carbodiimide
DCM      Dichloromethane
DEAD     Diethyl Azodicarboxylate
DEG      Diethylene Glycol
DIBAL-H  Diisobutylaluminum Hydride
DIPEA    N,N-Diisopropylethylamine
DME      1,2-Dimethoxyethane
DMF      N,N-Dimethylformamide
DMAP     4-Dimethylaminopyridine
DMBA     1,3-Dimethylbarbituric Acid
CMBP     (Cyanomethylene)tributylphosphorane
DMP      Dess-Martin Periodinane
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<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereoisomeric Ratio</td>
</tr>
<tr>
<td>E</td>
<td>Entgegen</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric Excess</td>
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<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>FCC</td>
<td>Flash Column Chromatography</td>
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<tr>
<td>Glc</td>
<td>Glucose</td>
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<tr>
<td>HATU</td>
<td>(1-Bis(dimethylamino)methylene-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid Hexafluorophosphate)</td>
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<tr>
<td>HFIP</td>
<td>Hexafluoroisopropyl Alcohol</td>
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<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond Correlation</td>
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<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
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<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
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<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>Heteronuclear Single-Quantum Correlation</td>
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<tr>
<td>IBX</td>
<td>2-Iodoxybenzoic Acid</td>
</tr>
<tr>
<td>IEDDA</td>
<td>Inverse Electron Demand Diels-Alder</td>
</tr>
<tr>
<td>INEPT</td>
<td>Insensitive Nuclei Enhanced by Polarization Transfer</td>
</tr>
<tr>
<td>iORC</td>
<td>Integrated Oxidation/Reduction/Cyclization</td>
</tr>
<tr>
<td>IR</td>
<td>Infra-Red</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium Bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium Diisopropylamine</td>
</tr>
<tr>
<td>LDMA</td>
<td>Lithium Dimethylamine</td>
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<tr>
<td>LiHMDS</td>
<td>Lithium Bis(trimethylsilyl)amide</td>
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<tr>
<td>mCPBA</td>
<td>Meta-chloroperoxybenzoic Acid</td>
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<tr>
<td>MCR</td>
<td>Multicomponent Reaction</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Mps</td>
<td>para-Methoxyphenylsulfonamide</td>
</tr>
<tr>
<td>Ms</td>
<td>Mesyl</td>
</tr>
<tr>
<td>MTBE</td>
<td>Methyl Tert-butyl Ether</td>
</tr>
<tr>
<td>MVK</td>
<td>Methyl Vinyl Ketone</td>
</tr>
<tr>
<td>MW</td>
<td>Micro-Wave</td>
</tr>
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<td>Abbreviation</td>
<td>Full Form</td>
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</tr>
<tr>
<td>Nap</td>
<td>Naphthyl</td>
</tr>
<tr>
<td>NHC</td>
<td>N-Heterocyclic Carbene</td>
</tr>
<tr>
<td>Ns</td>
<td>Nosyl</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic resonance</td>
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<tr>
<td>NPIF</td>
<td>(ortho-Nitrophenyl)phenyliodonium Fluoride</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium Chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>Pyridinium Dichromate</td>
</tr>
<tr>
<td>PE</td>
<td>Petroleum Ether</td>
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<tr>
<td>pfp</td>
<td>Pentafluorophenyl</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
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<tr>
<td>pin</td>
<td>Pinacol</td>
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<tr>
<td>PMB</td>
<td>p-Methoxybenzyl</td>
</tr>
<tr>
<td>Pr</td>
<td>Propyl</td>
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<tr>
<td>quant.</td>
<td>Quantitative Yield</td>
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<tr>
<td>Rf</td>
<td>Retention Factor</td>
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<tr>
<td>RCM</td>
<td>Ring Closing Metathesis</td>
</tr>
<tr>
<td>RT</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>TBA</td>
<td>Tribromoacetic Acid</td>
</tr>
<tr>
<td>TBAC</td>
<td>Tetrabutylammonium Chloride</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium Fluoride</td>
</tr>
<tr>
<td>TBDPS</td>
<td>Tert-butylidiphenylsilyl</td>
</tr>
<tr>
<td>TBS or TBDMS</td>
<td>Tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TCAC</td>
<td>Trichloroacetyl Chloride</td>
</tr>
<tr>
<td>TES</td>
<td>Triethylsilyl</td>
</tr>
<tr>
<td>TEMPO</td>
<td>(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic Acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>Trifluoroacetic Anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>Tetrahydropyranyl</td>
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<tr>
<td>Tf</td>
<td>Triflate</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
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<td>TLC</td>
<td>Thin Layer Chromatography</td>
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<tbody>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>Tetrapropylammonium Perruthenate</td>
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<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>TSE</td>
<td>Trimethylsilylethyl</td>
</tr>
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<td>TTF</td>
<td>Tetrathiafulvalene</td>
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<tr>
<td>TTMSS</td>
<td>Tris(trimethylsilyl)silane</td>
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<tr>
<td>UV</td>
<td>Ultra-Violet</td>
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General Introduction

The *Aspidosperma* family is one of the largest family of monoterpenic indole alkaloids comprising over 250 members. This group of alkaloids can be found mostly in plants of the *Apocynaceae* family, essentially present in tropical forest. These monoterpenic indole alkaloids fascinate the scientific community due to their congested polycyclic structures, high substitution patterns, and multiple stereocenters. These challenging features inspired chemists for decades, and pushed them to develop new methodologies toward the synthesis of complex heterocycles. One of the main research areas of our group is the development of domino reactions, and their use in the construction of substituted indoles. So far many palladium-catalysed syntheses as well as multicomponent reactions for the formation of substituted indoles were developed by our group. In a continuation of this work, we are always looking for new ways to build in a late-stage the indole polycyclic core of indole alkaloids via domino processes.

This thesis focuses on the use of a domino reaction called an integrated oxidation/reduction/cyclization (iORC) process to reach various members of the *aspidosperma* family of monoterpenic indole alkaloids, specifically the natural products 1-7.

![Chemical structures of natural products 1-7](image)

Our idea was to start from stable and easily accessible 1-(2-nitrobenzyl)-cyclopentene derivative 8. After an oxidative cleavage of the double bond and reduction of the nitro group, we should obtain putative diaminodicarbonyl intermediate 9 that should spontaneously cyclize into iminium indole intermediate 10.
We can notice that 10 has two nucleophilic positions: the N1 and C7 position. It is well known that the C7 position is more nucleophilic than the N1. Nevertheless, if C7 is already substituted with a bulky R1 group, the attack should occur from the nucleophilic nitrogen N1 and give tetracyclic aminal 11 bearing a cis-fused [6,6] ring system. This example, a total synthesis of (±)-Goniomitine has been done previously in our lab, and will be detailed in 1.3.1.

To force the attack from the C7 position, we envisaged two solutions. i) A structural constrain, such as a tether between R1 and R2 would help force the regioselectivity and give the cis-fused [6,6] ring system 12. ii) By removing all sterical hindrance in R1, the regioselectivity for the C7 attack could be high, allowing us to reach tetracyclic structure 13. In this example, we would like to address in more details the diastereocontrol of the iORC, as we plan to force the cyclization in a trans-fused [6,6] ring system.

It is important to note that stereogenic centre C7 temporarily becomes sp\(^2\) hybridized during the iORC and therefore, loses all stereochemical information. Therefore, the C20 quaternary centre will control the diastereoselectivity of the cyclization.

This thesis will start with a brief summary and state of the art of the topics related to this work, namely indole alkaloids, the use of domino process in their total synthesis, and an introduction to the iORC, along with the other syntheses done using this domino process (Chapter 1).
Afterward, this thesis will cover the work done toward the total synthesis of minfiensine 1, which used an early version of the iORC, lacking the oxidation step (Chapter 2).

![Diagram of minfiensine 1 synthesis](image)

The next two chapters cover the synthesis of aspidospermidine 3, dehydroaspidospermidine 2 and vincadifformine 4 (Chapter 3), and our approach toward the synthesis of aspidoalbidine 5 (Chapter 4) by using the iORC and taking advantage of structure-induced strain to promote the C7-C21 bond formation as key step.

![Diagram of aspidospermidine synthesis](image)

The next chapter investigates more into detail the regio- and stereoselectivity of the unrestrained iORC, and of their use in the total synthesis of kopsihainanine A 6 (Chapter 5).

![Diagram of kopsihainanine A synthesis](image)

The last chapter covers our approach toward the synthesis of kopsinitarine E 7 using the iORC on a much more complex substrate (Chapter 6).

![Diagram of kopsinitarine E synthesis](image)
Background

The chemistry of natural products has captivated the scientific community for hundreds of years. Since the first reported isolation of an alkaloid (morphine) in 1805 by Sertürner, chemists have fought many intellectual battles trying to reproduce the wonders of Nature in their flasks. Nature provides us with unlimited numbers of organic compounds, with a large spectrum of molecular masses, of complexity, of heteroatoms, and of many more features, each of them being an intellectual challenge. It is a fascinating field, that contains many sophisticated aspects. The starting point of all this is of course the isolation of the products from various biological media, such as bark of trees, algae, bacteria, or even mammals.

Every compound produced by a biological entity has a specific purpose. The direct consequence of this is the numerous biological effects caused by many of these natural products. These biological properties will often be a strong driving force for the synthetic study of a given natural product. The most potent compounds are often present in negligible quantity inside the biological entity. Therefore the study of such compounds is near impossible due to the tremendous amount of biomass which would be needed to extract a sufficient amount of said compound. This is without mentioning the difficulty to gain access to such a quantity of biomass. A relevant example would be the polyketide (+)-discodermolide, which was isolated in 1990 by Gunasekera and co-workers. This natural product was isolated from the deep-sea sponge Discodermia dissoluta, who grows only at more than 33 m deep in the Caribbean sea. In addition to the difficult access to the biomass, the quantity of (+)-discodermolide present within is small. Only 7 mg of compound per 434 g of sponge was found. It is therefore easy to imagine why the synthesis of such compounds is so attractive, allowing scientists to have easier access to the product in sufficient amounts. It will also give the chemists the ability to make derivatives of a given product, in the optic of increasing some of its biological effects, such as anti cancer or antimicrobial properties.

Chapter 1: Background

The total syntheses which constitute the body of this work are monoterpene indole alkaloids. Therefore, the first section of this chapter will go more into detail on indole alkaloids and their biosynthesis. As our synthetic strategy revolve around a domino reaction for the late-stage formation of the indole core of these natural products, we will give some examples of the synthesis of indole alkaloids which involved a key domino sequence. We will then introduce our iORC per se as well as the other work done with this method.

1.1 Monoterpene Indole Alkaloids

Alkaloids are natural products that can be extracted from the alkaline aqueous phase resulting from treatment of the corresponding biomass, as most of the time they present a basic nitrogen atom. They are produced by a large variety of biological entities and are classified by their skeleton structure. Amongst these alkaloids, we will focus on the products containing an indole moiety. A large number of them were discovered by extracting plants or fungi, which were known to have some beneficial effect in traditional medicine. For example the plants of the Strychnos genus are a major source of numerous alkaloids, these plants have been used in traditional and conventional medicine for ages. A famous example is the poison strychnine, extracted from the specie Strychnos nux vomica, it has been used since the ancient Chinese era. The beneficial effects of plant extracts from the Strychnos genus were also exploited in different traditional medicines. Naturally, the biological properties of these plants attracted the attention of chemists which led to the isolation of strychnine by Pelletier and Caventou in 1819. This was the first monoterpene indole alkaloid isolated. Since then, more than 2000 monoterpene indole alkaloids were discovered. Due to their potent biological activities, and their challenging polycyclic structure, numerous laboratories have spent years extracting, identifying or synthesizing these alkaloids.

As a result of this strong interest from the scientific community, a large number of reviews and books on indole alkaloids already exist. Therefore, instead of making a full ac-

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5For a review on indole alkaloids, see for example Grundon, M. F.; Saxton, J. E. In The Alkaloids, Grundon, M. E., Ed.; The Alkaloids, Vol. 6; Royal Society of Chemistry: Cambridge, 1976; Chapter 10, pp 189–251
count on the topic of the synthesis of indole alkaloids, we will only introduce the biosynthesis of this class of natural products.

1.1.1 Biosynthesis of monoterpene Indole Alkaloids

The biosynthetic pathway of most monoterpene indole alkaloids are already established and well studied. Secologanine 14 and tryptamine 15 are the core building blocks to most, if not all, of the monoterpene indole alkaloids (Scheme 1.1). They are synthesised respectively from 1-deoxy-D-glucose 5-phosphate 16 and tryptophan 17. After an enzymatic Pictet-Spengler reaction between these two products, strictosidine 18 is obtained. After removal of the glucose, some rearrangements lead to 4,21-dehydrogeissoschizine 19. This ammonium salt can lead to the Yohimbinoid Family, or be reduced into geissoschizine 20, which is a precursor of the Ajmalicine family. The Cinchona alkaloids are also derived from strictosidine 18.

From strictosidine 18 and geissoschizine 20 is derived the uniform numbering system of indole alkaloids proposed by Taylor and Le Men in 1965. We will use this numbering for the attribution of the NMR spectra as soon as an intermediate bearing all the carbons of the natural products is reached.

From geissoschizine 20 to aspidosperma alkaloids, the mechanism is less understood. Many enzymes involved in the process haven’t been isolated or identified. Nevertheless, there are a few theories and some isolated intermediates that allowed chemists to hypothesise a mechanism (Scheme 1.2).

After an oxidation, geissoschizine 20 could cyclise to intermediate 21, an akuammiline precursor, that could rearrange into preakuammicic 22 (a precursor of akuammicine alkaloids). Then, the iminium would be reduced to afford stemmadenine 23. From this alkaloid, an isomerisation of the double bond, followed by opening of the macrocycle through enzymatic dehydroxylation would afford Iboga precursor 24. This intermediate could undergo a Diels-Alder cycloaddition into tabersonine 25. A simple reduction into vincadifformine 4 gives an entrance into the vinca, aspidosperma, strychnos alkaloids and few other families.

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8 Le Men, J.; Taylor, W. I. Experientia 1965, 21, 508–510
1.2 The Domino Process in Total Synthesis of Indole Alkaloids

Using domino reactions\textsuperscript{10} has diverse advantages in organic synthesis mostly less work-up and purification steps, meaning cheaper and faster reaction sequences. It is then not surprising if a myriad of groups applied them in total synthesis. A tremendous number of total syntheses using domino reactions already exist (and it would take many books to cover them).

Domino processes by themselves are not new. Many classical chemical reactions, like Mannich reactions\textsuperscript{11} are by definitions domino processes. Therefore, it is easy to imagine the tremendous amount of examples of domino reactions accessible in the literature. The

\textsuperscript{11}Mannich, C.; Krösche, W. \textit{Arch. Pharm. (Weinheim)}. \textbf{1912}, \textit{250}, 647–667
fascination of chemists for these processes lies in the elegance and almost artistic fashion to perform chemical transformations. The simple reasoning to not just quench the resulting intermediate into a given product A, but instead having it reacting with another substrate toward a more complex product B is somewhat appealing. Lots of work were already done in this field, and multiple reviews on the use of domino reaction in total synthesis already exist.\textsuperscript{10,12} We will only present some selected total syntheses of indole alkaloids that are using domino reactions as key steps.

\textsuperscript{12}Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. \textit{Angew. Chem. Int. Ed.} \textbf{2006}, \textit{45}, 7134–7186
1.2.1 Corynanthe Type Indole Alkaloid Synthesis by Tietze

In 1992, Tietze and co-worker reported a synthesis of the tetracyclic core of corynanthe alkaloids by the use of a domino Pictet-Spengler/intramolecular ene reaction (Scheme 1.3).13 Intermediate 26 submitted to acidic medium went through a Pictet-Spengler cyclization into tricycle 27. This intermediate could be isolated in 66% yield. If SnCl$_4$ was added to the reaction mixture, an intramolecular ene reaction occurred to give racemic corynanthe core 28.

![Scheme 1.3 – Domino Pictet-Spengler/intramolecular ene reaction for the synthesis of corynanthe family indole alkaloids](image)

It is an interesting example of an ene reaction in a domino process. The ene reaction has most of the time a high activation energy, which makes it more difficult to be included in a domino process (often in the presence of other reagents or reactive intermediates).

1.2.2 Strictosidine Analogues Synthesis by Tietze

Between 1994 and 1997, Tieze published the syntheses of strictosidine type structure using a Domino Knoevenagel/hetero-Diels-Alder pathway (Scheme 1.4).14 After a Knoevenagel condensation of aldehyde 29 with dimethylbarbituric acid 30 or Meldrum’s acid 31, a hetero-Diels-Alder with as dienophile (E)-((but-1-en-1-yloxy)methyl)benzene produced the two strictosidine analogues 32 and 33 respectively. These products were converted into corynanthe alkaloid 34 or valesiachotamine alkaloid 35 by hydrogenolysis of the Cbz and Bz groups.

These examples illustrate the principle of a divergent strategy, where from the same starting material and different reagents, different alkaloids (here corynanthe alkaloid and valesiachotamine alkaloid) can be reached.

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1.2. The Domino Process in Total Synthesis of Indole Alkaloids

1.2.3 Corey’s Total Synthesis of (-)-Aspidophytine

In 1999, Corey and co-workers reported the use of a domino Mannich/allylation sequence to reach aspidophytine 36 (Scheme 1.5).15 Starting from indole 37 and dialdehyde 38, an acid-catalyzed condensation into iminium 39 took place. The indole moiety of this reactive intermediate cyclized on the iminium, forming indolenium salt 40. This intermediate cyclized again into pentacycle 41. In situ isomerization of the enamine into an iminium, followed by reduction with NaBH$_3$CN afforded pentacycle 42 in 66% yield from the starting amine and dialdehyde. This intermediate was converted to (-)-aspidophytine 36 in 6 steps. This synthesis is an elegant example of using indole reactivity to perform multiple cyclizations in one domino process.

1.2.4 Boger’s Total Synthesis of (-)-Vindorosine

Boger and co-workers reported in 2006 a total synthesis of (-)-vindorosine 43 via an inverse electron demand Diels–Alder reaction (IEDDA)/(1,3)-dipolar cycloaddition domino process (Scheme 1.6).16 From intermediate 44, an IEDDA between the electron-rich dienophile and the 1,3,4-oxadiazole moiety afforded intermediate 45. Subsequent elimination of nitrogen furnished dipolar intermediate 46 that underwent a (3+2) cycloaddition into ether-bridged

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15He, E.; Bo, Y.; Alton, J. D.; Corey, E. J. J. Am. Chem. Soc. 1999, 121, 6771–6772
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Scheme 1.5 – Domino Cyclizations for a total synthesis of (-)-aspidophytine

product 47. Both enantiomers of 47 were separated, and (-)-vindorosine 43 was then reached in 7 additional steps.

Scheme 1.6 – Domino IEDDA/(1,3)-dipolar cycloaddition for a total synthesis of (-)-vindorosine

Diels-Alder and retro Diels-Alder reactions are often used in domino reactions, as they often display good regio and diastereoselectivity and the resulting olefin can undergo subsequent transformations.

1.2.5 Qin’s Total Synthesis of (±)-Minfiensine

Qin and co-workers illustrated in 2008 the efficiency of a cyclopropanation/retro-Mannich/cyclization domino sequence towards total synthesis of minfiensine
1.3. The iORC Process and Related Total Syntheses

(Scheme 1.7). Starting directly with indole structure 48 (obtained in 3 steps from tryptamine with 70% yield), they obtained diazo ketone 49. It then cyclized in the presence of copper triflate through a one-pot cyclopropanation/ring opening/ring closing cascade reaction to form intermediate 50. \((\pm\)-Minfiensine 1 \) was then reached in 9 more steps.

\[
\begin{align*}
\text{48} & \xrightarrow[5\text{ steps}, 51\%]{\text{CuOTf}} \text{49} \\
\text{(\pm)-Minfiensine 1} & \xrightarrow[9\text{ steps, 14\%}]{\text{DCM}} \text{50}
\end{align*}
\]

Scheme 1.7 – Domino cyclopropanation/retro-mannich/cyclization process in Qin's total synthesis of \((\pm\)-minfiensine

The release of the ring strain of a cyclopropane is a good driving force for developing a process that does not require harsh conditions. It allows more flexibility in the development of one-pot procedures.

1.2.6 Danishefsky's Total Synthesis of (-)-Phalarine

Danishefsky reported in 2010 a total synthesis of the furanobisindole alkaloid (-)-phalarine (Scheme 1.8). Starting from aminoester derivative 51, their reaction sequence began with a Pictet Spengler reaction with formaldehyde into iminium salt 52. Subsequent attack from the C3 position of the indole gave indolenium intermediate 53. This was followed by a Wagner-Meerwein rearrangement into carbocation 54. The carbocation was then trapped by the phenol moiety affording 55 in 91% yield as a single diastereoisomer. Ten more steps were necessary to reach enantiopure (-)-phalarine 56.

1.3 The iORC Process and Related Total Syntheses

The Michael and Mannich additions are amongst the most powerful tools for C-C bond formation. Despite being well established reactions, Michael and Mannich reactions are still

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being studied and improved every year.

Intramolecular Mannich reactions between indole derivatives and imine or iminium species are well described systems. Nonetheless, the one-pot sequential condensations of on one hand a 2-aminophenylacetyl ketone moiety to form the indole and on the other an amine and carbonyl group to form an activated imine followed by reaction of these two species in situ haven’t been exploited to the best of our knowledge. The reason is the difficulty to obtain a stable intermediate with amines and carbonyles groups without prior unwanted condensation or polymerization. The first concept of the iORC was to form these two amines and carbonyl groups in situ in a domino process (Scheme 1.9). From stable and easily accessible 1-(2-nitrobenzyl)-cyclopentene derivative 8, an oxidative cleavage of the double bond and reduction of the nitro group, afforded putative diaminodicarbonyl intermediate 9 that should spontaneously cyclize into iminium indole intermediate 10 (cf. General Introduction).

We can notice that 10 has two nucleophilic positions: the N1 and C7 position. It is well known that the C7 position is more nucleophilic than the N1. Nevertheless, as C7 is already substituted with a bulky alkyl group, the attack occurred from the nucleophilic nitrogen N1 and gave the tetracyclic aminal 11 bearing the desired cis-fused [6,6] ring system.

\[ \text{Scheme 1.8 – Domino Pictet-Spengler/Cationic cyclization pathway in a total synthesis of } (-)-\text{phalarine} \]

\[ \text{Scheme 1.9 – The iORC process} \]

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1.3. The iORC Process and Related Total Syntheses

1.3.1 Total Synthesis of (±)-Goniomitine

In 2013, Zhu and co-workers published the total synthesis of goniomitine using the iORC domino sequence (Scheme 1.10).\textsuperscript{22} This synthesis was the proof of concept for this domino process.

From easily accessible potassium salt 57 and vinyl triflate 58, a palladium-catalyzed decarboxylative coupling followed by in situ deprotection of the silyl group afforded the alcohol 59. After a Mitsnou reaction to form the azide 60, the key step could be attempted. As planned, the bulky CH\textsubscript{2}CH\textsubscript{2}OBn chain blocked the attack from the C7 position and only the attack from the nitrogen was observed with full diastereoccontrol. After ozonolysis and subsequent reduction of both nitro and azide groups, O-benzylgoniomitine 61 was isolated as the only product in 80% yield. Deprotection of the benzyl group under standard conditions afforded racemic goniomitine 62 in 65% yield.

1.3.2 Total Synthesis of leuconolam–leuconoxine–mersicarpine

In the end of 2013, our group published a domino sequence similar to the iORC process in order to reach the leuconolam–leuconoxine–mersicarpine skeleton (Scheme 1.11).\textsuperscript{23} In this case, the domino sequence is not anymore an iORC, because the oxidation of the olefin was performed as a separate operation, and the reduction/cyclization sequence was refined to incorporate a lactamization and further oxidation steps. Nonetheless, the reaction pathway

\textsuperscript{22} Xu, Z.; Wang, Q.; Zhu, J. Angew. Chem. Int. Ed. 2013, 52, 3272–3276
Chapter 1: Background

Scheme 1.10 – Total Synthesis of goniomitine 62 using an iORC domino process

has strong similarities with our former iORC.

From boronic acid 63 and iodoenone 64, a Suzuki-Miyaura coupling afforded 65, then an ozonolysis afforded methyl ester 66. Following the idea of the iORC, the following step was the reduction of both the nitro group and the azide, giving the two amines needed for the cyclizations. A careful optimization allowed for selectivity between pathways a and b. Following pathway a, the alkyl amine 67 cyclized on the aryl ketone, to afford a 1H-3-aminoindole. This intermediate underwent lactamization of the ester by the indole nitrogen promoted by KOH, followed by in situ oxidation with oxygen and reduction with Me₂S to yield (-)-mersicarpine 68 which was isolated with 75% yield.

When acetic anhydride was used during the first reduction step (path b), the azide moiety was converted into an acetamine group (69). After two consecutive cyclizations, intermediate 70 was isolated in 50% yield. This intermediate is a precursor to scholarizine G, but is lacking the C6-C7 bond (the acetyl did not cyclize on the 3-oxindole). Submitting this intermediate to a strong base afforded (-)-scholarizine G 71 in 73% yield. Further transformations of this natural product allowed our laboratory to reach (+)-meoldinine E 72, (-)-leuconoxine 73 and (-)-leuconolam 74.

This work demonstrates the high versatility of the iORC process. Its potency to reach a large variety of families of monoterpenic indole alkaloid is quite exceptional.
1.3. The iORC Process and Related Total Syntheses

Scheme 1.11 – Total Synthesis of (-)-mersicarpine 68, (-)-scholarisine G 71, (+)-melodinine E 72, (-)-leuconoxine 73 and (-)-leuconolam 74
Approach Towards the Total Synthesis of Minfiensine

In 1989, Massiot and co-workers discovered an indole alkaloid named (+)-minfiensine 1, which possess an unprecedented pentacyclic structure. They isolated this new alkaloid from the African plant Strychnos minfiensis (Figure 2.1).24

This *strychnos* indole alkaloid raised the attention of the scientific community due to its highly congested pentacyclic ring system that presents an interesting synthetic challenge. In addition, different members of the *strychnos* indole alkaloid family have shown interesting anticancer activities.25 The pentacyclic core of this alkaloid was unique until 2012, when Morita and co-workers found in the Alstonia plant an indole alkaloid with a similar polycyclic system named (+)-alsmaphorazine C (Figure 2.2).26 The challenge of this quite unique congested skeleton encouraged many laboratories to search for a synthetic route and, until now, five laboratories have achieved the total synthesis of minfiensine.

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To the best of our knowledge, no biosynthetic pathway of minfiensine is reported. It is reasonable to postulate that minfiensine 1 originates from preakuammicine 22 (Scheme 2.1), as minfiensine’s structure is closely related to some members of the akuammiline indole alkaloid family. The first step is probably a decarboxylation, leading to tetrahydrovincanine 75. This structure is closely related to 18-desoxy-Wieland-Gumlich aldehyde 76 isolated from the same plant as minfiensine 1. From here, the remaining steps to go from tetrahydrovincanine 75 to minfiensine 1 are the cleavage of the N1-C2 bond and the formation of the N1-C3 bond. Unfortunately, there are no explanation so far on the enzymatic pathway leading to minfiensine 1.

Scheme 2.1 – Hypothesis of biosynthetic pathway for akuamiline alkaloid minfiensine 1

2.1 Previous Syntheses

16 years after the isolation of minfiensine 1, Overman and co-workers reported the first synthetic pathway to enantiopure alkaloid 1 in 21 steps and 3.2% overall yield,27 which has since

then been improved in 2008 to 15 steps and 6.5% overall yield. Qin and co-workers reported in 2008 a synthesis of the racemic alkaloid in 18 steps and 0.4% overall yield (See 1.2.5). A major breakthrough came from the MacMillan group the year after, who obtained the enantiopure alkaloid in only 9 steps and 21% yield. Finally the group of Padwa and Qiu synthesized (+)-minfiensine in 2011, the former in 11 steps and 3.3% overall yield and the latter in 10 steps and 6.2% overall yield respectively.

2.1.1 Overman's Synthesis of (+)-Minfiensine

Overman’s group published the first synthesis of (+)-minfiensine starting from 77 (Scheme 2.2). Five steps were needed to convert this amine into enamine intermediate 78. Then by using a catalytic asymmetric Heck-iminium ion cyclization sequence, indoline derivative 79 was obtained. Acidification of the reaction mixture resulted in the N4 attack of the C3 position, closing the aminal ring, affording 80. Nine more steps were required to reach (+)-minfiensine 1.

Scheme 2.2 – Overman’s Synthesis of (+)-minfiensine 1

Using the Pfaltz ligand for the formation of 79, they were able to form the quaternary center on the C7 with full enantiocontrol, which then dictated the stereoselectivity of the aminal formation.

2.1.2 MacMillan's Synthesis of (+)-Minfiensine

In 2009, a short enantioselective synthesis was published by MacMillan and co-workers.\textsuperscript{29} Their synthesis of (+)-minfiensine 1 started with protected tryptamine 81, synthesizing diene 82 in three steps (Scheme 2.3). This diene reacted with propionaldehyde after activation by a chiral organocatalyst. The resulting Diels-Alder product spontaneously cyclized with the Boc-protected amine to afford 83 with good yield and ee.

![Scheme 2.3 – MacMillan's Synthesis of (+)-Minfiensine 1](image)

After protection of the alcohol and alkylation of the amine (84), a radical 6-exo-dig cyclization closed the last ring of the natural product and form the allene 85. A palladium catalyzed hydrogenation afforded the E alkene with high selectivity. Finally, deprotection gave (+)-minfiensine 1.

2.1.3 Padwa's Synthesis of (±)-Minfiensine

The strategy of Padwa and co-workers is shown in Scheme 2.4.\textsuperscript{30} Starting from 87, obtained in 4 steps from 86, they decided to build the indole moiety using a domino cross-coupling/Diels-Alder/rearrangement process to reach 88. After this, Boc deprotection with MgI\textsubscript{2} with spontaneous cyclization to form the aminal moiety, palladium-catalyzed deallylation, and N-allylation afforded 89. Finally, a Heck-type reaction closed the last ring of the racemic natural product and (±)-minfiensine 1 was obtained in 4 more steps via functional group interconversions.
2.1. Previous Syntheses

Scheme 2.4 – Padwa’s synthesis of (±)-minfiensine 1 using a domino Cross-coupling/Diels-Alder/rearrangement process

Scheme 2.5 – Qiu’s total synthesis of (±)-minfiensine

2.1.4  Qiu’s Synthesis of (±)-Minfiensine

In Qiu’s strategy (Scheme 2.5) the indole is formed using the Fisher indole synthesis as the first step. The quaternary carbon at the C7 position was then installed with a palladium catalyzed allylation to reach intermediate 90. Protection of the indolenine moiety followed by a two-step oxidative cleavage of the terminal olefin and reductive amination of the resulting aldehyde afforded 91. It was then cyclized at the C3 position to form aminal 92. A Heck-type reaction allowed them to close the last ring of the pentacyclic core to reach racemic
minfiensine 1 after functional group interconversions.

2.2 Synthetic Studies of Minfiensine

These strategies, elegant as they are, all form the indole in an early stage, or start from an indole derivative (tryptamine). As far as we know, nobody has yet attempted to form both C-N bonds of the aminal in one step. This approach could be a powerful tool for the formation of indole alkaloids. With this in mind, we undertook the synthesis of minfiensine 1 featuring our domino process.

From a retrosynthetic point of view (Scheme 2.6), (±)-minfiensine 1 can be easily obtained from 93, following a similar Heck-type reaction as described in other syntheses.\(^{32}\)

![Scheme 2.6 – Retrosynthetic analysis of (±)-minfiensine](image)

The key step would be the formation of 94 through a reduction/cyclization sequence. To the best of our knowledge, such strategy was not yet described to reach this type of alkaloid. We planned to use a reductive domino double cyclization sequence in which the aminal was formed from a ketone and two latent amine functions (95). This reaction had the great advantage of creating the two amino functions \textit{in situ}, avoiding excessive protection/deprotection steps. We can consider this domino process as an early version of our iORC process, that did not include the oxidation step.

We can notice the presence in the key intermediate of the quaternary center in what

would be the C7 position of the future alkaloid structure. This stereocentre should direct the
diastereoselectivity of the different cyclisations. As our first plan was to reach intermediate 95 and study the feasibility of the key reaction of our synthesis, we decided not to focus on the chirality of this stereocentre for the moment, but to dedicate our efforts to a racemic version of the synthesis with the possibility to develop subsequently an enantioselective version.

2.2.1 Key Intermediate Formation: Intramolecular RCM Strategy

We pursued several strategies to obtain intermediate 95. Our first idea (Scheme 2.7) was to perform an alkylation and an allylation on methyl 2-(2-nitrophenyl)acetate 96. Alkylation with 97, would afford ester 98. Subsequent allylation with 99 would generate 2,2-disubstituted arylacetate 100. With this straightforward approach it was, in theory, possible to reach allyl ketone 101 from methyl ester 100 and then form highly functionalized cyclohex-3-en-1-one derivative 95 by ring closing metathesis (RCM).

![Scheme 2.7 – First pathway to the key intermediate](image)

The \( \alpha \) position of the ester has a low pKa value due to the strong electron withdrawing effect of the \( o \)-nitrophenyl group. This makes the anion a poor nucleophile. Furthermore, after the first addition, this position becomes quite hindered which makes the attack on the electrophile more difficult. The formation of this quaternary center was therefore a major issue in this strategy. When we inverted the sequence and started by adding 99, which worked well, the anion from this allylated product was not sufficiently nucleophilic to add onto 97 and no desired compound 100 was obtained. The more reactive methacrylate derivative 99 had therefore to be added in the second step. After careful screening of diverse bases and temperature, the yield of the first addition was pushed to a promising 73\%, but the second addition to form 100 was more tedious. Even after optimizing the base (amines, lithium bases, alcoholates, carbonate bases with or without crown ether), the solvent and the temperature,
the yield never exceeded 17%. This reaction resulted either in recovering the starting material, or decomposition if the temperature was too high or the base too strong. We attempted to modify the nucleophile, using an azidophenyl acetate 102 instead of the nitrophenyl acetate 96, but all alkylations tried on this substrate resulted in degradation of the reagent and a messy reaction mixture. It is noteworthy that such alkylation on 2-(2-azidophenyl)acetyl acid derivatives were never reported. We also attempted to form malonate compound 105. Sadly, the poor reactivity of the anion was again troublesome and the quaternary carbon was unreachable by alkylation (from 104) or S_N_Ar (from 106) regardless of our efforts. Reactions with similar substrates are known, but only on less bulky substituents, or with more activated electrophiles.\textsuperscript{33} The conversion after 24 h was less than 10% in the best conditions.

At this stage, we reasoned we could not afford such a poor yield for the formation of this quaternary centre. We needed a way to force the anion to react and increase the yield. It was decided to attempt the cross-metathesis first, and then form the quaternary centre intramolecularly.

### 2.2.2 Key Intermediate Formation: Cross Metathesis

For this strategy, we needed at first to change the ester of 98 to an allyl ketone. Several pathways were attempted. The results are shown in Scheme 2.9. We first saponified ester 98 to

\[\text{Scheme 2.8 – Attempts on malonate derivatives or azidophenyl derivative}\]

\[\begin{align*}
\text{96} & \xrightarrow{1. \text{H}_2, \text{Pd/C}} \text{97} \\
& \xrightarrow{2. \text{NaNO}_2, \text{NaN}_3} \text{103} \\
\text{104} & \xrightarrow{\text{I} \xrightarrow{\text{N}_3} \text{97}} \text{105} \\
& \xrightarrow{\text{Base} < 10\%} \text{106}
\end{align*}\]


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acid 109, and tried to synthesize allyl ester 107. We first considered performing a C-acylation
with but-3-enoyl chloride to form 108, followed by a palladium-catalyzed decarboxylation of
the allyl ester. Unfortunately the steric hindrance and low nucleophilicity of allyl ester 107
made the synthesis of 108 impossible. Only degradation or no conversion was observed.

Scheme 2.9 – Formation of homoallylic alcohol 112 or allyl ketone 110

We decided to avoid this problem by direct allylation of the acid chloride derived from
109, or through allylation of Weinreb amide 113 to allylketone 115 used as model substrate.
Numerous Lewis acids were tried in combination with allyltrimethylsilane, as well as different
allyl-metal derivatives, but then resulting only in very messy reactions without any major
compound being formed. We observed that the nitro group on the aromatic ring was sen-
sitive to Grignard-type reagents. Nitroaryls are known to react with organometals as in the
Bartoli indole synthesis. The azido group is also known to react strongly with Lewis-acids,
resulting in side-reactions. In our case, almost every Lewis acid tried resulted in degrada-

tion of the starting material. The desired allyl ketone 110 was never observed.

We therefore decided to try different types of allylations. In an attempt to make the reaction smoother, we planned to use an aldehyde instead of an acyl chloride. Here again, alylation of aldehyde 111 was not trivial. Numerous Lewis acids were tried in combination with allyltrimethylsilane, or different allyl-metal species. These attempts resulted only in degradation, except for allyl cerium complexes, formed in situ from cerium chloride and allylmagnesium bromide36 afforded the desired product, though the yield remained low (<20%). After many trials, we finally found that Brown Allylation of aldehyde 111 with an allylboronic acid pinacol ester worked well to afford homoallylic alcohol 112 in good yield as a mixture of two diastereoisomers.37 From this intermediate, formation of both TES-protected alcohol 114 and allyl ketone 110 proceeded smoothly.

With allyl products 110, 112 and 114 in our hand, we could attempt the cross metathesis with different acrylates (Scheme 2.10).38 Unfortunately, all possible combinations of the three acrylates 99, 116, 117 with unprotected alcohol 112, TES-protected alcohol 114 or the oxidized allyl ketone 110 did not provide the desired olefin when using either Grubbs II or Hoveyda-Grubbs II. Only starting material and degradation was observed. An attempt was made after tethering the two olefins by esterification, but resulting compound 119 also failed to undergo the RCM to 120. This behaviour might be due to the presence of an azide group. Some ruthenium catalysts are known to react with azides39 and the phosphine in the Grubbs II catalyst could also reduce the azide group. Examples of metathesis with substrates bearing an azide moiety are sparse and are often described as troublesome, giving low yields, especially if the azide group is close to the olefin.40

Since the metathesis proved unfruitful, we planned to screen conditions for a Baylis Hillman reaction38,41 on aldehyde 128 (Scheme 2.11), but only degradation was observed.

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2.2. Synthetic Studies of Minfiensine

Horner–Wadsworth–Emmons reaction with ethyl 2-(diethylphosphono)acrylate 125 and an external nucleophile did not afforded 126. Attempts without external nucleophile to reach directly cyclized 127 has proven unsuccessful.

After encountering so many problems at this stage of the synthesis, we decided to change our strategy in order to reach our key intermediate. We reasoned that because it contains a cyclohexenone ring, we could probably attempt to form it via a Diels-Alder reaction.

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2.2.3 Key Intermediate Formation: Cycloaddition Strategies

Our first cycloaddition strategy relied on an IEDDA reaction (Scheme 2.12). Starting from aldehyde 111, formation of a silyl enolate followed by cycloaddition with 2-buta-1,3-dienoate ethyl ester should afford desired cyclohexene 130. The diene needed for the reaction proven not to be stable, but could be formed in situ by heating sulfonene 131.

Scheme 2.12 – IEDDA to the key intermediate and model reaction for the cycloaddition on an enamine

This diene precursor is easily synthesised and is well described in IEDDA reactions with electron rich dienophiles to afford structures with the desired regioselectivity. Unfortunately, all our attempts at forming 130 were unsuccessful and only resulted in degradation. Instead, we envisaged to perform the cycloaddition using a base (enolate formation) or an amine (enamine formation). After a few unsuccessful trials with aldehyde 111, we decided to use a model substrate to continue studying this reaction. We decided to use the commercially available N-morpholinocyclohex-1-ene as enamine for this cycloaddition. The main difficulty encountered during this reaction was the easy polymerization of both starting materials. Product formation could only be observed under microwave assisted conditions. But the best yield which could be obtained was 30% of cis-fused cycloadduct 132, along with sig-

significant amount of side-product 133 and a large amount of diene dimer 134 (described as an important competitive reaction).\textsuperscript{47} The addition of a Lewis acid to this reaction resulted in a higher polymerization rate. Attempts to tune the electron density of diene by modifying the ester moiety of the sulfolene were done. But other sulfolene derivatives were too unstable to handle.

We therefore decided to rely on another cycloaddition for the formation of this cyclo-hexene derivatives (Scheme 2.13). Cycloaddition between electron-poor triple bonds and electron rich dienes are well described in the literature.\textsuperscript{48} We chose two vinyl ketones (135 and 137) as potential precursor to the diene needed for the reaction. We believed that the corresponding enolates, enamines or silyl enol ethers of these methyl enones would be suitable partners for a Diels-Alder reaction with methyl propiolate as dienophile. Resulting cycloadducts 136 or 138, thus obtained, should be easily transformed into key intermediate 95.

\begin{center}
\textbf{Scheme 2.13 – New cycloaddition strategy to reach key intermediate}
\end{center}

The regioselectivity of this type of cycloadditions is known to match the one required for our strategy.\textsuperscript{48c,49} The electron demand seems to be good in our case, having an elec-

Chapter 2: Approach Towards the Total Synthesis of Minfiensine
	ron deficient dienophile and an electron-rich diene. The main risk was that the nitrophenyl group would diminish the electron density of the diene. However we believed a correct catalyst should help us overcome this difficulty.

In the forward synthesis, intermediates 135 and 137 could be rapidly obtained as shown in Scheme 2.13, 2-(2-nitrophenyl)acetic acid could be converted to enone 135 using a Dakin-West reaction50 followed by a Knoevenagel Condensation.51

We first attempted to reach alcohol 140 in one step by opening tulipane,52 but this reaction proven to be messy and resulted in a low yield. We returned to using bromomethacrylate 99 (obtained in 2 steps); Homologation with formaldehyde and indium gave the desired alcohol 140 in good yield. Azidation and reduction into aldehyde 139 proceeded smoothly. Unfortunately, our attempts toward converting the aldehyde to methyl ketone 137 showed no desired product in all our attempts, resulting only polymerization of the acrolein moiety. The results of a model study (see below) prompted us to change our strategy before we could optimize the formation of 137.

From compound 135, we attempted to form the diene using a base (formation of an enolate), a silyl enolate (TBS or TMS enolate), or methylbenzylamine (as organocatalyst) followed by cycloaddition with methylpropiolate. Only starting material or decomposition was observed. Modification of the reactions conditions (Temperature, solvent, Lewis-acids) only changed the speed of decomposition. A more active dienophile such as prop-2-ynal29 was used without anymore success. Desired compound 136 was never observed. Probably the electron-withdrawing effects of the nitrophenyl substituent decreased too strongly the electron density of the diene making it unreactive towards Diels-Alder reaction. Another reason could be the steric clash between the aryl and the silyl group. This steric repulsion would increase the energy required to pass from the unreactive s-trans to the reactive s-cis intermediate.53

When 3-methylbut-3-en-1-one was used as a diene precursor (model substrate of 137, Scheme 2.14), the desired product 141a could only be observed in low yield, as an inseparable mixture with isomers 141b and 141c.10b Considering how poor the regioselectivity was, and how easily the double bond in 141a could migrate to 141b, we decided not to pursue


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Our last attempt was with the Diels-Alder reaction shown in Scheme 2.15. From dienophile 142, a cycloaddition with either described 2H-pyran-2-one or the commercially available methyl furane-2-carboxylate could be considered. Similar bridged bicyclic structures are known to be easy to open.\(^{54}\) The opening of our cycloadduct should afford intermediate 143.

**Scheme 2.14** – Test of cycloaddition

**Scheme 2.15** – New cycloaddition pathway

The pyranone is known to react with electron poor dienophiles,\(^{55}\) and the regioselectivity can vary according to literature. But in comparison with the work of Markó and co-workers,\(^{56}\) the possibility of having a good regioselectivity was high despite the need for high pressure and harsh reaction conditions. As for the furane, some examples exist, even if most of the Diels-Alder reaction used in similar molecules are intramolecular, like in the work of Padwa and co-workers\(^{57}\) or Kitagawa and co-workers.\(^{58}\)

To synthesise dienophile 142, we first substituted the ester 96 with iodoalkane 144 to

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afford ester 145 (Scheme 2.16). After a reduction, we obtained alcohol 146. Mesylation of alcohol 146 followed by elimination under basic conditions only afforded side-product 147 instead of olefin 142. Iodination of 146 resulted only in traces of desired iodine 148, the reaction yielding mostly overiodinated products and degradation. To our delight, tosylate 149 was stable enough to prevent the cyclization and was readily eliminated to olefin 142 in the presence of DBU and NaI.

Unfortunately, no reaction was observed when using lewis acids, high temperatures (up to 200 °C. Above, degradation was observed) and high pressures (up to 200 bar) for the pyranone or furane substrates. This lack of reactivity toward Diels-Alder reaction was probably due to steric hindrance of the dienophile.

After considering the strategies already reported and the length of our current strategies, the decision was taken to suspend our efforts toward the synthesis of minfiensine and to change targets.

2.3 Conclusion

In summary, the total synthesis of minfiensine was attempted using a reduction/cyclization domino sequence as a key step. The key intermediate needed for this domino sequence was never reached due to the steric hindrance around the quaternary center and the easy isomer-
ization of the olefine. Multiple strategies were attempted (summarized in Scheme 2.17). Our lack of success with these strategies, combined with the efficient syntheses published previously and the growing number of steps required to overcome the problems encountered convinced us to suspend our efforts towards this natural product, and change targets.

Scheme 2.17 – Summary of the different strategies used in this chapter
Dehydroaspidospermidine and Aspidospermidine

During the synthetic studies of minfiensine, our laboratory developed the iORC process to target goniomitine (cf. Section 1.3). As shown in Scheme 3.1, the C7 position of iORC iminium intermediate 10 was too hindered, and only cyclization via the nucleophilic N1 was observed, giving (+)-O-benzylgoniomitine as the sole product. The diastereoselectivity was controlled by the quaternary center C20.

In this new project, we wanted to apply the iORC domino process to reach aspidospermidine-type alkaloids. We postulated that a tether between the N4 iminium and the C7 (150) would force the cyclization to take place between C7 and C21 carbons. The installation of this connection would not be redundant steps, as this tether exists in the aspidospermidine-type natural products. As first target, we chose the dehydroaspidospermidine 2 and aspidospermidine 3. The pentacyclic skeleton of aspidospermidine has received attention as a testing ground for the evaluation of new reactions and synthetic strategies.
was then natural to start from this alkaloid to investigate our iORC sequence, before moving to more complicated structures (cf. Chapter 4 and 6).

3.1 Aspidospermidine, Background

(+)-Aspidospermidine 3 was first isolated by Biemann and co-workers in 1961 during a mass spectrometry study of the indole alkaloids from the bark of *Aspidosperma Quebracho-Blanco*. In this same paper, they also observed (+)-1,2-dehydroaspidospermidine 2 and reduced it to (+)-aspidospermidine 3 using zinc. From a biosynthetic point of view, this alkaloid comes from (+)-vincadifformine 4 (cf. Section 1.1.1), where a simple decarboxylation would afford (+)-dehydroaspidospermidine 2, and further reduction would give aspidospermidine 3. The pentacyclic structure of the *aspidosperma* family is an interesting synthetic challenge that pushed many chemists to pursue this synthesis. As a result, more than thirty total syntheses of aspidospermidine 3 are published so far. Most of them could be divided into three categories: Starting from an indole derivative, from a tryptamine derivative, or the syntheses where the indole is formed during the synthesis.

3.1.1 Previous syntheses from tryptamine derivatives

Wenkert and co-workers in 1983 made the tryptamine derivative 151 and used it in an intramolecular cycloaddition reaction to form (after oxidation with lead tetraacetate) intermediate 152 (Scheme 3.2). In 1991, they published the route to the natural product from intermediate 152. Tosylation followed by diastereoselective alkylation afforded intermediate 153. Further reductions gave racemic aspidospermidine 3.

![Scheme 3.2 – (±)-Aspidospermidine syntheses from Kunesch and co-workers](image)

Two similar enantiospecific total syntheses are shown in Scheme 3.3, from Fuji and co-workers in 1990 and Tomioka and co-workers in 2009.

3.1. Aspidospermidine, Background


\[ \text{Scheme 3.3 – (+)-Aspidospermidine syntheses from Fuji and Tomioka} \]

MacMillan and co-workers recently published an enantioselective total synthesis of aspidospermidine 3 (\textbf{Scheme 3.4}),\footnote{Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* 2011, *475*, 183–188} where the route toward the natural product started with tryptamine derivative \(158\). A new cascade reaction featuring a cycloaddition of \(158\) with propionaldehyde using an imidazolidinone catalyst, followed by 5-\textit{exo-trig} cyclization with the internal secondary amine afforded \(159\) in good yield and excellent ee. A Wittig reaction, N-Boc deprotection and N-allylation provided indoline derivative \(160\). A Heck cyclization closed the last ring to afford \(161\), which upon reduction provided \((+)-\)aspidospermidine 3.

3.1.2 Previous syntheses from indole derivatives

Many groups developed methodologies to functionalize or substitute the indole moiety, and the development of total syntheses using these new reactions is frequent. Here are some relevant examples of syntheses of aspidospermidine 3 starting from an indole derivative other
than tryptamine.

Bach’s group published in 2012 a total synthesis of \((\pm)\)-aspidospermidine 3 (Scheme 3.5),\(^{66}\) using a newly developed palladium-catalyzed 2-alkylation of indoles, allowing them to build precursor 162. Allylation followed by hydroboration of the newly installed double bond afforded intermediate 163. Oxidation of the alcohol, reductive amination and reduction of the amide afforded hemiaminal 164. Under acidic conditions, this hemiaminal was dehydrated to iminium 165 which underwent a Mannich-type reaction to afford 166. The last ring was closed in one step, affording \((\pm)\)-dehydroaspidospermidine 2, that was then reduced with NaBH\(_4\) to \((\pm)\)-aspidospermidine 3.

A similar strategy to close the last ring of aspidospermidine 3 was used by Rubiralta’s group in 1996 (Scheme 3.6).\(^{67}\) Rubiralta synthesized aspidospermidine 3 starting from dithiane 167. 1,4-addition on enone 168 afforded racemic 169. A reduction/cyclization protocol

3.1. Aspidospermidine, Background

was performed to reach intermediate 170. Closing the last ring by a nucleophilic substitution, and subsequent reduction of the dithiane afforded a mixture of (±)-aspidospermidine 3 and (±)-dehydroaspidospermidine 2.

Scheme 3.6 – Rubiralta’s synthesis of aspidospermidine

Andrade and co-workers reached (+)-aspidospermidine 3 in 2013 (Scheme 3.7).68 Starting from chiral N-sulfinyl indole 171, a domino Michael/Manich/N-alkylation afforded 172 with good diastereoselectivity. Intermediate 173 was then reached in 6 steps from the N-sulfinyl derivative 172. The sequence include a reduction of the ester into an aldehyde, a Wittig reaction and a RCM to close the azacyclopentene ring. Finally, a Bosch-Rubiralta spirocyclization69 closed the last ring, and a reduction afforded the natural product.

Scheme 3.7 – Andrade’s synthesis of (+)-aspidospermidine

Wenkert in 198870 decided to reach (+)-dehydroaspidospermidine 2 and (+)-aspidospermidine 3 from aminal lactone 174 (Scheme 3.8). Acidic treatment of 174 with indole afforded 175 as a single diastereoisomer. Cyclization of 175 into 176 in phosphoric acid proceeded with 61% yield. Reduction of amide and double substitution with ethylene bromide afforded dehydroaspidospermidine, that was converted into aspidospermidine with

Chapter 3: Dehydroaspidospermidine and Aspidospermidine

LiAlH₄. Waser and co-workers reached Wenkert’s intermediate 176 in a formal synthesis of aspidospermidine 3 using a homo-Nazarov reaction on an aminocyclopropane derivative.⁷¹

Scheme 3.8 – Wenkert’s synthesis of (+)-aspidospermidine

3.1.3 Syntheses of aspidospermidine with formation of the indole ring

The most common way to synthesize the aspidospermidine 3 was first described by Stork and co-workers in 1963 in a total synthesis of aspidospermine,⁷² and applied later on by Aubé and co-workers for aspidospermidine.⁷³ Tricycle 177 was used in a Fisher indole synthesis to afford dehydroaspidospermidine. Reduction of indolenine moiety gave aspidospermidine 3.

Many groups targeted intermediate 177 for the total synthesis⁷⁴ or the formal synthesis⁷⁵ of aspidospermidine 3.

Scheme 3.9 – Aubé’s indole synthesis of aspidospermidine

3.1. Aspidospermidine, Background

In 1994, Angelo and co-workers\textsuperscript{76} reached the natural compound from 178 (Scheme 3.10). Copper-assisted cyclization created the indole ring, and a few functional group interconversions afforded 179. Reduction of the carbonyl group, followed by Staudinger reduction and N-acylation provided 180. Acidic treatment allowed them to eliminate the alcohol, and cyclize the amine on the C21 position. Subsequent oxidation of the thioether to sulfoxide followed by a Pummerer rearrangement afforded 181. Desulfurization and reduction of the amide and enamine moieties afforded the natural product.

![Scheme 3.10 – Angelo's synthesis of (+)-aspidospermidine with formation of the indole ring](image)

Murphy and co-workers published in 1999\textsuperscript{77} a synthesis of (±)-aspidospermidine (Scheme 3.11), using their previously developed tetrathiafulvalene (TTF)-mediated radical-polar crossover reaction.\textsuperscript{78} This reaction extruded nitrogen from 182 and formed the aryl radical. A cyclization on the double bond gave benzylic radical that was oxidized to the benzylic cation and trapped with water. The formed alcohol was oxidized with PCC to afford 183. This intermediate was transformed into 184 in six steps. A Heck-type reaction on 184 closed the last ring. Reduction and deprotection of 184 afforded aspidospermidine 3.

One year after, Murphy's group reached the same precursor 184 from alcohol 185.\textsuperscript{79} A five step procedure converted 185 into 186. Azidation of primary alcohol afforded 187. An iodoazide radical cascade cyclization closed both 5 membered rings, and N-allylation with (Z)-3-bromo-1-iodopropene afforded 184.

Another interesting example is the racemic synthesis of (±)-rhazinilam and

\textsuperscript{79}Patro, B.; Murphy, J. A. Org. Lett. 2000, 2, 3599–3601
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Scheme 3.11 – Murphy’s Syntheses of (+)-aspidospermidine with formation of the indole ring

its subsequent transformation into (+)-aspidospermidine 3 by Gaunt and co-workers (Scheme 3.12).80 Using the pyrrol derivative 188, a palladium-catalyzed C-H alkenylation reaction afforded the intermediate 189. Reduction of the vinyl group and the nitro group, followed by macrocyclic lactonization using 2-chloro-1-methylpyridinium iodide (CMPI) as coupling reagent afforded 2-methoxycarbonyl-rhazinilam 190. From here, a three-steps reductive transannular cyclization process afforded (+)-aspidospermidine 3.

Scheme 3.12 – Gaunt’s Synthesis of (+)-aspidospermidine with formation of the indole ring

In 2002, Marino finished a total synthesis of (+)-aspidospermidine81 with a late-stage closing of the indole ring (Scheme 3.13). Starting from the chiral sulfoxide 191, a ketene lactonization with trichloroacetyl chloride (TCAC), followed by reduction and deprotection

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3.1. Aspidospermidine, Background

of the acetal provided lactone 192. Lactone opening with pyrrolidine, afforded aldehyde 193. Subsequent aldol condensation and amidation provided 194. Intramolecular aza-Michael addition followed by cyclization of the resulting enolate on the alkyl chloride and Saegusa reaction gave enone 195. Boc deprotection followed by Wolff-Kishner reduction afforded (+)-aspidospermidine 3.

Scheme 3.13 – Marino’s Syntheses of (+)-aspidospermidinewith formation of the indole ring

Banwell in 2005 started from precursor 196 for a racemic synthesis of aspidospermidine 3 (Scheme 3.14).82 An Ullmann cross-coupling with o-nitriodoobenzene followed with saponification of the acetate and azidation of the resulting alcohol afforded 197. Refluxing this azide in benzene forced an azacyclopropanation to afford 198. Acidic treatment of this cyclopropane gave the chloride derivative 199. Subjecting this intermediate to reducing conditions like TiCl₃/NH₄OAc, followed by N-acylation with 2-chloroacetyl chloride afforded indole 200. Halogen exchange, followed with cyclization and reduction afforded (+)-aspidospermidine 3 (3-step protocol developed by Toczko and Heathcock)83 in high yield.

Rawal in 200284 reported a catalytic enantioselective Diels-Alder reaction between diene 201 and ethylacrolein using antimonate salt of Jacobsen’s chiral Cr₃⁺-salen complex85 (Scheme 3.15). The resulting aldehyde 202 was submitted to a Wittig reaction and RCM reaction to afford bicyclic structure 203. (o-Nitrophenyl)phenyliodonium fluoride (NPIF) reagent arylated the silyl enolate and provided the nitrophenyl derivative 204. A reduction of the nitro function provided indole derivative 205. Deprotection of the amine with trimethylsilyl iodide followed by N-alkylation with 2-bromoethanol, mesylation of the alcohol and cyclization gave 1,2,14,15-tetrahydroaspidospermidine 206. Reduction of both double bonds gave

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Chapter 3: Dehydroaspidospermidine and Aspidospermidine

Scheme 3.14 – Banwell’s Synthesis of (±)-aspidospermidine with formation of the indole ring

(+)-aspidospermidine 3 in good yield.

Scheme 3.15 – Rawal’s synthesis of (+)-aspidospermidine with formation of the indole ring

3.2 Dehydroaspidospermidine

Dehydroaspidospermidine 2 was isolated from the same tree as aspidospermidine 3. It is the oxidized version of aspidospermidine, having an indolenine ring instead of an indoline.

Most of the syntheses of aspidospermidine pass by dehydroaspidospermidine with a subsequent reduction, and few papers synthesized aspidospermidine and oxidized it into dehydroaspidospermidine. Hence they were already discussed in the previous section. One of the few groups who synthesized dehydroaspidospermidine 3 without involving aspidospermidine 3 was Ban and co-workers in 198186 (Scheme 3.16). They reported an effective pho-

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3.3 Synthetic Studies of Aspidospermidine and Dehydroaspidospermidine

Scheme 3.16 – Ban’s synthesis of (±)-dehydroaspidospermidine

toisomerization of amine 207 into amine 208 that spontaneously cyclize into the amide 209. With just a few protections, alkylations and deprotections, they achieved the synthesis of (±)-dehydroaspidospermidine 2 in seven steps and 17% overall yield.

Other syntheses of aspidospermidine and dehydroaspidospermidine are reported. But the syntheses above are amongst the most relevant ones.87

3.3 Synthetic Studies of Aspidospermidine and Dehydroaspidospermidine

We could see that forming the indole moiety of aspidospermidine in a late-stage fashion is an interesting idea, as it reduces the sensitivity of the substrate toward acidic media, and diminishes the need for protecting groups. In addition, exploiting the reactivity of the indole during its formation, as a domino process could be a powerful tool to cyclize other rings. These are the power of our iORC process we wished to emphasis.

From a retrosynthetic point of view, 1,2-dehydroaspidospermidine 2 could be reached from iminium 150 (Scheme 3.17). The cyclization of this intermediate could only happen between the C7 and C21 due to the tether N4-C5-C6-C7. This intermediate contains an enamine and an iminium group. These functional groups could arise from their respective amino and carbonyl groups (intermediate 210). The aniline moiety could arise from a nitrobenzene, and the secondary amine from a protected amino group (Intermediate 211). We chose a nitrophenylsulfonamide protecting group due to the mild deprotection conditions that were

compatible with our iORC sequence.88

The aldehyde 211 could result from an ozonolysis of 212. This macrocycle is the key intermediate we planned to use for our key step. From this intermediate to dehydroaspidospermidine, we hope the whole sequence would be performed in a one pot fashion.

We planned to make macrocycle 212 from 213 by N-alkylation or Mitsunobu reactions with H₂NNs. This monoprotected diol could be the result of a decarboxylative coupling between potassium salt 215 and vinyl triflate 214. This palladium-catalyzed decarboxylative coupling between potassium 2-(2-nitrophenyl)acetate derivatives and vinyl triflates was developed by Zhu and co-workers in 2013.22 This reaction is a key point of our iORC strategy, as it allows us to build a large variety of precursors for our key domino process. A remarkable feature of this coupling is its ability to assemble intermediates bearing all the carbons needed in the natural product.

### 3.3.1 Key Intermediate Formation

The two partners of the decarboxylative coupling are easy to access. First, the potassium salt 215 had to be synthesized (Scheme 3.18). Starting from ester 145 (already synthesized in Section 2.2.3), we saponified the methyl ester with KOH, and treated the resulting acid 216 with equimolar amount of potassium tert-butoxyde to reach potassium salt 215.

Then, the vinyl triflate needed for the decarboxylative coupling had to be synthesized (Scheme 3.19). Starting from the commercially available 217, the enone 218 was obtained.

after 1,2-addition of a Normant-type Grignard reagent,\textsuperscript{89} followed by strong acidic work-up to eliminate ethanol. Silylation of the primary alcohol gave either TES-protected \textsuperscript{219} or TBS-protected \textsuperscript{220}. These enone derivatives could undergo a copper-assisted 1,4 addition, followed by the trapping of the enolate with Comins’ reagent, to give the corresponding vinyl triflate \textsuperscript{214} or \textsuperscript{58}. Deprotection of this last one afforded free alcohol \textsuperscript{221}.

It is noteworthy that the only important stereocenter of the natural product, \textit{i.e.} the one that will control the diastereosemochanical outcome of the \textit{iORC} is formed in a copper-assisted 1,4-addition. We naturally envisioned to make this addition enantioselective using reported procedures.

Copper-catalysed enantioselective 1,4-addition on enone are well described in the literature. Nevertheless, most examples are reported on linear or unstrained cyclic enones. The enantioselective conjugate addition of nucleophiles to cyclopentenones is a challenging process that has rarely been achieved. The main examples are from Copper-catalyzed addition of organomagnesium nucleophiles,\textsuperscript{90} silver catalized organoaluminium nucleophiles\textsuperscript{91} and palladium-catalyzed conjugate addition of arylboronic acid.\textsuperscript{92}

The route toward our vinyl triflate was already optimized and seemed to work well with copper-assisted 1,4-addition. We were hoping Alexakis’ N-heterocarbene (NHC) ligands

with catalytic amount of copper could work in our synthesis.\textsuperscript{93} The trials were done on our enone \textsuperscript{220} (Scheme 3.20). The newly formed cyclopentanone \textsuperscript{222} was benzoylated in order to measure the ee (UV detector). Despite our efforts, the copper catalyzed conjugate addition using Alexakis ligand afforded \textsuperscript{222} with a maximum of 5% ee.

![Scheme 3.20 – Asymmetric 1,4-addition trials](image)

The lack of stereoselectivity might come from the size of the alkyl chain. Most of the examples described in the development of this ligand were done on simple cyclopentenone with small substituents (Me, Et). Therefore, we synthesized the allylcyclopentenone \textsuperscript{224}\textsuperscript{94} and used the same conditions (Scheme 3.21). The ketone \textsuperscript{225} was obtained in good yield, but after cross metathesis to \textsuperscript{226} (for UV activity), the measured ee was 10%. An improvement not good enough to continue with this catalyst.

![Scheme 3.21 – Asymmetric 1,4-addition trials](image)

We wanted to pursue the 1,4-addition with Hoveyda’s methodology, using AlEt\textsubscript{3} and his silver-catalyst. The substrate \textsuperscript{227} (Scheme 3.22) was chosen to be optimal, due to the chelating effect of ester. Homoallylation of \textsuperscript{217} afforded substituted enone \textsuperscript{228}. Selective ozonolysis of terminal double bond afforded ester \textsuperscript{227}. After discussion with Professor Hoveyda, a sample of \textsuperscript{227} was sent to his group for preliminary trials on enantioselective addition. The results were promising, but showed some trouble for the one-pot triflation of the enolate. A higher temperature is needed to form the enol triflate, and Dieckmann condensation would occur. No further work was done for an enantioselective synthesis, as we focused our effort on the racemic synthesis.

Continuing with racemic vinyl triflates, we performed the decarboxylative coupling with potassium salt \textsuperscript{215} following the conditions optimised in our laboratory.


3.3. Synthetic Studies of Aspidospermidine and Dehydroaspidospermidine

(Scheme 3.23). We planned to reach diol 229 and monoprotected diol 213. It was previously observed that this decarboxylative coupling produce had as major side-product the protodecarboxylation product 230, and reduced triflate 231. The formation of these side-products was increased if the free alcohol 221 was used. In order to improve the yield of 213, we opted for the TES-protected vinyl triflate 214 as it could be removed selectively, and used 1.2-1.5 equivalent of potassium salt 215.

(Scheme 3.23) – Substrate preparation for asymmetric 1,4-addition trials

From the diol 229, we performed multiple attempts on double N-alkylation with o-nitrophenylsulfonamide, as described in the literature. Double $S_N2$ on the diiodine 232 or

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the dimesylate 233 were tried. Unfortunately, the double N-alkylation process has proven ineffective, showing lack of reactivity and easy degradation our substrate.

The double Mitsunobu of diol 229 was also troublesome. During the Mitsunobu (Scheme 3.24), triphenylphosphine and DEAD first react to form intermediate 234. In the presence of alcohol, this intermediate is in equilibrium with reactive species 235 and unreactive intermediate 236. The mechanism of the Mitsunobu reaction has been well studied and it was shown that intermediate 234 is in some cases an inhibitor of the reaction. This may explain why an excess of the alcohol is often needed to improve the yield, as the equilibrium will be pushed in favor of 235 and 236. Since the alcohol is sometimes difficult to obtain (as in our case, the alcohol is our substrate, and the nucleophile is commercially available), is would be interesting if it could be used as limiting reagent. In this purpose, Walker in 1995 showed that using neopentyl alcohol could push the equilibrium away from 234. As neopentyl alcohol is hindered, the $S_N2$ reaction of 235 where $R = \text{neopentyl}$ will be too slow compared to the substrate, and the only reactive specie will be the intermediate 235 with desired substrate $R-OH$, leading to an improvement of the yield. In our case, when trying the double Mitsunobu on 229, one possibility would be that intermediate 236 was too favorable, and the reaction was slow. Yet, it is known that sulfonamide, like $H_2NNs$ or $H_2NTs$ could react in the presence of $PPh_3$ and DEAD (or DIAD) to give undesired 237. This side-reaction would compete with the desired Mitsunobu and consume the starting material. If the presence of the two alcohols on the molecule slow down the Mitsunobu reaction, this side-reaction would become the fastest one, and low conversion was achieved, as all the phosphate and amine were consumed. Even (cyanomethylene)tributylphosphorane (CMBP) described to prevent formation of 237 showed no good reactivity with our substrate.

In order to obtain the macrocycle 212, we decided to go through the monoprotected alcohol 213 and perform a two step procedure (Scheme 3.25). Having only one alcohol on the molecule seems to accelerate the Mitsunobu reaction and allow the product to be formed before the side product 237. Deprotecting the TBS in a one-pot fashion, we could obtain the amino alcohol 239 in good yield using a variation of Walker’s conditions. The macrocyclisation was again performed with a Mitsunobu reaction. Optimization of the stoichiometry and concentration allowed us to push the cyclization yield up to 81%. We also attempted to mesy

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3.3. Synthetic Studies of Aspidospermidine and Dehydroaspidospermidine

![Scheme 3.24](image)

late the alcohol and perform an intramolecular N-alkylation reaction, but it proved inferior to Mitsunobu conditions.

![Scheme 3.25](image)

During the study of macrocycle 212, we were able to obtain a monocrystal of one of the diastereoisomer, and obtained an X-ray structure ([Figure 3.1](image)). One can observe the bent structure of the bridged olefin, showing the strain present in this structure (in solid state).100

### 3.3.2 IORC sequence and endgame

With macrocycle 212 in hand, we could start studying its reactivity toward our iORC domino sequence ([Scheme 3.26](image)). Our original plan was to use ozonolysis for the cleavage of the olefin. The advantage of this reaction was of course the possibility to remove the oxidant (ozone) by bubbling argon or nitrogen through the solution, making it the perfect tool for a one-pot processes. There are a few conditions known to influence ozonolysis. The main modifications in an ozonolysis are the solvent (DCM or MeOH are the most common ones), with or without Na2CO3, and quenching the ozonide with Me2S or PPh3. We found that the cleanest reaction condition with our substrate was the standard one, in DCM without base.

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Chapter 3: Dehydroaspidospermidine and Aspidospermidine

Figure 3.1 – X-Ray structure of one diastereoisomer of the key intermediate 212

and by quenching the reaction with Me₂S. The aldehyde intermediate 211 could be observed after work-up, but was not stable on silicagel. We decided then to continue with the one-pot procedure. Deprotection of the nosyl group appeared to have a rate dependent on the solvent. When the reaction mixture was kept in DCM, the deprotection took 24 h to reach completion. However, if MeCN was added, the reaction was finished in 2 h. Unfortunately, the intermediate at this stage was impossible to analyse. No product could be obtained after an aqueous work-up. Simple filtration and evaporation afforded a crude mixture, which NMR showed to have some aldol condensation between the C7 and the C21 (240). At that stage, we attempted to have the cyclized adduct 241. After the deprotection, the screening of Brønsted acids, Brønsted bases, Lewis acids, solvents and temperatures were done, but no desired product was ever observed. We expected the cyclization to be easier on the indole moiety, and decided to continue with the one-pot procedure.

The reduction step was the main problem of the iORC. Many reduction conditions exist for reducing nitroaryl groups,¹⁰¹ but the reducing conditions should not touch any iminium/imine/aldehyde/enamine intermediates. The conditions should be slightly acidic to promote the cyclizations, and the intermediates as well as final product should be stable enough in the reaction conditions to avoid degradation. As hydrogenations gave no reactions of degradations, activated zinc powder with HCl 0.5 M gave (±)-dehydroaspidospermidine 2, but only in low yield. All other attempted combinations of Zinc or Iron with various acids


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resulted in full degradation. To our delight, reduction using TiCl$_3$\textsuperscript{101e-g,i} afforded the desired natural product with up to 50% yield after tuning of the stoichiometry, pH of the solution (NH$_4$OAc as buffer) and reaction time. By quenching the excess of TiCl$_3$ with aqueous NaHCO$_3$, and adding excess of NaBH$_4$ in a one-pot fashion, (±)-aspidospermidine 3 would be isolated with similar yield.

### 3.4 Vincadifformine

Vincadifformine 4 was isolated in 1962,\textsuperscript{102} from the leaves of the tree *Vinca Difformis*. It is an indole alkaloid of the *Aspidosperma* family. Its biosynthesis is fully detailed in 1.1.1. Its first total synthesis was from Kutney and co-workers in 1968.\textsuperscript{103} Since then, numerous total syntheses were achieved.\textsuperscript{68,104} The synthetic connection between dehydroaspidospermidine

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Chapter 3: Dehydroaspidospermidine and Aspidospermidine

2 and vincadifformine 4 was already known in both directions\textsuperscript{65,105} (Scheme 3.27). Using Mander's reagent, dehydroaspidospermidine was converted into vincadifformine with 50% yield.\textsuperscript{65}

![Scheme 3.27 – Synthetic connection between vincadifformine and dehydroaspidospermidine](image)

3.5 Quebrachamine

Quebrachamine 242 is an *Aspidosperma* alkaloid highly related to dehydroaspidospermidine 2 (Scheme 3.28). It was first isolated by Hesse in 1882\textsuperscript{106} but no structure was given. In 1951, Gellert found a new alkaloid called kamassine\textsuperscript{107} but found out it was quebrachamine 242 one year later.\textsuperscript{108} Its correct structure was hypothesized by Witkop in 1960,\textsuperscript{109} before it was confirmed by Biemann one year after.\textsuperscript{110} Since then, more than twenty syntheses (total and formal) were published.\textsuperscript{62,70,72,74g,84,86b,111}


\textsuperscript{106}Hesse, O. *Justus Liebig's Ann. der Chemie* 1882, 211, 249–282


3.6. Conclusion

One possible biosynthetic pathway of quebrachamine 242 is from dehydroaspidospermidine 2. Biemann already suggest a possible connection between these two alkaloids in his structure determination of the aspidospermidine.\cite{Biemann1959} Previous studies by Schmid,\cite{Schmid1964} Trotter\cite{Trotter1965} and Rawal\cite{Rawal1984} have reported the possible synthetic connection between these two natural compounds, going from aspidospermidine and dehydroaspidospermidine to quebrachamine and vice versa (Scheme 3.28). The reaction should pass by the same iminium intermediate 150 used in our iORC.

\[ (+)-\text{Dehydroaspidospermidine} → 150 \rightarrow (-)-\text{Quebrachamine} \]

Scheme 3.28 – Possible biosynthetic pathway of quebrachamine

Iminium intermediates similar to 150 have already been reported for the synthesis of quebrachamine.\cite{Escolano2007} Therefore, we planned to intercept iminium 150 in our domino sequence by using stronger reducing conditions to obtain quebrachamine 242 instead of dehydroaspidospermidine 2. Unfortunately, the formation of quebrachamine has proven unsuccessful using the iORC domino process. Only dehydroaspidospermidine or degradation were observed.

3.6 Conclusion

In summary, the total syntheses of (±)-aspidospermidine 3, (±)-dehydroaspidospermidine 2 and (±)-vincadifformine 4 were accomplished (Scheme 3.29).\cite{Escolano2007} From the potassium carbonate 215 and vinyl triflate 214, a decarboxylative coupling developed in our laboratory allowed us to build intermediate 213 bearing all the carbons needed in the natural product. Two consecutive Mitsunobu reactions afforded the macrocyclic key intermediate 212 in good yield. Our key iORC sequence did a full skeleton reorganization in a diastereoselective fashion, allowing us to reach either (±)-dehydroaspidospermidine 2 or (±)-aspidospermidine 3. A known procedure allowed us to reach (±)-vincadifformine 4 in 50% yield.

\[ (+)-\text{Dehydroaspidospermidine} → 150 \rightarrow (+)-\text{Quebrachamine} \]

\[ (+)-\text{Dehydroaspidospermidine} → 150 \rightarrow (+)-\text{Quebrachamine} \]

\[ (+)-\text{Dehydroaspidospermidine} → 150 \rightarrow (+)-\text{Quebrachamine} \]

\[ (+)-\text{Dehydroaspidospermidine} → 150 \rightarrow (+)-\text{Quebrachamine} \]
Scheme 3.29 – Summary of the total synthesis of aspidospermidine, dehydroaspidospermidine and vincadifformine

These syntheses showed the power of our iORC domino sequence, and the simple synthesis of precursor 212 motivated us to pursue other natural products with similar key steps.
Approach Towards the Total Synthesis of Aspidoalbidine

(+)-Aspidoalbidine (or (+)-fendleridine) 5 is an aspidosperma alkaloid isolated in 1966 by Burnell and co-workers from the seeds of Aspidosperma fendleri (Figure 4.1). The name fendleridine was based on the name of the tree. 114 Although in 1963, Brown isolated (+)-N-acetylaspidoalbidine 244, 115 they gave the name "aspidoalbidine" to the postulated simplest member by analogy to aspidospermidine, discovered by Biemann two years before. 59 While both names seemed to be used nowadays for this natural product, we will use aspidoalbidine as it relates better to the aspidosperma family to which it belongs.

\[ \text{(+)-Limaspermidine 243} \quad \text{(+)-Aspidoalbidine 5} \quad \text{(+)-N-Acetylaspidoalbidine 244} \]

Figure 4.1 – Structures of limaspermidine 243, aspidoalbidine 5 and N-acetylaspidoalbidine 244

The biosynthesis of this alkaloid seems to arise from limaspermidine (18-hydroxyaspidospermidine) 243 via oxidation of the N4-C21 bond and cyclization.

4.1 Previous Syntheses of Aspidoalbidine

Few syntheses of both aspidoalbidine 5 and N-acetylaspidoalbidine 244 are reported. Most of them followed the biosynthetic pathway. They reached first limaspermidine, oxidized the N1-C21 bond and the alcohol group cyclized spontaneously on the iminium moiety. This

last oxidation step required the protection of the indole moiety, which is the main reason why most of the groups targeted N-acetylaspidioalbidine.

4.1.1 Ban’s Syntheses of (±)-N-Acetylaspidioalbidine and (±)-Aspidioalbidine

In 1975, Ban and co-workers reported the first total synthesis of (±)-N-acetylaspidioalbidine 244,116 and one year later reported the first total synthesis of (±)-aspidioalbidine 5 (Scheme 4.1).117 Starting from pentacyclic intermediate 245. Michael addition with ketene thioacetal monoxide provided intermediate 246. Hydrolysis of thioacetal group followed by reduction with LiAlH₄ provided alcohol derivative 247. Selective acetylation of indole afforded 248. Hydrogenation on both 247 and 248 with Adams’ catalyst afforded (±)-limaspermidine 243 and (±)-N-acetyllimaspermidine 249 respectively. Final oxidation of N1-C21 bond with mercury acetate in acidic medium afforded (±)-aspidioalbidine 5 or (±)-N-acetylaspidioalbidine 244.

In 1987, Ban and co-workers reported a formal synthesis of (±)-N-acetylaspidioalbidine 244 (Scheme 4.2).118 From the indole-protected precursor 250, addition of methyl oxalate, Wolff-Kishner reduction and esterification afforded methyl ester derivative 251. Reduction gave hemiaminal derivative 252. Under acidic conditions, the THP was cleaved and the hemiaminal was dehydrated to form iminium salt 253, which cy-

Scheme 4.1 – Ban’s synthesis of (±)-N-acetylaspidioalbidine and (±)-aspidioalbidine

117 Ban, Y.; Honma, Y.; Ohnuma, T. *Heterocycles* 1976, 5, 47–51
118 Yoshida, K.; Sakum, Y.; Ban, Y. *Heterocycles* 1987, 25, 47–50
4.1. Previous Syntheses of Aspidoalbidine

cлизed into (±)-dehydrolimaspermidine 254. Reduction and acetylation afforded (±)-N-acetyllimaspermidine 249 as the precursor of (±)-N-acethylaspidoalbidine 244.

Scheme 4.2 – Ban’s formal synthesis of (±)-N-acetylaspidoalbidine

4.1.2 Overman’s Formal Synthesis of (±)-N-Acetylaspidoalbidine

In 1991, Overman published a formal synthesis of (±)-N-acetylaspidoalbidine involving a tandem aza-Cope rearrangement/Mannich cyclization sequence as a key step (Scheme 4.3).\textsuperscript{119} Addition of 255 on ketone 256 followed by intramolecular acylation afforded lactone 257 in 76% yield. Wittig reaction followed by lactone opening gave key intermediate 258. The key-step started with formation of iminium 259. Oxy-cope rearrangement gave enol intermediate 260 and Mannich cyclization afforded ketone derivative 261, that condensed into indolenine 262. A four steps sequence allowed Overman and co-workers to reach (±)-N-acetyllimaspermidine 249.

4.1.3 Boger’s Synthesis of (±)-Aspidoalbidine

Boger and co-workers reported in 2010 a total synthesis of (±)-aspidoalbidine\textsuperscript{120} using their emblematic domino IEDDA/(1,3)-dipolar cycloaddition sequence (also presented for their total synthesis of vindorosine in Section 1.2.4). From intermediate 263 (Scheme 4.4), a thermal IEDDA occurred and afforded intermediate 264. Release of nitrogen resulted in dipolar intermediate 265. A (1,3)-dipolar cycloaddition afforded polycyclic structure 266 in 71% yield from 263. Conversion of the ester to the primary amide followed by dehydration to the nitrile and deprotection of silyl ether with HF resulted in the cyclized aspidoalbidine-core 267. Six steps were needed to reach aspidoalbidine 5. Separation of enantiomers four steps before the end allowed them to reach the enantiopure form of the natural product.

\textsuperscript{119}Overman, L. E.; Robertson, G. M.; Robichaud, A. J. J. Am. Chem. Soc. 1991, 113, 2598–2610

Chapter 4: Approach Towards the Total Synthesis of Aspidoalbidine

Scheme 4.3 – Overman’s Formal Synthesis of (±)-N-acetylaspidalbidine

Scheme 4.4 – Boger’s Total Synthesis of aspidalbidine

4.1.4 Banwell’s Synthesis of (±)-N-Acetylaspidalbidine

In 2012, Banwell and co-workers published a total synthesis of (±)-N-acetylaspidalbidine 244 (Scheme 4.5). Nitrile derivative 268 was converted in four steps into the enone intermediate 269. A domino reduction/cyclization sequence using Raney-Cobalt and TsOH afforded tertacyclic intermediate 270. Alkylation of the amine gave 271, and cyclization provided the pentacyclic structure 272. (±)-Limaspermidine 243 was obtained after reduction of the amide, and Ban’s procedure allowed them to reach (±)-N-acetylaspidospermidine 244.
Attempts to reproduce Ban’s conversion of (±)-limaspermidine 243 into (±)-aspidoalbidine 5 (without protection of indole) were not successful.

Scheme 4.5 – Banwell’s Total Synthesis of (±)-N-acetylaspidoalbidine

4.1.5 Shao’s Formal Synthesis of (+)-Aspidoalbidine

Shao and co-workers published in 2013 a formal synthesis of (+)-N-acetylaspidoalbidine similar to Banwell’s work (see above). Having developed a palladium-catalyzed decarboxylative allylation, they used this methodology to build indole precursor 273 (Scheme 4.6). Reductive cyclization of the cyano group on the ketone, followed by oxidation resulted in aldehyde 274. Reduction of aldehyde with LiAlH₄, followed by benzyl deprotection and alcohol protection afforded intermediate 275. Following Banwell’s route, alkylation of amine afforded 276, which was cyclized in two steps into protected (+)-dehydrolimaspermidine 277. Reduction of 277 with LiAlH₄ afforded (+)-limaspermidine 243 as precursor of (+)-aspidoalbidine.

4.1.6 Canesi’s Formal Synthesis of (±)-N-Acetylaspidoalbidine

In 2012, Canesi and co-workers developed an oxidative 1,3-alkyl shift process and used it in the formal synthesis of (±)-N-acetylaspidoalbidine (Scheme 4.7). From alkyne 278, their 1,3-alkyl shift process afforded alkene 279 in good yield. Diiodination gave olefin 280 as a mixture of isomers. Amination and intramolecular 1,4-addition provided intermediate 281 in low yield, as only one isomer of 280 had the correct conformation to favor the cyclization.

Chapter 4: Approach Towards the Total Synthesis of Aspidoalbidine

Scheme 4.6 – Shao’s Formal Synthesis of (+)-aspidoalbidine

Scheme 4.7 – Canesi’s Formal Synthesis of (+)-N-acetylaspidoalbidine

Mesylation of the alcohol followed by cyclization afforded tricyclic structure 282. Hydrogenolysis of the iodide and hydrogenation of the two olefins afforded intermediate 283. From this intermediate, six steps (deprotection of the aldehyde moiety and its reduction into alcohol, Fischer indole synthesis, reduction and acetylation) provided (+)-N-acetyllimaspermidine 249.

4.1.7 Qiu’s Total Synthesis of (+)-N-Acetylaspidoalbidine

In 2014, Qiu and co-workers reported a Diels-Alder cycloaddition between tryptamine derivative 284 and propynal (Scheme 4.8). The resulting cycloadduct 285 was transformed to 286 by a three steps sequence. Reduction of the aminal followed by oxidation of alcohol afforded aldehyde 287. Domino Michael addition gave pentacyclic intermediate 288.

Wittig reaction followed by functional group manipulations afforded \((\pm)-\text{limaspermidine}\) \(243\). Qiu and co-workers attempted to change the oxidation conditions to reach \((\pm)-\text{N-acetylaspidoalbidine}\) \(244\). Nevertheless, most reported conditions for tertiary amine oxidation suffered from irreproducibility and non-completion of the reaction. Iodine oxidation of tertiary amine (reported on alkaloids by Szántay in 2001)\(^{124}\) gave the final product in 21% yield.

![Scheme 4.8 – Qiu’s Total Synthesis of \((\pm)-N\text{-acetylaspidoalbidine}\)](image)

4.2 Synthetic Studies of Aspidoalbidine

Considering the close relation between aspidospermidine and aspidoalbidine, we decided to pursue the total synthesis of this *Aspidosperma* alkaloid. As most previous syntheses passed by 18-hydroxyaspidospermidine (limaspermidine), then oxidize the C21-N4 bond into its iminium form, we wanted to see if similar iminium intermediates were not readily accessible through our iORC process.

From a retrosynthetic analysis perspective (Scheme 4.9), \((\pm)-\text{aspidoalbidine}\) 5 could arise from \((\pm)-\text{dehydroaspidoalbidine}\) 289. Disconnecting the aminal ether would give the iminium 290. Following the iORC disconnection (cf. Chapter 3), we can consider the disconnection of the iminium moiety and indolenine moiety to the putative diamino-dicarbonyl

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\(^{124}\) Moldvai, I.; Szántay, C.; Szántay, C. *Heterocycles* 2001, 55, 2147–2155
Chapter 4: Approach Towards the Total Synthesis of Aspidoalbidine

intermediate 291. This intermediate could result from the reduction of a nitro group, the de-protection of a secondary amine, and intramolecular Dieckmann condensation from macrocycle 292. If we compare this intermediate with aldehyde 211 in Scheme 3.17, the only difference in the key step would be to perform the ozonolysis from 293 with a work-up leading to the methyl ester instead of aldehyde. Cyclopentene derivative 293 is again closely related to the key intermediate 212 used for aspidospermidine. Taking inspiration from the aspidospermidine synthesis presented in the previous chapter, we could reach this 10-membered ring by two Mitsunobu reaction and a hydroboration from precursor 294. This precursor could arise from our palladium-catalyzed decarboxylative coupling between potassium carboxylate 215 and vinyl triflate derivative 295.

4.2.1 Key intermediate synthesis

The synthesis of potassium carboxylate 215 was already detailed in 3.3.1. For the vinyl triflate derivative 295, we decided to follow the same strategy as for triflate derivative 214 (with ethyl instead of vinyl, see 3.3.1). We planned that the presence of the vinyl group instead of an ethyl moiety would not interfere with the synthetic route used in the total synthesis of aspidospermidine. Starting from TES-protected enone 219 (Scheme 4.10). A copper-assisted 1,4-addition of vinylmagnesium bromide, followed by trapping of the enolate with Comins’ reagent afforded triflate derivative 295. To our delight, the palladium-catalyzed decarboxylative coupling between potassium carboxylate 215 and vinyl triflate derivative 295 afforded product 294 as a mixture of diastereoisomers in 58% yield.

From monoprotected diol 294, Mitsunobu reaction with nosylamine afforded protected aminoalcohol 296 (Scheme 4.11). Deprotection with catalytic amount of HCl in methanol gave aminoalcohol 297. A second Mitsunobu afforded desired macrocycle 298. The results of this cyclization was different from the aspidospermidine case. In large scale,
4.2. Synthetic Studies of Aspidoalbidine

Scheme 4.10 – Synthesis of triflate and decarboxylative coupling

dimerization of 297 appeared as major side-product (60%). To avoid this side-reaction, higher dilution had to be used in the scale up of this intramolecular Mitsunobu reaction. Selective anti-Markovnikov hydroxylation of terminal double bond in the presence of more hindered olefins were already described in the literature, using hindered borane like Cy₂BH,¹²⁵ or 9-BBN.¹²⁷ In our case, attempts with these boranes as well as simpler ones were performed. Only 9-BBN afforded alcohol 299 with good yield. Finally, protection with TBSCI gave 293.

Scheme 4.11 – Mitsunobu cyclization

4.2.2 iORC Study

Our first ozonolysis attempts were on free alcohol 299 (Scheme 4.12). Many conditions were reported on ozonolysis to afford a methyl ester instead of aldehyde.\textsuperscript{128} If an ozonolysis is performed in the presence of methanol and a mild base, peroxide 300 should be formed. Quenching this peroxide into methyl ester 301 is a well described procedure, commonly performed by treatment with acids,\textsuperscript{129} hypochlorites,\textsuperscript{130} $\text{Ac}_2\text{O}/\text{Et}_3\text{N}$\textsuperscript{131} or $\text{Ac}_2\text{O}/$pyridine.\textsuperscript{132} If the base used during ozonolysis is strong (NaOH, or sodium methanolate), direct formation of methyl ester 301 should be observed. In our case, all attempts gave dirty mixture of peroxide 302 and lactone 303 with poor mass balance. Methyl peroxide 300 or methyl ester 301 were never observed. The reason could be that the intramolecular cyclization was faster than the attack of the solvent, or methyl ester was formed, but lactonization happened under the reaction conditions. It is also possible that methyl peroxide degraded before conversion to methyl ester. In any case, if lactonization was easy, removing the methanol in the reaction mixture should favor it, and in fact reaction was much cleaner without methanol. Unfortunately, using $\text{Ac}_2\text{O}$ and $\text{Et}_3\text{N}$ provided large amount of peroxide 302 and low conversion into lactone 303. Amongst all the conditions tried, only $\text{Ca(OCl)}_2$ afforded lactone 303 cleanly with good yield (70%).

\begin{center}
\includegraphics{Scheme4_12}
\end{center}

Scheme 4.12 – Ozonolysis mechanism

Now that ozonolysis was optimized, we looked into the rest of the domino sequence (Scheme 4.13). Large scale ozonolysis of 299 afforded lactone 303 with reproducible yield. We

\textsuperscript{130}Fisher, T. J.; Dussault, P. H. \textit{Tetrahedron Lett.} \textbf{2010}, 51, 5615–5617
4.2. Synthetic Studies of Aspidoalbidine

first attempted direct Dieckmann cyclization using organic or inorganic bases, in different solvents at various temperature. It was possible to observe which conditions could deprotonate substrate 303 (DBU, > 50 °C), as the reaction was performed on each diastereoisomer separately and epimerization could be observed when deprotonation at C7 occurred. However, no cyclization into 304 was observed.

![Scheme 4.13 – Study of key step](image)

Deprotection of nosyl group afforded an unstable crude mixture of amine 305 and presumably enamine 306. The deprotection was much cleaner if performed in acetonitrile compared to DCM. Cyclization attempts into 307 were attempted with various bases, acids or Lewis acids, but without success. We thought that as the C7 position of 305 needed to be activated, it would be beneficial to already reduce the nitro group, in order to form the indole. The position C7 would then be nucleophilic with milder activation conditions. Unfortunately, only degradation was observed no matter the reduction conditions tried or the acidity of the solution. Never any dehydroaspidoalbidine 289 was observed.

One of the problems may come from the conformation of the lactone moiety that disfavors any type of cyclization. We decided then to use the TBS-protected precursor 293 to avoid lactone formation (Scheme 4.14).

The work toward the total synthesis of aspidoalbidine is unfortunately not finished at the moment. Preliminary results showed that synthesis of methyl ester 292 was less clean than lactone 303. From ester 292 Dieckmann condensation to 304 has proven unsuccessful under Brønsted acid, Brønsted base or Lewis acid conditions. When stronger conditions were used, degradation appeared. Deprotection of 308 gave unstable amine derivative 308 that could not be converted into tricyclic intermediate 307 or dehydroaspidoalbidine 289. The ozonolysis of 293 into acid 309 is still ongoing. We planned to activate acid 309 via the corresponding acid chloride to facilitate the Dieckmann cyclization.
4.3 Conclusion

By changing the ethyl into a vinyl group, we could synthesize vinyl triflate 295 with similar route as for aspidospermidine (Scheme 4.15). Decarboxylative coupling with potassium salt 215 afforded intermediate 294. Two successive Mitsunobu reactions allowed us to reach ten-membered ring 298. Hydroboration followed by silyl protection gave the key intermediate 293 needed for our iORC process. Unfortunately, this key domino process proceeded less easily than for the previous examples. The Dieckmann condensation was difficult, or the product too unstable to be observed. The study of our key step is still ongoing.
Scheme 4.15 – Summary of the synthetic efforts towards aspidoalbidine
CHAPTER 5

Kopsihainanine A

The *Apocynaceae* is a family of tropical or subtropical floral plants, which most of the members are poisonous and produce milky latex. The *Kopsia* genus of this family is widely distributed in Asia and Australia and is rich in alkaloids. From the leaves of *Kopsia hainanensis*, a plant used in Chinese medicine, Gao and co-workers in 2011 isolated two monoterpenoid indole alkaloids, (+)-kopsihainanine A 6 and (+)-kopsihainanine B 310 (Figure 5.1).

![Figure 5.1 – (+)-kopsihainanine A 6 and (+)-kopsihainanine B 310](image)

Gao and co-workers suggested the biosynthesis of kopsihainanine A 6 from kopsihainanine B 310 (Scheme 5.1). Decarboxylation and retro-Michael gave vinylketone structure 311. An oxidation of the terminal olefin afforded glyoxal intermediate 312. This intermediate should condense into the hemiaminal 313, and has keto-enol equilibrium with diol 313 and kopsihainanine A 6.

Even without any reported biosynthesis of kopsihainanine B 310, we could postulate a biosynthetic pathway (Scheme 5.2). From vincadifformine 4, an oxidation into minovincine 315 occurred. Kutney postulated in 1971 that this oxidation is more likely to happen at this stage instead of happening on an earlier intermediate. We postulated that an intramolecular conjugated addition of minovincine 315 could afford 316. Similar cyclizations were de-

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scribed during the biomimetic synthesis of kopsijasminilam\textsuperscript{135} and pauciflorine A and B by Kuehne and co-workers.\textsuperscript{136}

Reduction of the ketone would afford kopsinine 317. From this alkaloid, the cyclization of C6 on C22 is required. Kuehne and co-workers showed similar transformation in acidic

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5.1 Previous Syntheses of Kopsihainanine A

media in 1985. Such cyclization would convert kopsinine into kopsanone. The selective α-keto hydroxylation of C16 carbon is needed to reach kopsine. Such hydroxylation was performed on similar substrate in 10 steps by Magnus in a racemic total synthesis of kopsine in 1989. From kopsine, acyloin rearrangement could afford α-hydroxyketone. This α-hydroxyketon structure is also present in the alkaloid dasyarachine, found in Kopsia dasyrachis by Kam and co-workers. They found in the same plant methyl chanofructicosinate which is closely related to kopsihainanine B. Therefore we suggested an oxidative cleavage of the α-hydroxyketone moiety of to reach kopsihainanine B.

5.1 Previous Syntheses of Kopsihainanine A

Scheme 5.3 – Previous syntheses of kopsihainanine A

Up to date, four total syntheses were published. The first three are shown in Scheme 5.3. The difference between these three syntheses resides on the route towards cyano

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140 Kam, T. S.; Subramaniam, G.; Chen, W. Phytochemistry 1999, 51, 159–169
141 Kam, T. S.; Choo, Y. M.; Chen, W.; Yao, J. X. Phytochemistry 1999, 52, 959–963
intermediate 323. The first one was a racemic total synthesis by She and co-workers in 2012.142 Starting from ketone 322, conjugate addition afforded racemic cyano derivative 323. In 2013, Lupton and co-workers143 and Shao and co-workers87f published at the same time a palladium-catalyzed decarboxylative allylation of precursor 325 using PHOX-type ligand to reach one enantiomer of 323.

From this intermediate, hydrolysis of the cyano group into primary amide derivative 324 followed by reduction with LiAlH4 afforded cyclized intermediate 326. Anti-Markovnikov hydroxylation of allyl group followed by mesylation and cyclization afforded protected 16-dehydroxykopsihainanine A 327. Oxidation of α position of amide followed by deprotection gave alkaloid 6. It is interesting to report that She did obtain an aluminum complex of kopsihainanine A due to the last deprotection step. The product they obtained was not soluble in CDCl3, in opposition to the isolated natural product. Shao, using the same last step for the synthesis (deprotection of the N-Benzyl protected indole using AlCl3) observed the same solubility issue. But after treatment of the natural product with Rochelle's salt, the free natural product was obtained.


5.2 Retrosynthetic Study

In our previous uses of our iORC domino process, we showed that with bulky group in the position 3 of indole, the intermediate 10 would cyclize from N1 to afford protected (±)-goniomitine 61 (Scheme 5.5). With a tether, we could force the cyclization from 150 to (±)-dehydroaspidospermidine 2 and (±)-aspidospermidine 3. However, both cyclizations gave cis-fused [6,6] ring systems. By targeting (±)-kopsihainanine A 6, we planned to address two questions: (1) Will the cyclization of 334 (without tether) still be highly regioselective for the C7 attack? And (2) How to force the trans-fused [6,6] ring systems needed for (±)-kopsihainaine A 6?

142Jing, P.; Yang, Z.; Zhao, C.; Zheng, H.; Fang, B.; Xie, X.; She, X. Chemistry 2012, 18, 6729–6732
5.2. Retrosynthetic Study

Scheme 5.4 – Mukai’s synthesis of (+)-kopsihainanine A 6

Scheme 5.5 – ROB cyclization: Diastereoselectivity issue

The regioselectivity should not be troublesome, as other similar transformation happened with good yields, but almost all the examples gave cis-selectivity. Which mean the diastereoselectivity will be a problem. If we manage to control these two factors, we would obtain intermediate 335, which could be transformed in few steps into the racemic alkaloid (±)-6.

On a retrosynthetic perspective, (±)-kopsihainanine A 6 could be obtained from 336 in a similar way as the previous syntheses (Scheme 5.6). To force the trans-selectivity, we de-
Cided to already have the amide bond on iminium intermediate 337. This way, the cyclization in trans should be favoured. This amide formation is not a redundant step for the synthesis, as it is present in the natural product. Following our iORC procedure, this iminium could arise from the putative dicarbonyl intermediate 338. As the previous cases, forming the aniline from a nitrophenyl moiety, and the two carbonyl by an ozonolysis resulted in synthon 339. A Staudinger lactamization from the azide and a carboxylic acid leads us to precursor 340. This precursor could be reached via the same palladium-catalyzed decarboxylative coupling as the aspidospermidine, using slightly different starting materials.

![Scheme 5.6 – Retrosynthesis of kopsihainanine A 6](image)

### 5.3 Synthetic studies of Kopsihainanine A

In order to reach precursor 340, we planned to start from 220 (cf. Chapter 3). A chain with a carboxylic acid precursor should be added (Scheme 5.7). Our first attempt was with Normant-type Grignard reagent, which did not give desired product 341 but only yielded 1,2-adduct 342. Organozinc generated either from methyl 3-iodopropanoate or from (1-Ethoxycyclopropoxy)trimethylsilane resulted in messy reactions or degradations. Desired 1,4-adduct 343 was never observed.

To avoid these difficulties, we chose to perform a 1,4 homoallylation using similar conditions as before and oxidize the olefin on a late stage. Trapping of the enolate with Comins’ reagent gave vinyl triflate 344. Our palladium-catalyzed decarboxylative coupling between

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5.3. Synthetic studies of Kopsihainanine A

triflate 344 and potassium salt 345 afforded compound 346 in good yield. We could observe the improvement of the yield compared to our previous syntheses due to the low steric hindrance of this potassium salt. One-pot azidation of the alcohol gave intermediate 347.

**Scheme 5.7 – attempts of direct 1,4-Addition**

At this stage, an oxidation of the terminal olefin of 347 into the methyl ester is required. The presence of the second olefin made this oxidation quite challenging (Scheme 5.9). Ozonolysis under non-reductive conditions (Ac₂O/Et₃N) gave directly the methyl ester 349 with 25% yield. When a Lemieux-Johnson or Lemieux Von-Rudloff oxidation were attempted,¹⁴⁷ we could notice that a catalytic amount of osmium or manganate was not sufficient, no matter how much of the co-catalyst was used. No conversion was observed until more than 1.0 equivalent of the metal was added. And as soon as the stoichiometry was passed, the reaction occurred. This finding was unexpected and suggested that the first equiv-

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alent of oxidant was somehow complexed with the substrate. Potassium permanganate being cheaper and safer than osmium tetroxide, we focused our effort on the Lemieux Von-Rudloff oxidation (KMnO₄/NaIO₄).

As shown in Scheme 5.9, the hydroxyketone 348 was first formed, and then oxidized by NaIO₄ or KMnO₄ into the carboxylic acid 340. Use of TMS-diazomethane gave the methyl ester 349. The optimization of the permanganate oxidation was somehow tedious. The first oxidation of the terminal olefin into the hydroxyketone happened in few second. The subsequent oxidation into the carboxylic acid was much slower. If harsher conditions were applied, the trisubstituted olefin started to get oxidized.

On small scale, the standard one-pot Lemieux Von-Rudloff worked well, giving carboxylic acid in 71% yield and 91% BRSM. But when the reaction was run on 0.5-1.5 mmol, the yield dropped to 40-50%. A more robust version of this oxidation could be done stepwise on 3 mmol scale, using only KMnO₄ to reach cleanly the hydroxyketone, and after work-up oxidysing it into the carboxylic acid using only NaIO₄.

As an attempt to improve the overall yield, oxidation of homoallyl group was tried before the decarboxylative coupling (Scheme 5.10). A short screening of previously tried conditions showed us that enolate moiety of intermediate 344 was highly sensitive to oxidation. Fortunately, careful ozonolysis in the presence of NaOH could afford methyl ester 350 along with minor quantity of ozonide 351. As the terminal olefin was slightly more reactive than the vinyl triflate, if ozone was highly diluted and added slowly, the reaction could be stopped when all the terminal olefin had reacted without formation of overoxidation products.

Decarboxylative coupling with potassium salt 345 afforded ester derivative 352. As the
5.3. Synthetic studies of Kopsihainanine A

overall yield of both decarboxylative coupling and oxidation was lower than before, we kept the pathway coupling-azidation-Lemieux-von-Rudloff.

From methyl ester 349, preliminary studies on our iORC showed that cyclization would occur exclusively from C7, no trace of the attack from nucleophilic N1 was observed. Unfortunately, the cis-selectivity was observed as predicted. Optimized conditions used zinc in acidic medium to reduce the azide and nitro groups, and afforded 40% of intermediate 353. We were wondering if lactamization of 353 into 354 could take place. However, only degradation were observed when bases where applied, 148 tautomeric catalyst (hydroxypyridine)149 or coupling on the aminoacid derivative of 333.150

As the regioselectivity was not an issue, we pursue our plan to form lactam 339. Even if eight-membered ring are not easy to make, the Thorpe–Ingold effect of the spirocyclopentene should help the cyclization. 151 From acid 340, direct anhydrous Staudinger lactamization152 or Staudinger reduction followed by coupling reaction153 did not provided the desired lactam.

149 Rony, P. R. J. Am. Chem. Soc. 1969, 91, 6090–6096
Pentafluorophenyl ester $355$ was made with EDCI as coupling agent, and Staudinger reaction afforded lactam $339$. $^{154}$ However, the combined yield of both step was low.

Using Maarseveen’s Staudinger ligation methodology, $^{155}$ the coupling between thio-phosphine ligand $356$ and acid $340$ afforded thioether $357$ with good yield if HATU and DIPEA were used. Releasing the phosphine with DABCO $^{156}$ allowed the intramolecular Staudinger lactamization of $357$ to take place, affording lactam $339$ quantitatively.

Having lactam $339$ in hand, optimization of our iORC could be done. During the oxidation step, the presence of base (NaHCO$_3$) gave dirty mixtures. When Me$_2$S was used as reducing agent, careful analysis of the crude mixture revealed the presence of the two intermediate $358$ and $359$. The ratio between them was dependant on the conditions. Similar cyclizations were already observed by Schultz and co-workers in 1999. $^{157}$ A surprising observation was the formation of $358$ as major product if Me$_2$S was used, and $359$ if PPh$_3$ was used.


used. The cleanest reaction happened when the ozonide was quenched with PPh₃, giving exclusively 359. During the optimization of the reduction of nitro group, we observed that most reduction conditions afforded unstable side-product 361, with only traces of desired product 336. Reduction with zinc or TiCl₃ in acidic media afforded 361 as only product. This side-product would be due to the reactive iminium intermediate 360. The strongly activated olefin was easily reduced and the difficulty was to find reducing conditions strong enough to reduce the nitro group, but mild enough to allow intermediate 360 to cyclize into 336 before being reduced to 361. Raney Nickel Hydrogenation in acidic conditions seemed to give desired product 336 without the side-product, but in low yield. If Raney Nickel was used in neutral or basic anhydrous conditions (wash of the raney nickel with dry THF), an unstable polar intermediate that couldn’t be analysed was formed. If acid was added on this unknown intermediate after full conversion, this intermediate would cyclized into desired product 336. Using this method, the yield could be pushed to 58%, but the yields were not reproducible, due to the difficulties to control the stoichiometry of the Nickel (slurry solution in H₂O). Adams’ catalyst showed similar activity as Raney nickel, but could be weighted. As a results, the yield could be improved to 63% as a single diastereoisomer with no traces of side-product 361.

For the end game (Scheme 5.14), we first considered to protect the indole moiety of 336 in situ with TMS₁⁵⁸ or COO⁻,¹⁵⁹ followed by the oxidation conditions used by She (LDA, O₂, Na₂S₂O₃), and removal of the protecting group in the work-up. Unfortunately, the oxidation was not successful. We decided to first optimise the oxidation with a more stable

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Chapter 5: Kopsihainanine A

protecting group, like TBS (362). Surprisingly, every oxidations resulted in deprotection of the indole. When the protected indole 362 was treated with strong base at -50 °C, deprotection occured. Similar results were observed with Boc or TIPS-protected indole. However, we noticed that even if the deprotected indole was present, the oxidation still occured with low yield. We decided to directly optimize the oxidation on the free indole. α-Hydroxylation of amide are well described in litterature, and many conditions exists.\(^\text{160}\) Deep screening of this last oxidation step were performed, and optimum conditions happened to be lithium dimethylamine (LDMA), HMPA and bis(trimethylsilyl)peroxide. Under these conditions, the desired alkaloid was obtained with 91% yield as single diastereoisomer. Using LDMA as the base was essential for the success of the above transformation, as other bulkier bases led essentially to no reaction or degradation depending on the nature of the oxidant. The result is in line with She's observation that the amide enolate is difficult to form because of the steric hindrance around the α-pseudoaxial proton of the amide.

![Scheme 5.14 – Final oxidation toward (±)-kopsihainanine A 6](image)

5.4 Conclusion

In summary, the total synthesis of (±)-kopsihainanine A 6 was accomplished (Scheme 5.15).\(^\text{100}\) Once again, our palladium-catalyzed decarboxylative coupling afforded an intermediate bearing all the carbons needed for the natural product (346). An azidation, followed by regioselective Lemieux von-Rudloff oxidation of the terminal double bond and a Staudinger lactamization developped by Maarseveen and co-workers allowed us to reach eight-memberd lactam 339 efficiently. Finally, our iORC could cyclize on C7 with a trans-selectivity (through intermediate 360) to afford 18-dehydroxykopsihainanine A 336. Oxidation of 336 was performed with LDMA and bistrimethylsilylperoxide to afford (±)-kopsihainanine A 6 in 91% as a single diastereoisomer. We demonstrated that selectivity

\(^{160}\)For a review, see Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. In Org. React. 2004; Vol. 62, p 1, ; and references cited within
of the cyclization could be achieved by design of our iORC precursor. Macrolactamization of precursor reversed the selectivity of our iORC process from cis to trans.

Oxidation with a non hindered base as LDMA afforded the final alkaloid in good yield without any need for protection of the indol nitrogen. This work showed us the importance to design the iORC precursor in order to select the cis/trans diastereoselectivity of the cyclization.

![Scheme 5.15 – iORC on precursor 339 and endgame](image)
Approach Towards the Total Synthesis of Kopsinitarine E

In 1994 and 1996, Kam and co-workers discovered in the leaves of Malayan tree *Kopsia teoi* four unprecedented cage-like structures they called kopsinitarine A-D 363-366 (Figure 6.1).\(^{161}\) A decade later, they reported kopsinitarine E 7, found in the same plant species.\(^{162}\)

These alkaloids possess the *Kopsia* pentacyclic skeleton, with the C18 connected to the C2 position. C17 is oxidized to create an additional bridged hemiaminal ether moiety with oxidized C5. C16 is also oxidized and formed a bridged \(\alpha\)-hydroxy-ketone with the C22 carbonyl, which itself is connected to C6. As a result, these structures form congested cage-like skeletons. The complexity of such highly oxidised structures makes their synthesis a fascinat-

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approaching challenge. To this day and to the best of our knowledge, no total synthesis of kopsinitarine A-E has been reported.

However, some related alkaloids were synthetized. For example aspidofractinine 367 and kopsinine 317 possess a similar C2-C16 connection, but not the bridged hemiaminal or bridged ketone of the kopsinitarine structure. Kopsanone 318 and kopsine 319 are to our knowledge the closest structures to the kopsinitarine skeleton that have been synthesized.

No reports on the potential biosynthetic pathway of kopsinitarines skeletons are reported. Nevertheless, there is one report from Kam and co-workers in 2001, in which they isolated kopsiloscine C 368 (an oxidized version of kopsinine 317) from Kopsia sin gapurensis, and used electrochemical oxidation to reach the cage-like structure of the kopsinitarine skeleton (Scheme 6.1). By submitting natural product 368 to an anodic oxidation with 0.95 V in an attempt to form dimeric indole alkaloid structures, they obtained 12-demethoxykopsinitarine D 371 as a side-product with 17% yield.

From a mechanistic point of view, they suggested first the oxidation of the tertiary amine to form iminium intermediate 369, from this intermediate, equilibration of this iminium moiety to its enamine form, followed by intramolecular enamine-ester reaction, creates the C6-C22 bond. However from this point, in order to have cyclisation of the C17 alcohol on the iminium, epimerization of the C17 center is required. Via which mechanism this epimerization occurs is not known. Once iminium 370 is reached, the alcohol on the C17 position and the iminium moiety have the proper conformation for cyclisation to reach 12-demethoxykopsinitarine D 371. Such a transformation sequence could be similar to the biosynthetic pathway.

6.1 Synthetic Studies of Kopsinitarine E

The skeleton of kopsinitarine alkaloids, with its congested cage-like structure and the high number of C-O bonds it possesses represents an appealing challenge. Hence we chose...
6.1. Synthetic Studies of Kopsinitarine E

Kopsinitarine E 7 as our next target. Its structure is highly related to aspidospermidine. We were therefore convinced that the iORC method would allow us to readily form the core structure of this alkaloid. The difficulty lies in the high number of reactive sites this alkaloid shows (α-hydroxyketone, indole, hemiaminal ether). Targeting such complex alkaloid would require to have a highly functionalized iORC precursor. Therefore, we planned to use this synthesis to investigate the sensitivity of our key step towards the presence of a large number of functional groups.

6.1.1 Retrosynthetic Approach

From a retrosynthetic perspective (Scheme 6.2), kopsinitarine E 7 could arise from precursor 372 through indole protection and cyclization of the C17 alcohol on the C5 hemiaminal.168 This cyclization would require the correct stereochemistry on C17. Intermediate 372 would come from 373 through reduction of the amide moiety,169 decarboxylation of quaternary ester and deprotection of the diol moiety. The indoline of 373 could be the result of an intramolecular Mannich reaction on indolenine 374. This step would mean that the stereo-

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Chapter 6: Approach Towards the Total Synthesis of Kopsinitarine E

Oxidation of the C16 carbon before this step is not relevant for our synthesis. From the previous iORC processes described in Chapter 5, we knew that controlling the diastereoselectivity of our key domino process would be challenging. To force the cyclization of the fused [6,6] ring system in a trans fashion, we needed to already have the connection between C6 and C22. If we disconnect this bond (Dieckmann cyclization), any iORC to form precursor 375 would give the undesired cis selectivity. To circumvent this, we have to perform the iORC before this disconnection. Following our iORC, indolenine 374 could result from the cyclization of iminium 376. This structure would come from aldehyde intermediate 377, which in turn would arise from the ozonolysis and reduction of nitroaryl intermediate 378.

Scheme 6.2 – Retrosynthetic analysis of kopsinitarine E 7

This key intermediate could be reached from a Dieckmann condensation and Staudinger lactamization of azide precursor 379. For the lactamization, saponification of one of the methyl esters of the malonate moiety is needed. Theoretically, it should be easier to saponify a malonate ester than the C20 methyl ester.170 We planned to reach intermediate 379 from potassium salt 380 and vinyl triflate 381 via our palladium-catalyzed decarboxylative coupling as used in our previous syntheses. This vinyl triflate could result from enone 382, using conjugated 1,4-addition and enol trapping with Comins’ reagent. A Stetter react-

6.1. Synthetic Studies of Kopsinitarine E

The reaction following aldol condensation could form enone 382 from aldehyde 383. We are hoping that the diol moiety on enantiopure enone 382 would help direct the nucleophile during the conjugate addition and allow us to form the quaternary center of vinyl triflate 381 in a diastereoselective fashion.

The choice of protecting group on the diol moiety would depend on the stereochemistry used. Dieckmann condensation to afford 378 would be favoured if the ester is close to the 1,3-dicarbonyl position. This conformation will require a different protecting group depending on the diol configuration. If we use a syn-diol, as in mesotartaric acid derivatives, a cyclic ketal protecting group would be a good choice. Nonetheless, if the two alcohols are anti as in D-tartaric acid, such cyclic protection would push away the ester and the cyclization might become difficult. Two silyl or benzyl groups would therefore be a better choice.

6.1.2 Synthetic Route Towards Cyclopentenone 382

Our first synthetic attempts towards cyclopentenone derivative 382 started with known 3-iodocyclopentenone172 (Scheme 6.3). A Heck coupling with methyl acrylate afforded 384.173 We anticipated that the trans-disubstituted olefin would be more accessible than the cyclic trisubstituted one and could therefore be oxidized selectively. Unfortunately, all our dihydroxylation attempts with oxidants such as AD-mix, mCPBA or DMDO resulted in messy mixtures and no diol 385 was observed.

We decided to develop a synthesis to reach derivatives of aldehyde 383. This strategy was chosen due to the relation between aldehyde 383 and chiral pool reagents such as tartaric acids (meso- or D-), isoascorbic acid, or monosaccharids (L-erythrose or L-threose).

We first planned to reach this aldehyde from dimethyl meso-tartrate 386, synthesized

Scheme 6.3 – First pathway to enone derivatives

Chapter 6: Approach Towards the Total Synthesis of Kopsinitarine E

by dihydroxylation of maleic acid\textsuperscript{174} (Scheme 6.4). Protection of the diol moiety afforded \textsuperscript{387} A desymmetrisation of \textsuperscript{387} was planned using enzymes, as good ee's and yields were reported on many meso-1,2-diester substrates.\textsuperscript{175} Even if some examples on five-membered ring meso-1,2-diesters showed inferior results,\textsuperscript{176} we were confident in this strategy since the D-tartrate derivative of our substrate seemed to be working well.\textsuperscript{177} However, the selective saponification of the desired ester function proved unsuccessful after using a range of esterases (porcine liver esterase, hog liver esterase, or liver acetone powder), yielding only traces of the desired acid.

![Scheme 6.4](image)

\textbf{Scheme 6.4 – First pathway to aldehyde derivatives}

We then turned our attention to our study on enantiopure derivatives from the chiral pool. As such, we targeted derivatives of unnatural dimethyl D-(-)-tartrate (Scheme 6.5). Double TBS protection proceeded smoothly to afford \textsuperscript{389} but selective reduction of one of the methyl ester did not afford alcohol \textsuperscript{390} or aldehyde \textsuperscript{391}. When a reducing agent like DIBAL-H (with or without MgBr\textsubscript{2}),\textsuperscript{179} BH\textsubscript{3}-Me\textsubscript{2}S/NaBH\textsubscript{4},\textsuperscript{180} or NaBH\textsubscript{4}/LiCl\textsuperscript{181} was used, a messy reaction or reduction of both esters was observed. A second attempt \textit{via} the saponification of one ester\textsuperscript{182} followed by BH\textsubscript{3} reduction of the acid to alcohol,\textsuperscript{183} acid chloride for-


\textsuperscript{177}Piel, J.; Boland, W. \textit{Tetrahedron Lett.} \textbf{1997}, 38, 6387–6390


\textsuperscript{181}Mahadevegowda, S. H.; Khan, F. A. \textit{Tetrahedron 2013}, 69, 8494–8504

\textsuperscript{182}Trost, B. M.; Miege, F. \textit{J. Am. Chem. Soc.} \textbf{2014}, 136, 3016–3019

mation/reduction\textsuperscript{184} or thioesterification/reduction\textsuperscript{182,185} was attempted. These attempts only resulted in messy reactions with no traces of the desired product observed.

\begin{center}
\textbf{Scheme 6.5} – Aldehyde derivatives from dimethyl D-(−)-tartrate
\end{center}

Another precursor from the chiral pool studied was D-isoascorbic acid, an epimer of vitamin C. A described procedure allowed us to convert this product into 2,3-O-isopropylidene-D-erythronolactone \textbf{392 (Scheme 6.6)}\textsuperscript{186} We were planning to open the lactone with methanol to reach \textbf{393} and oxidize the alcohol moiety into an aldehyde. Unfortunately, the basic conditions needed for the opening of the lactone epimerized the product and only \textit{trans} \textbf{394} was observed. As the use of Et\textsubscript{3}N\textsuperscript{187} did not resulted in good yields, we used sodium methoxide as nucleophile\textsuperscript{188} to obtain \textbf{394} in 63\% yield. Other lactone opening conditions were attempted to avoid this epimerization, such as MeMgCl or Ti(OiPr\textsubscript{4} in MeOH. Saponification with LiOH in water was also tried. These reactions only resulted in degradation of the starting lactone. The major problem of this strategy lied in the polarity of these compounds. All these derivatives are highly water-soluble and could not be extracted. In addition, the products were too sensitive to be distilled. The oxidation of alcohol \textbf{394} proved to be not trivial. Among all the conditions attempted (IBX, DMP, PCC, PDC, TPAP, Swern, Parikh-Doering, Corey-Kim, Oppenauer), the Swern oxidation using DIPEA seemed to be the cleanest. As no aqueous work-up was possible, this aldehyde was used in the following reaction after filtration. Unfortunately, Stetter reaction on aldehyde \textbf{395} with NHC catalyst\textsuperscript{189} gave \textbf{396} with unreproducible results since the stoichiometry and purity of aldehyde \textbf{395} could not be controlled.

In an attempt to diminish the polarity and volatility of intermediates \textbf{392-396}, we decided to change the acetonide for a more hydrophobic group and chose 4-heptylidene ketal \textbf{397 (Scheme 6.7)}. This bulkier protecting group allowed these intermediates to be extracted

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\textsuperscript{186}Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozza, L. \textit{Org. Synth.} \textbf{1985}, \textit{63}, 127


and purified more easily. Unfortunately, it also seemed to change the equilibrium of the lactone opening reaction and conversion of 397 into ester 398 could not be driven to completion. An optimum yield of 46% of ester 398 was obtained with 90% yield based on recovered starting materials. Optimization of the alcohol oxidation and the Stetter reaction\cite{190} was still ongoing at the end of this thesis. Currently, optimal conditions give 16% yield of desired 1,4-diketone 399.

### 6.1.3 Synthetic attempts towards potassium salt 380

In order to reach potassium salt 380 we planned to start from ester 400 obtained by esterification of 2-(2-nitrophenyl)acetic acid with tert-butyl alcohol (Scheme 6.8).\cite{191} Alkylation of 400 with dimethyl bromomalonate to afford 401 were attempted without success. The simi-

\cite{190}Novák, L.; Rohály, J.; Gálik, G.; Fekete, I.; Varjas, L.; Szántay, C. Liebigs Ann. der Chemie 1986, 509–524


94
lar pKa of both electrophile and nucleophile, caused proton transfer and subsequent degradation of the electrophile. Reversing the reactivity by using dimethyl malonate and bromide derivative $402^{192}$ proved unsuccessful as well, intermediate $401$ was never observed.

![Scheme 6.8](image)

**Scheme 6.8** – First Pathway to potassium salt $380$

In an attempt to have a more suitable electrophile, we tried using iodide $403$ (obtained in two steps from glycerol) to alkylate $400$. To our surprise, instead of adduct $404$, a mixture of quinoline 1-oxide derivatives $405$ and $406$ were obtained in 41% yield, with $405$ being the major product.

![Scheme 6.9](image)

**Scheme 6.9** – Second Pathway to potassium salt $380$

A possible mechanism is shown in **Scheme 6.10**. After the desired nucleophilic substitution, deprotonation of the substrate could occur, leading to $407$. This intermediate could undergo a 1,8-O,O-silyl migration to reach $408$. To the best of our knowledge, 1,8-silyl migrations have not been reported yet.$^{193}$ but it is conceivable that the rigidity of the structure $407$ allowed the required promiscuity between the silylated alcohol and the nitro group. Silylated

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nitro groups have been previously reported. In these studies they underline the weakness of the resulting N–OSi bond, this could explain how we lost both silyl groups during the reaction. We postulated that formaldehyde could be eliminated from 408 to afford anionic intermediate 409. It would then be conceivable to have elimination of TBSOH from intermediate 410. This intermediate would again have the correct conformation for a 1,8-silyl migration towards enolate 411. This structure would be in equilibrium with aldehyde 412, that could condense into 413. Hydrolysis of the silyl group would give observed side-product 405.

\[
\text{Scheme 6.10} \quad \text{– Mechanism hypothesis for the formation of quinoline 1-oxide 405}
\]

Considering the trouble encountered with these derivatives, we decided to modify our strategy. We hoped to reach potassium salt 380 from olefin 414 (Scheme 6.11). However, Knoevenagel reaction with ester 400 has proven unsuccessful. Attempts to transform bromide derivative 402 into a phosphine derivative to perform a Wittig-type reaction with dimethyl ketomalonate resulted only in a messy reaction mixture.

Oxidation of ester 400 to keto ester 415 (unpublished procedure from our labora-

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followed by Knoevenagel condensation with dimethyl malonate afforded olefin 414. However, the yield was low due to the four electron-withdrawing groups making this product highly unstable. When using TiCl₄·THF and pyridine, our best reaction conditions, only 10% yield of olefin 414 was obtained. Horner–Wadsworth–Emmons reaction with phosphorylated derivatives of malonic ester were attempted but did not afford any product 414.

Scheme 6.11 – Third Pathway to potassium salt 380

Since potassium salt 380 seemed troublesome to synthesise, we planned to change strategy from our decarboxylative coupling to a Heck, or reductive Heck, reaction (Scheme 6.12). Knoevenagel condensation of dimethyl malonate or Meldrum’s acid with 2-nitrobenzaldehyde afforded compounds 417 and 418 respectively. Heck, or reductive Heck, reactions with vinyl triflate as model substrate should allow us to reach the scaffold we needed for our synthesis. During this screening, Palladium catalysts (Pd(OAc)₂, Pd(PPh₃)₂Cl₂ or Pd(PPh₃)₄), were tested with or without ligands (PPh₃, P(nBu)₃, dppp, dppe,

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X-Phos, BINAP, NHC or AsPh₃), base (Et₃N, piperidine, or K₂CO₃), additives (TBAC) and hydride sources (HCO₂H or HCO₂Na) in various solvents such as DMF, MeCN or water in oxygen-free conditions. In most attempts, the starting materials were unreactive at less then 60 °C. When heated more, one could observe the disappearance of vinyl triflate, suggesting the palladium oxidative addition was working, but the coupling with the olefin never occurred. All vinyl triflate was consumed, while olefin 417 was recovered. In all attempts using olefin 418, degradation of the olefin occurred at higher temperature (>80 °C).

Direct cobalt-catalyzed conjugate addition of triflate reagents into similar activated double bond were attempted, as well as alkenylchromium reagents prepared from 419. Both reactions showed only degradations, apparently due to sensitivity of the nitrophenyl moiety to metals.

Finally, synthesis of boronic ester 422 was planned in prevision of a Suzuki coupling with triflate 419. Unfortunately, copper-catalyzed 1,4-Addition of pinacol diborane to reach 422 has proven unsuccessful. The borane was not stable enough and total protodeboronation was observed. We are currently exploring similar couplings with model triflate 419.

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6.2 Conclusion

In summary, we studied the total synthesis of kopsinitarine E via a palladium-catalyzed coupling/iORC pathway. Several attempts were made for the synthesis of the starting materials needed for the decarboxylative or Heck coupling (Scheme 6.13). The formation of enone was attempted from various pathways, such as dihydroxylation of, desymmetrisation of meso-tartrate derivative, or from isopropylidene ketal. Unfortunately, no success were obtained with these strategies. On the last one, the high solubility of such ketal intermediates caused many difficulties. By changing the protecting group of for the 4-heptylidene ketal, the solubility issue could be solved and preliminary results towards enone seemed promising. The optimisation of the route towards enone is still ongoing. The plan was to convert this enone in vinyl triflate using a conjugate addition and trapping of the enolate with Comins' reagent. Using or as coupling parter with vinyl triflate, we planned to reach. This intermediate could be cyclized into, which would be the iORC precursor to reach indole intermediate. Few more reactions should allow us to reach kopsinitarine E. Many attempts were done towards the potassium carboxylate without success. Alkylation, Wittig-type reaction or Knoevenagel reaction did not succeed to afford desired product. For this reason, the Heck coupling was chosen due to the easy access to olefin. Preliminary results on Heck and reductive Heck using with a known vinyl triflate as model substrate did not presented promising results so far. Nevertheless, as many other coupling reactions are conceivable, this total synthesis is still pursued.
Chapter 6: Approach Towards the Total Synthesis of Kopsinutarine E

Scheme 6.13 – Current State of the Synthetic Study of Kopsinarine E
General Conclusion

In summary, we developed a domino sequence called an integrated oxidation/reduction/cyclization (iORC) process allowing us to reach easily the polycyclic core of *Aspidosperma* alkaloids. This reaction uses latent functionalities hidden within molecules, like double bonds, and nitro or azide to generate *in situ* carbonyls and amines which in turn spontaneously condense to form three or more cycles during a skeletal rearrangement process that affords the indole polycyclic skeleton of our target products with a high degree of chemo-, regio-, and diastereoselectivity.

Our first target was minfiensine 1 (Scheme 7.1). The goal of this strategy was to reach intermediate 95, and to perform a domino reduction/cyclization sequence. This represented an unpolished version of our iORC which lacked the oxidation step. Such a reaction should have allowed us to reach aminal 94, which could supposedly be transformed into minfiensine 1 in a short and straightforward manner. In our synthetic study towards minfiensine 1, five main strategies were attempted in order to reach key intermediate 95. Instalment of the quaternary C7 center by allylation or alkylation failed due to the steric hindrance around this center. Cross metathesis of an allyl ketone to install the olefin moiety did not succeed due to the incompatibility of our substrate with metathesis catalysts. Furthermore, the various cycloadditions to afford the cyclohexenone moiety proved unsuccessful. Cyclohexenone structure 95 proved difficult to reach and our synthetic route became too long to remain attractive. It was therefore decided to stop this synthesis and focus on our newly developed iORC.

The next studies focused on the use of our domino iORC sequence. We first chose to target aspidospermidine 3 and dehydroaspidospermidine 2 (Scheme 7.2). The key macrocycle 212 was reached in only 6 steps and 17.4% overall yield featuring our palladium-catalyzed decarboxylative coupling to build in one step a compound having all the carbons needed for the synthesis of the natural product. Two consecutive Mitsunobu reactions closed the macrocycle needed in our key intermediate 212. Our key domino process allowed us to reach se-
Chapter 7: General Conclusion

5 different strategies attempted
Not reached

Scheme 7.1 – Summary of the synthetic study towards minfiensine 1 and the different strategies attempted to reach 94

lectively dehydroaspidospermidine 2 or aspidospermidine 3 with an optimised yield of 50% from 212. Full diastereocontrol was observed as we formed a cis-fused [6,6] ring system. From dehydroaspidospermidine 2, vincadifformine 4 could be synthetized in one step and 50% yield.

Scheme 7.2 – Summary of the total synthesis of dehydroaspidospermidine 2, aspidospermidine 3 and vincadifformine 4

Following a similar synthetic route as for aspidospermidine, we attempted to reach aspidoalbidine 5 with our iORC (Scheme 7.3) from macrocycle 293, obtained in 9 steps and 11.4% overall yield. This macrocycle was obtained using a palladium-catalyzed decarboxylative coupling to link the two main fragments of the molecule and two Mitsunobu reactions to close the ten-membered ring. Anti-Markovnikov hydroxylation of the terminal olefin afforded the primary alcohol moiety of key intermediate 293. Our key-step is still under development at this time and aspidoalbidine 5 has not yet been reached though we believe this is just a matter of time until we obtain our target structure.
As all these previous examples of iORC domino process gave cis-fused [6,6] ring system, we decided to change the diastereoselectivity of this reaction and force the reaction into giving a trans-fused [6,6] ring system. This would allow us to reach kopsihainanine A 6 (Scheme 7.4). In order to change the selectivity, we introduced a constrain in the key intermediate to push the reaction towards our desired conformation. We formed 8-membered ring 339 in 8 steps and 36% overall yield, featuring our palladium-catalyzed decarboxylative coupling, and a Staudinger lactamization. To our delight, performing our key domino process on this lactam allowed us to reach intermediate 336 with a trans-fused C/D ring system in 63% yield with full stereocontrol. An α-keto hydroxylation concluded our total synthesis of racemic kopsihainanine A 6 in 91% yield.

Our final synthetic study was designed to see how far could we go for generating molecular complexity by the iORC process (Scheme 7.5). We targeted kopsinitarine E 7 via indole-nine 423. This intermediate was supposed to be reached by performing our iORC domino process on highly substituted precursor 424. Unfortunately, the presence of these functional groups made the synthesis of precursor 424 challenging. This project was still at an early stage.

To conclude, we were able to demonstrate the power of our iORC and our ability to control the cyclization step from a regioselective perspective (goniomitine versus aspidospermidine), as well as a diastereoselective perspective (aspidospermidine versus kopsinainanine A). The quaternary center in C20 of these aspidosperma alkaloids is the one controlling the...
relative stereoselectivity, and if the formation of this center could be done in an enantioselective manner, the total syntheses of these alkaloids would become enantioselective. We are currently considering this synthetic challenge. Nonetheless, such domino processes have some drawbacks. The sensitivity of the key step towards the reductive conditions used makes this transformation challenging, as a slightly different substrate requires totally different reductive conditions to achieve good yields. In addition, we sometimes experienced troubles to reach iORC precursors as for the synthesis of kopsinitarine E or minfiensine. However, the ability to trigger such skeleton rearrangement and form complex polycyclic indole skeletons from simple precursors is certainly a great asset and a significant addition to the strategies available for the total synthesis of indole alkaloids, and could allow easy synthetic entry into many other families of indole alkaloids.
Experimental Section

8.1 General Remarks

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 ($T > 100 \degree C$) or under vacuum with a heat gun ($T > 200 \degree C$).

When solvents are indicated as dry they were either purchased as such, distilled prior to use or were dried by a passage through a column of anhydrous alumina or copper using a Puresolv MD 5 from Innovative Technology Inc., based on the Grubb’s design.\textsuperscript{207}

Reactions heated by microwave irradiation were performed in a CEM Discover SP microwave instrument.

Flash column chromatographies\textsuperscript{208} were performed using Silicycle P60 silica: 230-400 mesh (40-63 $\mu$m) silica.

Reactions were monitored using Merck Kieselgel 60F254 aluminium or glass backed plates. TLC’s were visualized by UV fluorescence (254 nm) then one of the following: KMnO$_4$, PMA, ninhydrin, pancaldi, $p$-anisaldehyde, vanillin.

NMR spectra were recorded on a Bruker AvanceIII-400, Bruker Avance-400, Bruker DRX-400, or Bruker AvanceII-800 spectrometer at room temperature, $^1$H frequency is at 400.13 MHz,

\begin{thebibliography}{99}
\end{thebibliography}
Chapter 8: Experimental Section

$^{13}$C 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: CHCl$_3$ [$^1$H: 7.26 ppm, $^{13}$C: 77.2 ppm], MeOH [$^1$H: 3.31 ppm, $^{13}$C 49.0 ppm], DMSO [$^1$H: 2.50 ppm, $^{13}$C 39.5 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. 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 accessory 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 ionisation (EI positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI$^+_{1}$). 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).

Enantiomeric excesses were determined with a Thar SFC Investigator system using chiral stationary phase columns by comparing the samples with the appropriate racemic samples, column and elution details specified in each entry.

Melting points are uncorrected and were recorded on a Stuart SMP30 melting point apparatus.

When a rigorously inert and dry atmosphere was needed reactions were carried out in a Pure-Lab HE 4GB 2500 Glove-box System from Innovative Technologies inc.

For all general procedures the order of addition of reagents has to be respected.
8.2 Experimental Procedures of Chapter 2

Ethyl 2-(hydroxymethyl)acrylate 425

Following a reported procedure, a solution of paraformaldehyde (4.8 g, 0.16 mol, 4.0 equiv) in H$_2$O (11 mL) and phosphoric acid (1.0 M solution, 0.40 mL) was heated to 90 °C for 5 h. The reaction mixture was allowed to cool down to RT, and triethyl phosphonoacetate (8.0 mL, 40 mmol) was added. A solution of K$_2$CO$_3$ (6.1 g, 40 mmol, 1.0 equiv) in H$_2$O (6.0 mL) was added dropwise carefully, by avoiding the reaction mixture to go higher than 40 °C. The reaction was then stirred at 40 °C for 5 minutes. The reaction mixture was then cooled down to 0 °C. Brine and Et$_2$O were added to the mixture. The solution was then extracted with Et$_2$O. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by vacuum distillation (Bp = 55 °C/0.1 mbar) afforded compound 425 as a colorless oil (4.0 g, 77% yield). The spectroscopic data of this compound were in accord with those reported in the literature.

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.25 (s, 1H, C$_4$-H), 5.82 (s, 1H, C$_4$-H), 4.32 (d, $J = 6.6$ Hz, 2H, C$_3$-H), 4.24 (q, $J = 7.1$ Hz, 2H, C$_6$-H), 2.36 (t, $J = 6.6$ Hz, 1H, O$_5$-H), 1.31 (t, $J = 7.1$ Hz, 3H, C$_7$-H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 166.5 (C$_2$), 139.6 (C$_1$), 125.8 (C$_4$), 62.8 (C$_6$), 61.0 (C$_3$), 14.3 (C$_7$).

$R_f$(PE/EtOAc 8:2) = 0.2.

2-azidoethyl 4-methylbenzenesulfonate 426

209 Villieras, J; Rambaud, M Org. Synth. 1988, 66, 220
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Following a reported procedure, to a solution of 2-chloroethanol (4.3 mL, 63 mmol) in DMF (20 mL) was added sodium azide (5.7 g, 88 mmol, 1.4 equiv). The solution was stirred at 80 °C for 24 h. The reaction mixture was allowed to cool down to RT, and then filtered through Celite. The Celite was washed with THF and the solution was directly used for the next reaction.

To the crude 2-azidoethanol in solution (THF/DMF 2:1) was added triethylamine (26 mL, 0.19 mol, 3.0 equiv) and tosyl chloride (14 g, 72 mmol, 1.2 equiv). The mixture was stirred overnight. The solution was then concentrated in vacuo, diluted in DCM and washed with H₂O, 1 M HCl, 10% NaOH, brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 5:1) afforded compound 426 as a yellow oil (11 g, 70% yield). The spectroscopic data of this compound were in accord with those reported in the literature.¹¹

¹¹Macleod, F.; Lang, S.; Murphy, J. A. Synlett 2010, 21, 529–534


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1H NMR (400 MHz, CDCl₃): δ 7.82 (d, J = 8.3 Hz, 2H, C₄,₈−H), 7.37 (d, J = 8.3 Hz, 2H, C₅,₇−H), 4.16 (t, J = 5.2 Hz, 2H, C₂−H), 3.48 (t, J = 5.2 Hz, 2H, C₁−H), 2.46 (s, 3H, C₉−H).
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13C NMR (101 MHz, CDCl₃): δ 145.3 (C₃), 132.6 (C₆), 130.0 (C₅,₇), 128.0 (C₄,₈), 68.1 (C₁), 49.6 (C₂), 21.7 (C₉).
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Rᶠ (PE/EtOAc 8:2) = 0.28.
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methyl 2-(2-nitrophenyl)acetate 96

To a solution of 2-(2-nitrophenyl)-acetic acid (10.0 g, 55.0 mmol) in methanol (300 mL) was added 3.0 mL of conc. H₂SO₄. The solution was heated at reflux for 2 h. The solution was then concentrated under reduced pressure, diluted with EtOAc, washed with saturated NaHCO₃, brine, dried over Na₂SO₄ and concentrated in vacuo. The crude compound 96 thus obtained was used for the next step without further purification (yellow wax, 10.7 g). The spectroscopic data of this compound were in accord with those reported in the literature.²¹²


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1H NMR (400 MHz, CDCl₃): δ 8.12 (dd, J = 7.9, 1.2 Hz, 1H, C₂−H), 7.60 (td, J = 7.9, 1.2 Hz, 1H, C₄−H), 7.48 (td, J = 7.9, 1.2 Hz, 1H, C₃−H), 7.36 (dd, J = 7.9, 1.2 Hz, 1H, C₅−H), 4.03 (s, 2H, C₇−H), 3.71 (s, 3H, C₉−H).
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8.2. Experimental Procedures of Chapter 2

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 170.5 (C$^8$), 148.9 (C$^1$), 133.7 (C$^4$), 133.5 (C$^5$), 129.9 (C$^3$), 128.8 (C$^6$), 125.5 (C$^2$), 52.4 (C$^9$), 39.7 (C$^7$).

$R_F$ (EtOAc) = 0.71.

**Ethyl 2-(bromomethyl)acrylate 99**

Following a reported procedure,$^{210}$ to a solution of acrylate 425 (8.0 g, 61 mmol) in Et$_2$O (65 mL) at -10°C was added dropwise PBr$_3$ (2.3 mL, 25 mmol, 0.40 equiv). The solution was stirred and allowed to warm up slowly to RT over a period of 4 h. The solution was then cooled down to -10°C, water was added slowly, and the mixture was extracted with Et$_2$O. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, and concentrated *in vacuo*. Purification by vacuum distillation (Bp = 55°C/8.0 mbar) afforded compound 99 as a colorless oil (11 g, 91% yield). The spectroscopic data of this compound were in accord with those reported in the literature.$^{210}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.33 (d, $J = 0.7$ Hz, 1H, C$^4$-H), 5.94 (d, $J = 0.7$ Hz, 1H, C$^4$-H), 4.27 (q, $J = 7.1$ Hz, 2H, C$^8$-H), 4.18 (d, $J = 0.8$ Hz, 2H, C$^3$-H), 1.33 (t, $J = 7.1$ Hz, 3H, C$^9$-H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 165.0 (C$^2$), 137.7 (C$^1$), 129.1 (C$^4$), 61.5 (C$^8$), 29.5 (C$^3$), 14.3 (C$^9$).

$R_F$ (PE/EtOAc 8:2) = 0.68.

**2-azidoiodoethane 97**

Sodium iodide (4.7 g, 31 mmol, 1.5 equiv) was added to a solution of 426 (5.0 mL, 21 mmol) in acetone (100 mL). The solution was stirred at reflux for 18 h. The reaction mixture was allowed to cool down to RT, and concentrated under reduced pressure. Water was added and the mixture was extracted with Et$_2$O. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. Purification by vacuum distillation (Bp
Chapter 8: Experimental Section

= 70 °C/20 mbar) afforded compound 97 as a colorless oil (3.1 g, 75% yield). The spectroscopic data of this compound were in accord with those reported in the literature.\(^{211}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 3.66 (t, J = 7.1 \text{ Hz}, 2 \text{H}, \text{C}^2-\text{H}), 3.25 (t, J = 7.1 \text{ Hz}, 2 \text{H}, \text{C}^1-\text{H}).\)

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta 53.1 \text{ (C}^2\), 1.0 \text{ (C}^1\).\)

\(R_f\) (PE/EtOAc 5:1) = 0.78.

1-ethyl 5-methyl 2-methylene-4-(2-nitrophenyl)-pentanedioate 427

The ester 96 (0.20 g, 1.0 mmol) was dissolved in DMF (1.0 mL). The acrylate 99 was added (0.12 g, 1.2 mmol, 1.2 equiv), followed by cesium carbonate (0.33 g, 2.0 mmol, 2.0 equiv). The reaction mixture was then stirred at 45 °C for 9 h. The solution was then cooled down to RT, acidified with 0.5 M HCl and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. Purification by FCC (PE/DCM 1:1) afforded compound 427 as a yellow oil (0.19 g, 61% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.89 (dd, J = 7.8, 1.1 \text{ Hz}, 1 \text{H}, \text{C}^3-\text{H}), 7.57 (td, J = 7.8, 1.1 \text{ Hz}, 1 \text{H}, \text{C}^1-\text{H}), 7.49 (dd, J = 7.8, 1.3 \text{ Hz}, 1 \text{H}, \text{C}^6-\text{H}), 7.42 (td, J = 7.8, 1.3 \text{ Hz}, 1 \text{H}, \text{C}^2-\text{H}), 6.11 (d, J = 1.0 \text{ Hz}, 1 \text{H}, \text{C}^{10}-\text{H}), 5.42 (d, J = 1.0 \text{ Hz}, 1 \text{H}, \text{C}^{10}-\text{H}), 4.55 (t, J = 8.1 \text{ Hz}, 1 \text{H}, \text{C}^7-\text{H}), 4.20 (q, J = 7.2 \text{ Hz}, 2 \text{H}, \text{C}^{14}-\text{H}), 3.66 (s, 3 \text{H}, \text{C}^{13}-\text{H}), 3.24 (dd, J = 14.1, 8.1 \text{ Hz}, 1 \text{H}, \text{C}^8-\text{H}), 2.82 (dd, J = 14.1, 8.1 \text{ Hz}, 1 \text{H}, \text{C}^8-\text{H}), 1.29 (t, J = 7.2 \text{ Hz}, 3 \text{H}, \text{C}^{15}-\text{H}).\)

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta 172.4 \text{ (C}^{12}, 166.5 \text{ (C}^1\), 149.5 \text{ (C}^4\), 137.2 \text{ (C}^9\), 133.1 \text{ (C}^1\), 132.98 \text{ (C}^5\), 130.7 \text{ (C}^6\), 128.4 \text{ (C}^2\), 127.9 \text{ (C}^{10}\), 124.9 \text{ (C}^3\), 61.1 \text{ (C}^{14}\), 52.4 \text{ (C}^{13}\), 45.7 \text{ (C}^7\), 35.3 \text{ (C}^8\), 14.3 \text{ (C}^{15}\).

IR: 1736 (s), 1714 (s), 1572 (s), 1352 (m), 1194 (s).

HRMS: (ESI\(^+\)) m/z: [M + H]\(^+\) Calcd for C\(_{15}\)H\(_{18}\)NO\(_6\): 308.1134; Found: 308.1126.

\(R_f\) (PE/DCM 1:1) = 0.23.
methyl 4-azido-2-(2-nitrophenyl)butanoate 98

The ester 96 (0.20 g, 1.0 mmol) was dissolved in DMF (2.0 mL). Compound 97 was added (0.43 g, 2.1 mmol, 2.0 equiv), followed by cesium carbonate (0.33 g, 2.1 mmol, 2.0 equiv). The reaction mixture was then stirred at 60 °C for 18 h. The solution was then cooled down to RT, acidified with 0.5 M HCl and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (toluene) afforded compound 98 as a yellow oil (0.19 g, 73% yield).

1H NMR (400 MHz, CDCl₃): δ 7.95 (dd, J = 7.9, 1.2 Hz, 1H, C₃−H), 7.61 (td, J = 7.9, 1.2 Hz, 1H, C₁−H), 7.50-7.42 (m, 2H, C₂,₆−H), 4.29 (t, J = 7.2 Hz, 1H, C₇−H), 3.67 (s, 3H, C₁₃−H), 3.46-3.29 (m, 2H, C₉−H), 2.50 (dq, J = 14.2, 7.0 Hz, 1H, C₈−H), 2.09 (dq, J = 14.2, 7.0 Hz, 1H, C₈−H).

13C NMR (101 MHz, CDCl₃): δ 172.3 (C₁₂), 149.1 (C⁴), 133.4 (C¹), 132.8 (C⁵), 130.3 (C⁶), 128.6 (C²), 125.2 (C₃), 52.5 (C₁₃), 49.3 (C⁹), 44.1 (C⁷), 31.9 (C₈).

IR: 2098 (w), 1734 (w), 1528 (s), 1352 (w).


Rf (Toluene) = 0.45.

5-ethyl 1-methyl 2-(2-azidoethyl)-4-methylene-2-(2-nitrophenyl)pentanedioate 100

The ester 98 (30 mg, 0.12 mmol) was dissolved in DMF (0.30 mL). Compound 99 was added (27 mg, 0.14 mmol, 1.2 equiv), followed by cesium carbonate (75 mg, 0.18 mmol, 1.5 equiv). The reaction mixture was then stirred at 40 °C for 24 h. The solution was then cooled down.
to RT, acidified with 0.5 M HCl and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (PE/EtOAc 9:1) afforded compound **100** as a yellow oil (7.7 mg, 17% yield).

**$^1$H NMR (400 MHz, CDCl$_3$):** $\delta$ 7.96 (dd, $J = 7.9, 1.4$ Hz, 1H, C$_3^-$H), 7.58 (td, $J = 7.9, 1.4$ Hz, 1H, C$_1^-$H), 7.47 (td, $J = 7.9, 1.1$ Hz, 1H, C$_2^-$H), 7.33 (dd, $J = 7.9, 1.1$ Hz, 1H, C$_6^-$H), 6.26 (d, $J = 1.1$ Hz, 1H, C$_{12}^-$H), 5.41 (d, $J = 1.1$ Hz, 1H, C$_{12}^-$H), 4.01-3.84 (m, 2H, C$_{14}^-$H), 3.68 (s, 3H, C$_{17}^-$H), 3.63 (d, $J = 13.8$ Hz, 1H, C$_{10}^-$H), 3.35-3.16 (m, 2H, C$_9^-$H), 3.12 (d, $J = 13.8$ Hz, 1H, C$_{10}^-$H), 2.44-2.28 (m, 2H, C$_8^-$H), 1.16 (t, $J = 7.1$ Hz, 3H, C$_{15}^-$H).

**$^{13}$C NMR (101 MHz, CDCl$_3$):** $\delta$ 172.5 (C$_{16}$), 166.9 (C$_{13}$), 149.9 (C$_4$), 136.2 (C$_{11}$), 134.0 (C$_5$), 132.4 (C$_2$), 130.3 (C$_{12}$), 129.1 (C$_6$), 128.3 (C$_1$), 126.0 (C$_3$), 61.0 (C$_{14}$), 52.1 (C$_{17}$), 52.0 (C$_7$), 47.5 (C$_9$), 38.1 (C$_{10}$), 35.0 (C$_8$), 14.0 (C$_{15}$).

**IR:** 2924 (s), 2851 (w), 2099 (m), 1718 (m), 1530 (s), 1357 (w).

**HRMS:** (ESI$^+$) m/z: [M+H]$^+$ Calcd for C$_{17}$H$_{21}$N$_4$O$_6$: 377.1456; Found: 377.1464.

$R_f$ (DCM) = 0.5.

**ethyl 2-(acetoxy methyl)acrylate 116**

Following a reported procedure,$^{213}$ to a solution of acrylate 425 (50 mg, 0.38 mmol) in DCM (1.5 mL) at 0°C was added dropwise Et$_3$N (80 $\mu$L, 0.58 mmol, 1.5 equiv). Acetyl chloride (40 $\mu$L, 0.58 mmol, 1.5 equiv) was then added dropwise. The solution was stirred for 20 min. The mixture was quenched with brine. The phases were separated and the aqueous one was washed with DCM. The combined organic phases were dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded compound **116** as a yellow oil (45 mg, 68% yield). The spectroscopic data of this compound were in accord with those reported in the literature.$^{213}$

**$^1$H NMR (400 MHz, CDCl$_3$):** $\delta$ 6.36 (d, $J = 1.1$ Hz, 1H, C$_4^-$H), 5.83 (d, $J = 1.1$ Hz, 1H, C$_4^-$H), 4.81 (s, 2H, C$_3^-$H), 4.24 (q, $J = 7.1$ Hz, 2H, C$_8^-$H), 2.10 (s, 3H, C$_{11}^-$H), 1.31 (t, $J = 7.1$ Hz, 3H, C$_9^-$H).

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8.2. Experimental Procedures of Chapter 2

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 170.6 (C$^{10}$), 165.3 (C$^2$), 135.6 (C$^1$), 127.4 (C$^4$), 62.6 (C$^3$), 61.1 (C$^8$), 21.0 (C$^{11}$), 14.3 (C$^9$).

$R_f$ (DCM) = 0.54.

4-azido-2-(2-nitrophenyl)butanoic acid 109

![Diagram of synthetic pathway]

To a solution of ester 98 (0.50 g, 1.9 mmol) in a mixture of THF/H$_2$O (1:1, 20 mL) was added LiOH (91 mg, 3.8 mmol, 2.0 equiv). The solution was stirred at RT for 3 h. HCl (1.0 M) was then added and the solution was extracted with DCM. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded acid 109 as a yellow oil (0.40 g, 85% yield).

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.00 (dd, $J = 8.1, 1.3$ Hz, 1H, C$^3$–H), 7.64 (td, $J = 8.1, 1.3$ Hz, 1H, C$^1$–H), 7.52–7.45 (m, 2H, C$^{2,6}$–H), 4.32 (t, $J = 7.1$ Hz, 1H, C$^7$–H), 3.42 (dt, $J = 13.6, 7.1$ Hz, 1H, C$^9$–H), 3.30 (dt, $J = 13.6, 7.1$ Hz, 1H, C$^9$–H), 2.52 (dq, $J = 14.1, 7.1$ Hz, 1H, C$^8$–H), 2.10 (dq, $J = 14.1, 7.1$ Hz, 1H, C$^8$–H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 176.9 (C$^{12}$), 149.0 (C$^4$), 133.7 (C$^5$), 132.4 (C$^6$), 130.9 (C$^1$), 129.0 (C$^2$), 125.5 (C$^3$), 49.3 (C$^9$), 44.5 (C$^7$), 31.5 (C$^8$).

IR: 2926 (w), 2856 (w), 2750 (w), 2635 (w), 2571 (w), 2102 (w), 1701 (s), 1612 (w), 1578 (w), 1518 (s), 1431 (m), 1410 (m), 1342 (s), 1241 (s), 938 (m), 706 (s).

HRMS: (ESI$^+$) m/z: [M – H]$^-$ Calcd for C$_{10}$H$_9$N$_4$O$_4$$: 249.0624; Found: 249.0631.

$R_f$ (EtOAc) = 0.61.

N-methoxy-N-methyl-2-(2-nitrophenyl)acetamide 113

![Diagram of synthetic pathway]
To a solution of 2-(2-nitrophenyl)acetic acid (50 mg, 0.27 mmol) in DCM (0.60 mL) at 0 °C was added freshly distilled N,O-dimethylhydroxylamine (25 mg, 0.41 mmol, 1.5 equiv) and DCC (62 mg, 0.30 mmol, 1.1 equiv). The solution was stirred at RT for 24 h. HCl (1.0 M) was then added and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (EtOAc) afforded pure Weinreb amide 113 as a yellow oil (60 mg, quantitative yield).

^1H NMR (400 MHz, CDCl₃): δ 8.09 (dd, J = 7.7, 1.4 Hz, 1H, C₃−H), 7.58 (td, J = 7.7, 1.4 Hz, 1H, C¹−H), 7.45 (td, J = 7.7, 1.3 Hz, 1H, C²−H), 7.36 (dd, J = 7.7, 1.3 Hz, 1H, C⁶−H), 4.17 (s, 2H, C⁷−H), 3.81 (s, 3H, C¹⁰−H), 3.22 (s, 3H, C⁹−H).

^13C NMR (101 MHz, CDCl₃): δ 170.5 (C₆), 149.2 (C⁴), 133.5 (C⁶), 133.4 (C¹), 130.7 (C⁵), 128.3 (C²), 125.2 (C³), 61.3 (C¹₀), 37.9 (C⁷), 32.4 (C⁹).

IR: 2936 (w), 2856 (w), 2359 (w), 2342 (w), 1665 (s), 1525 (s), 1350 (m).

HRMS: (ESI⁺) m/z: [M + H]⁺ Calcd for C₁₀H₁₃N₂O₄⁺: 225.0870; Found: 225.0869.

Rf (PE/EtOAc 8:2) = 0.07.

4-azido-2-(2-nitrophenyl)butan-1-ol 428

To a solution of ester 98 (6.7 g, 25 mmol) in Et₂O (25 mL) was added LiBH₄ (1.1 g, 51 mmol, 2.0 equiv). The solution was stirred at RT for 2 h. Saturated NH₄Cl was then added and the solution was extracted with Et₂O. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (DCM) afforded compound 428 as an orange oil (4.8 g, 81% yield).

^1H NMR (400 MHz, CDCl₃): δ 7.77 (dd, J = 7.8, 1.3 Hz, 1H, C³−H), 7.61 (td, J = 7.8, 1.3 Hz, 1H, C¹−H), 7.50 (dd, J = 7.8, 1.3 Hz, 1H, C⁶−H), 7.41 (td, J = 7.8, 1.3 Hz, 1H, C⁵−H), 3.86 (dd, J = 9.3, 5.3 Hz, 2H, C¹₂−H), 3.49 (tt, J = 9.3, 5.9 Hz, 1H, C⁷−H), 3.37-3.15 (m, 2H, C⁹−H), 2.15 (dt, J = 14.0, 7.6, 5.6 Hz, 1H, C⁸−H), 1.97 (dt, J = 14.0, 7.6, 5.6 Hz, 1H, C⁸−H), 1.70 (t, J = 5.3 Hz, 1H, O¹³−H).

^13C NMR (101 MHz, CDCl₃): δ 151.2 (C⁴), 135.5 (C⁵), 132.7 (C¹), 128.4 (C⁶), 127.73 (C²), 124.3 (C³), 66.5 (C¹₂), 49.4 (C⁹), 39.5 (C⁷), 31.1 (C⁸).
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IR: 2920 (w), 2878 (w), 2360 (w), 2094 (s), 1520 (s), 1353 (s), 1038 (m).

HRMS: (ESI\(^+\)) m/z: \([M + H]^+\) Calcd for C\(_{10}\)H\(_{13}\)N\(_4\)O\(_3\): 237.0982; Found: 237.0992.

\(R_f\) (DCM) = 0.19.

4-azido-2-(2-nitrophenyl)butan-1-al 111

To a solution of alcohol 428 (4.5 g, 19 mmol) in DMSO (20 mL) was added IBX (6.0 g, 25 mmol, 1.3 equiv). The solution was stirred at RT for 3 h. Saturated NaHCO\(_3\) was then added and the solution was filtered and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 8:2) afforded compound 111 as an orange oil (3.5 g, 80% yield).

\(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.75 (s, 1H, C\(_{12}\)−H), 8.02 (dd, \(J = 7.9, 1.0\) Hz, 1H, C\(_3\)−H), 7.67 (td, \(J = 7.9, 1.0\) Hz, 1H, C\(_1\)−H), 7.52 (td, \(J = 7.9, 1.0\) Hz, 1H, C\(_2\)−H), 7.31 (dd, \(J = 7.9, 1.0\) Hz, 1H, C\(_6\)−H), 4.28 (t, \(J = 7.6\) Hz, 1H, C\(_7\)−H), 3.40 (dt, \(J = 13.1, 6.7\) Hz, 1H, C\(_9\)−H), 3.31 (dt, \(J = 13.1, 6.7\) Hz, 1H, C\(_8\)−H), 2.52 (ddt, \(J = 14.2, 7.6, 6.7\) Hz, 1H, C\(_8\)−H), 2.02 (ddt, \(J = 14.2, 7.6, 6.7\) Hz, 1H, C\(_8\)−H).

\(^{13}\text{C}\) NMR (101 MHz, CDCl\(_3\)): \(\delta\) 197.9 (C\(_{12}\)), 149.8 (C\(_4\)), 133.7 (C\(_5\)), 131.2 (C\(_2\)), 130.7 (C\(_6\)), 129.1 (C\(_1\)), 125.5 (C\(_3\)), 51.4 (C\(_7\)), 49.1 (C\(_9\)), 29.0 (C\(_8\)).

IR: 2934 (w), 2838 (w), 2725 (w), 2097 (s), 1724 (s), 1523 (s), 1348 (s).

HRMS: (ESI\(^+\)) m/z: \([M − N + H]^+\) Calcd for C\(_{10}\)H\(_{11}\)N\(_3\)O\(_3\)\(^+\): 221.0795; Found: 221.0805.

\(R_f\) (DCM) = 0.73.
methyl 2-(2-azidophenyl)acetate 102

A solution of 96 (1.0 g, 5.1 mmol) in methanol (10 mL) under nitrogen was treated with 10% palladium on activated charcoal (0.25 g, 5.0 mol%). The nitrogen atmosphere was then replaced by hydrogen. The solution was stirred for 4 h. It was then filtered through Celite, washed with saturated NaHCO₃ and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude amine that was used without further purification.

The crude amine was dissolved in aqueous HCl (2.0 M, 30 mL). A solution of NaNO₂ (0.50 g, 7.2 mmol, 1.4 equiv) in 6.0 mL H₂O was added dropwise. After 15 min, a solution of NaN₃ (0.40 g, 6.1 mmol, 1.2 equiv) in 6.0 mL H₂O was added carefully. The reaction mixture was stirred for 3 h. The solution was then extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 9:1) afforded compound 102 as a yellow oil (0.59 g, 61% yield).

**¹H NMR (400 MHz, CDCl₃):** δ 7.36 (td, J = 7.9, 1.3 Hz, 1H, C²−H), 7.25 (dd, J = 7.9, 1.3 Hz, 1H, C⁶−H), 7.19 (dd, J = 7.9, 1.1 Hz, 1H, C³−H), 7.14 (td, J = 7.9, 1.1 Hz, 1H, C¹−H), 3.73 (s, 3H, C¹⁰−H), 3.64 (s, 2H, C⁸−H).

**¹³C NMR (101 MHz, CDCl₃):** δ 171.6 (C⁹), 138.7 (C¹), 131.5 (C⁶), 128.8 (C²), 125.6 (C⁵), 124.8 (C¹), 118.2 (C³), 52.2 (C¹⁰), 36.5 (C⁸).

**IR:** 2953 (w), 2120 (s), 1737 (s), 1491 (m), 1286 (s), 1161 (s), 750 (s).

**HRMS:** (ESI⁺) m/z: [M + Na]⁺ Calcd for C₉H₈N₃NaO₂⁺: 214.0587; Found: 214.0592.

**Rf** (DCM) = 0.7.

dimethyl 2-(2-nitrophenyl)malonate 104
To a suspension of NaH (60% in oil, 0.60 g, 1.4 mmol, 2.2 equiv) in DMF (9.0 mL) at 0 °C was added dimethyl malonate (1.7 g, 1.3 mmol, 2.0 equiv) dropwise. A solution of o-fluoronitro-benzene (0.70 mL, 0.6 mmol) in DMF (2.0 mL) was then added dropwise. The solution was then heated at 70 °C for 2 h. The reaction mixture was then cooled down, quenched with saturated NH₄Cl, then extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 9:1) afforded compound 104 as a yellow oil (0.14 g, 89% yield). The spectroscopic data of this compound were in accord with those reported in the literature.²¹⁴

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\):} \delta 8.09 (dd, J = 7.8, 1.1 Hz, 1H, C³−H), 7.67 (td, J = 7.8, 1.1 Hz, 1H, C¹−H), 7.54 (td, J = 7.8, 1.4 Hz, 1H, C²−H), 7.52 (dd, J = 7.8, 1.4 Hz, 1H, C⁶−H), 5.35 (s, 1H, C⁷−H), 3.82 (s, 6H, C₁₀,₁₁−H).\]

\[ ^{13}C \text{ NMR (101 MHz, CDCl}_3\):} \delta 167.7 (C₈,₉), 148.7 (C⁴), 133.6 (C₁), 131.4 (C⁶), 129.4 (C²), 127.9 (C⁵), 125.3 (C³), 54.1 (C⁷), 53.2 (C₁₀,₁₁).\]

\[ R_f \text{ (DCM) = 0.17.}\]

**dimethyl 2-(2-azidoethyl)malonate 106**

To a suspension of NaH (60% in oil, 23 mg, 1.0 mmol, 1.3 equiv) in THF (1.0 mL) at 0 °C was added dimethyl malonate (0.10 g, 0.76 mmol) dropwise. After 15 minutes, 1-azido-2-iodoethane 97 (0.20 g, 1.0 mmol, 1.3 equiv) was added dropwise. The solution was then stirred at RT overnight. The reaction mixture was then cooled down, quenched with saturated NH₄Cl, then extracted with EtOAc. Purification by FCC (PE/EtOAc 8:2) afforded compound 106 as a yellow oil (0.14 g, 89% yield).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\):} \delta 3.79 (s, 6H, C₅,₇−H), 3.56 (t, J = 7.2 Hz, 1H, C¹−H), 3.42 (t, J = 6.6 Hz, 2H, C³−H), 2.20 (dt, J = 7.2, 6.5 Hz, 2H, C²−H).\]

\[ ^{13}C \text{ NMR (101 MHz, CDCl}_3\):} \delta 169.2 (C⁴,₆), 52.8 (C₅,₇), 49.1 (C¹), 48.7 (C³), 28.2 (C²).\]

\[ \text{IR:} 2955 \text{ (w)}, 2924 \text{ (w)}, 2853 \text{ (w)}, 2099 \text{ (s)}, 1732 \text{ (s)}, 1437 \text{ (m)}, 1343 \text{ (w)}, 1250 \text{ (m)}, 1155 \text{ (s).}\]

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HRMS: (ESI\(^+\)) m/z: [M + Na]\(^+\) Calcd for C\(_7\)H\(_{11}\)N\(_3\)NaO\(_4\): 224.0642; Found: 224.0635.

\(R_f\) (PE/EtOAc 7:3) = 0.67.

**allyl 4-azido-2-(2-nitrophenyl)butanoate 107**

![Reaction Scheme](image)

To a solution of acid 109 (0.60 g, 2.4 mmol) in DMF (4.8 mL) was added NaHCO\(_3\) (0.20 g, 2.6 mmol, 1.1 equiv) and allyl bromide (1.4 g, 12 mmol, 5.0 equiv). The solution was stirred at RT for 48 h. The mixture was then concentrated under reduced pressure, diluted with DCM, washed with H\(_2\)O, saturated NaHCO\(_3\) brine, dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. Purification by FCC (DCM) afforded compound 107 as a yellow oil (0.45 g, 65% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.95 (dd, \(J = 8.0, 1.2\) Hz, 1H, C\(_3\)−H), 7.61 (td, \(J = 8.0, 1.2\) Hz, 1H, C\(_1\)−H), 7.51-7.42 (m, 2H, C\(_2,6\)−H), 5.82 (ddt, \(J = 17.2, 10.6, 5.7\) Hz, 1H, C\(_{12}\)−H), 5.27-5.18 (m, 2H, C\(_{13}\)−H), 4.65-4.56 (m, 2H, C\(_{11}\)−H), 4.31 (t, \(J = 7.1\) Hz, 1H, C\(_7\)−H), 3.48-3.30 (m, 2H, C\(_9\)−H), 2.51 (m, 1H, C\(_8\)−H), 2.11 (m, 1H, C\(_8\)−H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 171.5 (C\(_{10}\)), 149.2 (C\(_4\)), 133.4 (C\(_1\)), 132.8 (C\(_5\)), 131.5 (C\(_{12}\)), 130.3 (C\(_6\)), 128.6 (C\(_2\)), 125.2 (C\(_3\)), 118.7 (C\(_{13}\)), 66.0 (C\(_{11}\)), 49.4 (C\(_9\)), 44.2 (C\(_7\)), 31.9 (C\(_8\)).

IR: 2926 (w), 2865 (w), 2361 (w), 2337 (w), 2097 (s), 1734 (s), 1526 (s), 1170 (s).

HRMS: (ESI\(^+\)) m/z: [M + Na]\(^+\) Calcd for C\(_{13}\)H\(_{14}\)N\(_4\)NaO\(_4\): 313.0907; Found: 313.09165.

\(R_f\) (DCM) = 0.49.

**7-azido-5-(2-nitrophenyl)hept-1-en-4-ol 112**

![Reaction Scheme](image)

To a solution of allylboronic acid pinacol ester (1.6 mL, 8.5 mmol, 1.7 equiv) in THF (20 mL)
at 0 °C was added the aldehyde 111 (1.2 g, 4.9 mmol). The solution was stirred at 0 °C for 3 h, and then at RT overnight. Saturated aqueous NaHCO₃ was added, and the mixture was stirred for 30 min at RT. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:1) afforded compound 112 as a yellow oil (1.2 g, 88% yield as an inseparable mixture of two diastereoisomers).

H NMR (400 MHz, CDCl₃): δ 7.72 (m, 1H, C³−H), 7.59 (m, 1H, C¹−H), 7.51 (m, 1H, C²−H), 7.40 (m, 1H, C⁶−H), 5.76 (m, 1H, C¹²−H), 5.23-5.10 (m, 2H, C¹³−H), 3.88 (m, 1H, C¹⁰−H), 3.36 (m, 1H, O¹⁴−H), 3.25-3.10 (m, 2H, C⁹−H), 2.36 (m, 1H, C⁷−H), 2.21-1.83 (m, 4H, C⁸,¹¹−H).

C NMR (101 MHz, CDCl₃): δ 151.9 (C⁴), 151.3 (C⁴), 135.4 (C⁵), 134.5 (C⁵), 133.9 (C¹²), 133.9 (C¹²), 132.5 (C¹), 132.3 (C¹), 129.9 (C⁶), 128.9 (C⁶), 127.7 (C²), 127.6 (C²), 124.1 (C³), 123.8 (C³), 119.3 (C¹³), 119.1 (C¹³), 73.5 (C¹⁰), 72.9 (C¹⁰), 49.5 (C⁹), 49.4 (C⁹), 42.2 (C¹¹), 41.5 (C¹¹), 39.9 (C⁷), 39.8 (C⁷), 32.0 (C⁸), 30.3 (C⁸).

IR: 3436 (w), 3079 (w), 2936 (w), 2878 (w), 2096 (s), 1730 (w), 1524 (s), 1355 (s), 1251 (m), 998 (m).

HRMS: (ESI⁺) m/z: [M + Na]⁺ Calcd for C₁₃H₁₆N₄NaO₃⁺: 299.1115; Found: 299.1124.

Rf (DCM) = 0.48.

**7-azido-5-(2-nitrophenyl)hept-1-en-4-one 110**

To a solution of alcohol 112 (3.0 mg, 0.010 mmol) in DCM (1.0 mL) was added DMP (8.0 mg, 0.020 mmol, 1.8 equiv). The solution was stirred at RT for 1 h. Aqueous 2% NaOH was then added and the solution was extracted with DCM. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded compound 110 as a yellow oil (2.2 mg, 80% yield).

H NMR (400 MHz, CDCl₃): δ 7.90 (dd, J = 7.9, 1.2 Hz, 1H, C³−H), 7.59 (td, J = 7.9, 1.2 Hz, 1H, C¹−H), 7.46 (td, J = 7.9, 1.1 Hz, 1H, C²−H), 7.33 (dd, J = 7.9, 1.1 Hz, 1H, C⁶−H), 5.81 (ddt, J = 17.1, 10.1, 6.9 Hz, 1H, C¹²−H), 5.14 (dd, J = 10.1, 1.2 Hz, 1H, C¹³−H), 5.04 (dd, J = 17.1, 1.2 Hz, 1H, C¹³−H), 4.48 (t, J = 7.1 Hz, 1H, C⁷−H), 3.35-3.13 (m, 4H, C⁸,¹¹−H), 2.38 (ddt,
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\[ J = 16.9, 7.1, 6.9 \text{Hz}, 1\text{H}, C^8\text{H} \], 1.94 (ddt, \( J = 16.9, 7.1, 6.9 \text{Hz}, 1\text{H}, C^8\text{H} \)).

\(^{13}\text{C NMR (101 MHz, CDCl}_3\)): \( \delta \) 205.7 (C\(^{10}\)), 150.0 (C\(^{4}\)), 133.4 (C\(^{1}\)), 131.9 (C\(^{5}\)), 129.9 (C\(^{9}\)), 129.7 (C\(^{12}\)), 128.7 (C\(^{2}\)), 125.0 (C\(^{3}\)), 119.5 (C\(^{13}\)), 49.2 (C\(^{9}\)), 49.0 (C\(^{7}\)), 47.0 (C\(^{11}\)), 31.4 (C\(^{8}\)).

\(\text{IR}\): 2958 (w), 2929 (w), 2854 (w), 2096 (s), 1716 (m), 1526 (s), 1350 (s), 1259 (s), 788 (s).

\(\text{HRMS}\): (ESI\(^+\)) m/z: [M + Na]\(^+\) Calcd for C\(_{13}\)H\(_{14}\)N\(_4\)NaO\(_3\): 297.0958; Found: 297.0969.

\( R_f \) (DCM) = 0.71.

**ethyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-acrylate 117**

Following a reported procedure,\(^{215}\) the acrylate 425 (1.2 g, 9.2 mmol) was dissolved in DCM (30 mL). Imidazole (1.6 g, 24 mmol, 2.5 equiv) was added slowly, followed by TBSCI (1.5 g, 10 mmol, 1.1 equiv). The mixture was stirred for 2 h and then quenched with saturated NaHCO\(_3\). The mixture was extracted with DCM. The combined organic phases were washed with brine, dried over Na\(_2\)SO\(_4\) and concentrated \(\text{in vacuo}\). Purification by FCC (PE/EtOAc 9:1) afforded compound 117 as a colorless oil (2.3 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.\(^{215}\)

\(^{1}\text{H NMR (400 MHz, CDCl}_3\)): \( \delta \) 6.25 (q, \( J = 2.0 \text{Hz}, 1\text{H}, C^4\text{H} \)), 5.90 (q, \( J = 2.0 \text{Hz}, 1\text{H}, C^4\text{H} \)), 4.37 (t, \( J = 2.0 \text{Hz}, 2\text{H}, C^3\text{H} \)), 4.22 (q, \( J = 7.1 \text{Hz}, 2\text{H}, C^5\text{H} \)), 1.30 (t, \( J = 7.1 \text{Hz}, 3\text{H}, C^6\text{H} \)), 0.92 (s, 9H, C\(^{10,11,12}\)–H), 0.09 (s, 6H, C\(^{7,8}\)–H).

\(^{13}\text{C NMR (101 MHz, CDCl}_3\)): \( \delta \) 166.0 (C\(^2\)), 139.9 (C\(^1\)), 123.6 (C\(^4\)), 61.5 (C\(^3\)), 60.5 (C\(^5\)), 25.9 (C\(^9\)), 18.4 (C\(^{10,11,12}\)), 14.2 (C\(^6\)), -5.4 (C\(^{7,8}\)).

\( R_f \) (DCM) = 0.17.

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((7-azido-5-(2-nitrophenyl)hept-1-en-4-yl)oxy)-triethylsilane 114

The compound 112 (0.10 g, 0.36 mmol) was dissolved in DCM (1.0 mL) at 0 °C. Imidazole (0.12 mL, 0.72 mmol, 2.0 equiv) and TESCl (0.10 g, 1.5 mmol, 4.0 equiv) were added. The reaction mixture was stirred for 1 h at 0 °C, then 1 h at RT. The solution was then quenched with saturated NaHCO₃ and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 9:1) afforded compound 114 as a yellow oil (97 mg, 69% yield as an inseparable mixture of two diastereoisomers).

1H NMR (400 MHz, CDCl₃): δ 7.72 (m, 1H, C3−H), 7.54 (m, 1H, C1−H), 7.47 (m, 1H, C2−H), 7.37 (m, 1H, C6−H), 5.72 (m, 1H, C12−H), 5.03-4.90 (m, 2H, C13−H), 3.96 (m, 1H, C10−H), 3.41-3.22 (m, 2H, C9−H), 3.11 (m, 1H, C7−H), 2.34-1.94 (m, 4H, C8,11−H), 1.02-0.85 (m, 9H, C15−H), 0.64-0.48 (m, 6H, C14−H).

13C NMR (101 MHz, CDCl₃): δ 151.2 (C4), 135.8 (C5), 135.1 (C5), 133.5 (C12), 133.4 (C12), 132.0 (C1), 132.0 (C1), 130.2 (C6), 129.8 (C6), 127.4 (C2), 127.4 (C2), 124.2 (C3), 123.9 (C3), 117.9 (C13), 75.0 (C10), 74.8 (C10), 49.6 (C7), 49.6 (C7), 40.7 (C9), 40.4 (C11), 40.0 (C11), 32.0 (C8), 28.3 (C8), 6.9 (C15), 5.0 (C14).

IR: 2957 (w), 2877 (w), 2099 (w), 1528 (w), 1355 (w), 905 (s), 726 (s).

HRMS: (ESI⁺) m/z: [M + H]⁺ Calcd for C19H31N4O3Si+: 391.2160; Found: 391.2179.

Rf (PE/EtOAc 9:1) = 0.59.

2-((tert-butyldimethylsilyloxy)methyl)acrylic acid 118

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Following a reported procedure,\(^{216}\) to a solution of acrylate 117 (20 mg, 0.080 mmol) in a mixture of THF/H\(_2\)O (1:1, 0.50 mL) was added LiOH (4.0 mg, 0.16 mmol, 2.0 equiv). The reaction mixture was stirred overnight at RT. It was then quenched with saturated NH\(_4\)Cl. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The crude product 118 thus obtained was used for the next step without further purification as a colorless oil (11 mg, 65% yield). The spectroscopic data of this compound were in accord with those reported in the literature.\(^{217}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.40 (q, \(J = 2.0\) Hz, 1H, C\(4^–\)H), 6.03 (q, \(J = 2.0\) Hz, 1H, C\(4^–\)H), 4.38 (t, \(J = 2.0\) Hz, 2H, C\(3^–\)H), 0.93 (s, 9H, C\(9,10,11^–\)H), 0.10 (s, 6H, C\(6,7^–\)H).

\(^13\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 170.5 (C\(2\)), 138.9 (C\(1\)), 126.4 (C\(3\)), 61.3 (C\(3\)), 25.9 (C\(8\)), 18.4 (C\(9,10,11\)), -5.4 (C\(5,7\)).

\(R_f\) (PE/EtOAc 5:5) = 0.50.

6-azido-4-(2-nitrophenyl)-3-((triethylsilyl)oxy)-hexanal 128

To a solution of compound 114 (0.10 g, 0.25 mmol) in a mixture DCM/MeOH (1:1, 1.0 mL) at -78 °C was added NaHCO\(_3\) (60 mg, 0.63 mmol, 2.5 equiv). O\(_3\) was then bubbled through the solution for 20s. Argon was bubbled through the solution to remove the ozone and Me\(_2\)S (excess) was added to the solution. It was then allowed to warm up to RT. The mixture was stirred for 4h. The mixture was then filtered through Celite and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 9:1) afforded compound 128 as a slightly yellow oil (79 mg, 80% yield as an inseparable mixture of two diastereoisomers).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.69 (m, 1H, C\(12^–\)H), 7.76 (m, 1H, C\(3^–\)H), 7.59 (m, 1H, C\(1^–\)H), 7.49-7.31 (m, 2H, C\(2,6^–\)H), 4.53 (m, 1H, C\(10^–\)H), 3.42 (m, 1H, C\(7^–\)H), 3.23-3.05 (m, 2H, C\(9^–\)H), 2.64-2.42 (m, 2H, C\(11^–\)H), 2.39-1.83 (m, 2H, C\(8^–\)H), 1.03-0.85 (m, 9H, C\(14^–\)H), 0.70-0.55 (m, 6H, C\(13^–\)H).


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$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 200.2 (C$^{12}$), 200.2 (C$^{12}$), 151.4 (C$^4$), 134.4 (C$^5$), 133.4 (C$^5$), 132.4 (C$^1$), 132.1 (C$^1$), 130.1 (C$^6$), 129.1 (C$^6$), 128.1 (C$^2$), 128.0 (C$^2$), 124.3 (C$^3$), 123.8 (C$^3$), 70.9 (C$^{10}$), 70.1 (C$^{10}$), 50.1 (C$^7$), 49.4 (C$^7$), 43.1 (C$^{11}$), 41.8 (C$^{11}$), 31.6 (C$^8$), 30.1 (C$^8$), 6.9 (C$^{14}$), 5.0 (C$^{13}$).

IR: 2957 (w), 2877 (w), 2099 (s), 1725 (w), 1529 (s), 1356 (m), 1244 (w), 1114 (w), 1007 (w), 746 (m).

HRMS: (ESI$^+$) m/z: [M + Na]$^+$ Calcd for C$_{18}$H$_{28}$N$_4$NaO$_4$Si+: 415.1772; Found: 415.1781.

$R_f$ (PE/EtOAc 8:2) = 0.48.

7-azido-5-(2-nitrophenyl)hept-1-en-4-yl 2-((tert-butyldimethylsilyloxy)methyl)acrylate 119

To a solution of the alcohol 112 (40 mg, 0.15 mmol) and the acid 118 (40 mg, 0.18 mmol, 1.2 equiv) in DCM (1.0 mL) at 0°C was added DCC (0.16 g, 0.75 mmol, 5.0 equiv), followed by DMAP (9.4 mg, 0.080 mmol, 0.50 equiv). The reaction mixture was stirred for 30 min at 0°C, and then overnight at RT. The reaction was then quenched with saturated NaHCO$_3$. The mixture was extracted with DCM. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product 119 was then used without further purification as a yellow oil (16 mg, 22% yield as an inseparable mixture of two diastereoisomers).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.76 (m, 1H, C$^3$–H), 7.61 (m, 1H, C$^1$–H), 7.54-7.41 (m, 2H, C$^{6,2}$–H), 6.24 (m, 1H, C$^{16}$–H), 5.93 (m, 1H, C$^{16}$–H), 5.66 (m, 1H, C$^{12}$–H), 5.34 (m, 1H, C$^{10}$–H), 5.12-5.00 (m, 2H, C$^{13}$–H), 4.48-4.30 (m, 2H, C$^{17}$–H), 3.66 (m, 1H, C$^{7}$–H), 3.27-3.05 (m, 2H, C$^9$–H), 2.35-2.16 (m, 2H, C$^{11}$–H), 2.13 (m, 1H, C$^8$–H), 1.94 (m, 1H, C$^8$–H), 1.02-0.88 (m, 9H, C$^{20,21,22}$–H), 0.21-0.05 (m, 6H, C$^{18,19}$–H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 165.3 (C$^{14}$), 164.9 (C$^{14}$), 151.3 (C$^4$), 139.5 (C$^{15}$), 134.3 (C$^{12}$), 132.8 (C$^5$), 132.5 (C$^5$), 132.4 (C$^1$), 132.3 (C$^1$), 128.7 (C$^6$), 128.2 (C$^6$), 128.0 (C$^{16}$), 124.5 (C$^3$), 124.3 (C$^2$), 124.0 (C$^3$), 118.8 (C$^{13}$), 118.6 (C$^{13}$), 75.4 (C$^{10}$), 74.8 (C$^{10}$), 61.5 (C$^{17}$), 61.3 (C$^{17}$), 49.1
(C7), 49.0 (C7), 39.9 (C9), 39.6 (C9), 37.3 (C11), 37.2 (C11), 31.8 (C8), 30.6 (C8), 25.9 (C23), 18.4 (C20,21,22), -5.4 (C18,19).

IR: 2954 (w), 2930 (w), 2885 (w), 2857 (w), 2098 (m), 1715 (m), 1529 (s), 1356 (m), 1260 (s), 1091 (s), 839 (s), 780 (m).

HRMS: (ESI+) m/z: [M + Na]+ Calcd for C23H34N4NaO5Si+: 497.2191; Found: 497.2200.

Rf (PE/EtOAc 9.5:0.5) = 0.19.

eethyl 2-(diethoxyphosphoryl)acrylate 125

Following a reported procedure,44e a solution of paraformaldehyde (2.5 g, 82 mmol, 2.0 equiv) in MeOH (100 mL) and piperidine (0.40 mL, 4.1 mmol, 0.1 equiv) was stirred at RT. Triethyl phosphonoacetate (9.2 g, 41 mmol) was added over 30 minutes. The solution was then refluxed for 24 h. The solvent was evaporated under reduced pressure. The crude compound was dissolved in toluene (100 mL). p-Toluenesulfonic acid monohydrate (0.80 g, 4.1 mmol, 0.10 equiv) was added and the solution was refluxed with a Dean-Stark apparatus for 8 h. Purification by vacuum distillation (Bp = 90 °C/1.0 mbar) afforded compound 125 as a colorless oil (7.6 g, 78% yield). The spectroscopic data of this compound were in accord with those reported in the literature.218

1H NMR (400 MHz, CDCl3): δ 7.00 (dd, J = 42.0, 1.6 Hz, 1H, C2−H), 6.76 (dd, J = 20.4, 1.6 Hz, 1H, C2−H), 4.30 (q, J = 7.2 Hz, 2H, C4−H), 4.29-4.11 (m, 4H, C6,8−H), 1.41-1.30 (m, 9H, C5,7,9−H).

13C NMR (101 MHz, CDCl3): δ 163.8 (d, J = 16 Hz, C3), 143.3 (d, J = 5 Hz, C2), 133.2 (d, J = 186 Hz, C1), 62.8 (d, J = 6 Hz, C6,8), 61.6 (s, C4), 16.4 (d, J = 7 Hz, C7,9), 14.1 (s, C5).

Rf (EtOAc) = 0.44.

1-(2-nitrophenyl)propan-2-one 429

Following a reported procedure,\textsuperscript{51} to a solution of 2-(2-nitrophenyl)acetic acid (9.5 g, 52 mmol) in Ac\textsubscript{2}O (25 mL) at RT was added 1-methylimidazole (2.1 mL, 51 mmol, 0.5 equiv). The solution was stirred for 12 h. It was then poured into water. The crude product was extracted with Et\textsubscript{2}O. The combined organic layers were washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo}. The crude compound 429 thus obtained was used for the next step without further purification as a yellow oil. The spectroscopic data of this compound were in accord with those reported in the literature.\textsuperscript{219}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): $\delta$ 8.12 (dd, $J = 7.9, 1.1$ Hz, 1H, C\textsubscript{3}−H), 7.60 (td, $J = 7.9, 1.1$ Hz, 1H, C\textsubscript{1}−H), 7.47 (td, $J = 7.9, 1.2$ Hz, 1H, C\textsubscript{2}−H), 7.28 (dd, $J = 7.9, 1.2$ Hz, 1H, C\textsubscript{6}−H), 4.13 (s, 2H, C\textsubscript{7}−H), 2.33 (s, 3H, C\textsubscript{9}−H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): $\delta$ 203.7 (C\textsubscript{8}), 148.7 (C\textsubscript{4}), 133.7 (C\textsubscript{1}), 133.6 (C\textsubscript{6}), 130.5 (C\textsubscript{5}), 128.5 (C\textsubscript{2}), 125.4 (C\textsubscript{3}), 48.7 (C\textsubscript{7}), 30.1 (C\textsubscript{9}).

$R_f$(PE/EtAc 6.5:3.5) = 0.5.

3-(2-nitrophenyl)but-3-en-2-one 135

Following a reported procedure,\textsuperscript{51} a solution of crude 1-(2-nitrophenyl)propan-2-one 429 (From 52 mmol of 2-(2-nitrophenyl)acetic acid), morpholine (1.1 g, 13 mmol, 0.25 equiv), and 37% HCHO in H\textsubscript{2}O (13 mL) in AcOH (55 mL) was heated at 100 °C for 24 h. The solution was concentrated under reduced pressure, and Et\textsubscript{2}O and H\textsubscript{2}O were added. The organic layer was separated, washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 8:2) afforded compound 135 as a slightly yellow wax (2.3 g, 23% yield in two

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steps). The spectroscopic data of this compound were in accord with those reported in the literature.51

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.10 (dd, $J = 7.8, 1.2$ Hz, 1H, C$_3^-$H), 7.64 (td, $J = 7.8, 1.2$ Hz, 1H, C$_1^-$H), 7.52 (td, $J = 7.8, 1.3$ Hz, 1H, C$_2^-$H), 7.32 (dd, $J = 7.8, 1.3$ Hz, 1H, C$_6^-$H), 6.29 (s, 1H, C$_{10}^-$H), 6.02 (s, 1H, C$_{10}^-$H), 2.49 (s, 3H, C$_9^-$H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 197.3 (C$_8$), 148.4 (C$_4$), 133.7 (C$_1$), 133.4 (C$_5$), 132.1 (C$_6$), 129.3 (C$_7$), 129.3 (C$_2$), 125.6 (C$_{10}$), 124.6 (C$_3$), 26.3 (C$_9$).

$R_f$(PE/Et$_2$O 8:2) = 0.07.

ethyl 2,5-dihydrothiophene-3-carboxylate 430

Following a reported procedure,44b a solution of 1,4-dithiane-2,5-diol (0.46 g, 3.0 mmol, 0.60 equiv) and Et$_3$N (0.90 mL, 6.5 mmol, 1.3 equiv) in DCM (37 mL) was heated at reflux. A solution of the acrylate 125 (1.2 g, 5.0 mmol) in DCM (5.0 mL) was added dropwise. The reaction mixture was stirred at reflux for 4 h. When the reaction was finished, the mixture was cooled down, diluted with DCM, washed with HCl (5%), brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification by vacuum distillation (Bp = 190°C/1.5 mbar) afforded compound 430 as a colorless oil (0.59 g, 75% yield). The spectroscopic data of this compound were in accord with those reported in the literature.220

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.91 (m, 1H, C$_1$H), 4.24 (q, $J = 7.1$ Hz, 2H, C$_6$H), 4.01-3.85 (m, 4H, C$_3$-$^4$H), 1.32 (t, $J = 7.1$ Hz, 3H, C$_7$H).

$R_f$(PE/Et$_2$O 8:2) = 0.42.

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ethyl 2,5-dihydrothiophene-3-carboxylate 1,1-dioxide 131

Following a reported procedure, a solution of 430 (0.30 g, 1.9 mmol) in DCM (3.0 mL) was stirred at 0 °C when a solution of mCPBA (0.85 g, 3.8 mmol, 2.0 equiv) in DCM (10 mL) was added dropwise. The mixture was allowed to warm up slowly (3 h) and then stirred overnight at RT. The solution was then filtered, washed with saturated Na2CO3, brine, dried over Na2SO4, and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded compound 131 as a colorless oil (0.31 g, 86% yield).

1H NMR (400 MHz, CDCl3): δ 7.03 (m, 1H, C1−H), 4.28 (q, J = 7.1 Hz, 2H, C6−H), 4.03-3.98 (m, 4H, C3,4−H), 1.32 (t, J = 7.1 Hz, 3H, C7−H).

13C NMR (101 MHz, CDCl3): δ 162.0 (C5), 133.1 (C1), 130.3 (C2), 61.8 (C3), 57.8 (C6), 55.1 (C4), 14.2 (C7).

IR: 2983 (w), 2939 (w), 1716 (s), 1632 (w), 1316 (s), 1266 (s), 1213 (s), 1135 (m), 1072 (s), 1018 (w), 731 (w).

HRMS: (ESI+) m/z: [M + Na]+ Calcd for C7H10NaO4S+: 213.0197; Found: 213.0203.

Rf (PE/Et2O 8:2) = 0.07.

((4-azido-2-(2-nitrophenyl)but-1-en-1-yl)oxy)(tert-butyl)dimethylsilane 431

A solution of the aldehyde 111 (0.10 g, 0.43 mmol) in DCM (1.0 mL) was stirred at 0 °C. Et3N (0.30 mL, 2.1 mmol, 5.0 equiv) was added, followed by TBSOTf (0.20 mL, 0.86 mmol, 2.0 equiv). The reaction mixture was stirred for 5 h at 0 °C. DCM was added, followed by aqueous 5% NaHCO3. The mixture was extracted with DCM. The combined organic phases were washed with brine, dried over Na2SO4 and concentrated in vacuo. Purification by FCC (PE/EtOAc 9:1)
afforded compound 431 as a yellow oil (75 mg, 50% yield as a mixture of inseparable isomers. Ratio: 1:1.5).

\(^1\text{H NMR (400 MHz, CDCl}_3\): } \Delta 7.87 \text{ (dd, } J = 7.9, 1.4 \text{ Hz, 1H, C}^3\text{−H, minor), 7.81 \text{ (dd, } J = 8.0, 1.5 \text{ Hz, 1H, C}^4\text{−H, major), 7.58-7.49 \text{ (m, 2H, C}^1\text{−H, minor+major), 7.42-7.30 \text{ (m, 4H, C}^{2,6}\text{−H, minor+major), 6.35 \text{ (s, 1H, C}^{10}\text{−H, minor), 6.33 \text{ (s, 1H, C}^{10}\text{−H, major), 3.35 \text{ (t, } J = 7.3 \text{ Hz, 2H, C}^8\text{−H, minor), 2.61 \text{ (t, } J = 7.3 \text{ Hz, 2H, C}^8\text{−H, minor}), 0.96 \text{ (s, 9H, C}^{14,15,16}\text{−H, major), 0.71 \text{ (s, 9H, C}^{14,15,16}\text{−H, minor), 0.18 \text{ (s, 6H, C}^{11,12}\text{−H, major), 0.03 \text{ (s, 6H, C}^{11,12}\text{−H, minor).}}

\(^{13}\text{C NMR (101 MHz, CDCl}_3\): } \Delta 150.0 \text{ (C}^4\text{, minor+major), 140.7 \text{ (C}^{10}\text{, major), 138.8 \text{ (C}^{10}\text{, minor), 134.4 \text{ (C}^1\text{, major + minor), 132.4 \text{ (C}^5\text{, minor + major), 131.2 \text{ (C}^6\text{, major + minor), 127.9 \text{ (C}^2\text{, major), 127.7 \text{ (C}^2\text{, minor), 124.4 \text{ (C}^3\text{, major), 124.3 \text{ (C}^3\text{, minor), 115.9 \text{ (C}^7\text{, major), 113.6 \text{ (C}^7\text{, minor), 50.5 \text{ (C}^9\text{, minor), 49.6 \text{ (C}^9\text{, major), 32.5 \text{ (C}^8\text{, minor), 28.6 \text{ (C}^8\text{, major), 25.7 \text{ (C}^{14,15,16}\text{, major), 25.4 \text{ (C}^{14,15,16}\text{, minor), 18.3 \text{ (C}^{18}\text{, major), 18.1 \text{ (C}^{18}\text{, minor), -5.2 \text{ (C}^{11,12}\text{, major), -5.5 \text{ (C}^{11,12}\text{, minor).}}

\text{IR: } 2954 \text{ (w), 2931 \text{ (w), 2858 \text{ (w), 2095 \text{ (m), 1650 \text{ (w), 1527 \text{ (s), 1353 \text{ (w), 1256 \text{ (m), 1179 \text{ (s), 838 \text{ (s), 784 \text{ (s).}}}

\text{HRMS: (ESI\textsuperscript{+}) m/z: [M + Na\textsuperscript{+} Calcd for C}_{16}\text{H}_{24}\text{N}_4\text{NaO}_3\text{Si}: 371.1510; Found: 371.1505.}}

R_f(PE/Et}_2\text{O 9:1) = 0.58.}

\text{tert-butyl(dimethyl((3-(2-nitrophenyl)but-3-en-2-yl)oxy)silane 432}

\text{Diisopropylamine (0.040 mL, 0.29 mmol, 1.4 equiv) was stirred at -78 °C when } n\text{-BuLi was added dropwise (1.6 M solution in Et}_2\text{O, 0.18 mL, 0.29 mmol, 1.4 equiv)). } \text{The solution was stirred for 30 minutes. THF (1.0 mL) was then added and the solution was stirred for 5 minutes. A solution of ketone 135 (40 mg, 0.21 mmol) in THF (0.50 mL) was added dropwise. The reaction mixture was stirred for 30 minutes. TBSCI (44 mg, 0.29 mmol, 1.4 equiv) was then added. The solution was stirred for 30 minutes, then 15 minutes at RT. It was then quenched with saturated NaHCO}_3. \text{The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na}_2\text{SO}_4 \text{and concentrated in vacuo. Purification by FCC (PE/Et}_2\text{O 9.5:0.5) afforded compound 432 as a yellow oil (9.6 mg, 15% yield).}
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**1H NMR (400 MHz, CDCl$_3$):** δ 7.85 (dd, $J = 7.8, 0.9$ Hz, 1H, C$_3$–H), 7.65–7.56 (m, 2H, C$_2$–H), 7.39 (td, $J = 7.8, 1.1$ Hz, 1H, C$_1$–H), 5.66 (s, 1H, C$_{10}$–H), 5.44 (s, 1H, C$_{10}$–H), 4.48 (m, 1H, C$_9$–H), 3.45 (m, 1H, C$_9$–H), 1.02 (s, 9H, C$_{14,15,16}$–H), 0.37 (s, 3H, C$_{11}$–H), 0.10 (s, 3H, C$_{12}$–H).

**13C NMR (101 MHz, CDCl$_3$):** δ 155.1 (C$_8$), 149.0 (C$_4$), 143.7 (C$_7$), 135.6 (C$_5$), 132.8 (C$_1$), 132.5 (C$_6$), 128.7 (C$_2$), 124.2 (C$_3$), 115.8 (C$_{10}$), 95.6 (C$_9$), 25.9 (C$_{14,15,16}$), 18.4 (C$_{13}$), -4.5 (C$_{11,12}$).

**IR:** 2956 (w), 2930 (w), 2857 (w), 1586 (w), 1529 (s), 1472 (w), 1350 (s), 1257 (m), 1218 (m), 1017 (m), 826 (s), 784 (s).

**HRMS:** (ESI$^+$) m/z: [M + H]$^+$ Calcd for C$_{16}$H$_{24}$NO$_3$Si+: 306.1520; Found: 306.1526.

**$R_f$ (PE/Et$_2$O 9:1) = 0.33.**

**ethyl 4-hydroxy-2-methylenebutanoate 140**

Following a reported procedure,$^{221}$ to a solution of the acrylate 99 (2.5 g, 11 mmol) in a mixture of THF/H$_2$O (1:1, 33 mL) was added indium (1.3 g, 11 mmol, 1.0 equiv) followed by aqueous 37% formaldehyde (0.75 mL, 11 mmol, 1.0 equiv). The mixture was stirred at RT overnight. The reaction was quenched with HCl (2.0 M) and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (PE/EtOAc 5:1) afforded compound 140 as a yellow oil (1.6 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.$^{221}$

**1H NMR (400 MHz, CDCl$_3$):** δ 6.25 (s, 1H, C$_4$–H), 5.69 (s, 1H, C$_4$–H), 4.24 (q, $J = 7.1$ Hz, 2H, C$_7$–H), 3.83 (t, $J = 5.7$ Hz, 2H, C$_5$–H), 2.61 (t, $J = 5.7$ Hz, 2H, C$_3$–H), 1.32 (t, $J = 7.1$ Hz, 3H, C$_8$–H), OH peak not observed.

**13C NMR (101 MHz, CDCl$_3$):** 168.3 (C$_2$), 137.7 (C$_1$), 127.8 (C$_4$), 62.4 (C$_5$), 61.5 (C$_7$), 35.4 (C$_3$), 14.2 (C$_8$).

**$R_f$ (PE/EtOAc 9:1) = 0.07.**

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ethyl 2-methylene-4-((methylsulfonyl)oxy)-butanoate 433

To a solution of the acrylate 140 (3.0 g, 20 mmol) in DCM (70 mL) at 0 °C was added Et$_3$N (5.7 mL, 40 mmol, 2.0 equiv) followed by MsCl (3.2 mL, 40 mmol, 2.0 equiv). The mixture was stirred at RT overnight. The reaction was quenched with saturated NH$_4$Cl and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (PE/EtOAc 9:1) afforded compound 433 as a yellow oil (4.4 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.$^{222}$

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.31 (s, 1H, C$^4$−H), 5.73 (d, J = 1.0 Hz, 1H, C$^4$−H), 4.37 (t, J = 6.6 Hz, 2H, C$^5$−H), 4.22 (q, J = 7.1 Hz, 2H, C$^7$−H), 2.99 (s, 3H, C$^9$−H), 2.76 (t, J = 6.6 Hz, 2H, C$^3$−H), 1.31 (t, J = 7.1 Hz, 3H, C$^8$−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): 166.3 (C$^2$), 135.2 (C$^1$), 128.4 (C$^4$), 68.0 (C$^5$), 61.0 (C$^7$), 37.4 (C$^9$), 32.3 (C$^3$), 14.2 (C$^8$).

$R_f$ (PE/EtOAc 8:2) = 0.16.

ethyl 4a-morpholino-1,4,4a,5,6,7,8,8a-octahydro-naphthalene-2-carboxylate 132

To a solution of 1-(N-morpholino)cyclohex-1-ene (22 mg, 0.13 mmol) in dioxane (0.50 mL) was added 131 (30 mg, 0.16 mmol, 1.2 equiv). The solution was then heated by microwave irradiation (150 W) at 120 °C for 2 h. HCl (1.0 M) was added and the reaction mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over

Na$_2$SO$_4$ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded compounds 132, 133 and 134. The spectroscopic data of compound 134 were in accord with those reported in the literature.$^{223}$

**Compound 132:**

Red oil, 12 mg, 30% yield.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.83 (m, 1H, C$^8$−H), 4.19 (q, $J = 7.1$ Hz, 2H, C$^{17}$−H), 3.76-3.57 (m, 4H, C$^{12,13}$−H), 2.60-2.41 (m, 4H, C$^{11,14}$−H), 2.45 (m, 1H, C$^7$−H), 2.30-2.20 (m, 2H, C$^{7,10}$−H), 2.09 (d, $J = 19.2$ Hz, 1H, C$^{10}$−H), 1.99 (m, 1H, C$^5$−H), 1.68-1.21 (m, 11H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 167.5, 136.8, 128.3, 68.0, 60.3, 44.8, 33.6, 32.0, 29.7, 28.1, 27.5, 27.4, 22.7, 21.8, 14.3.

IR: 2925 (m), 2852 (w), 2811 (w), 1708 (s), 1658 (w), 1451 (w), 1247 (s), 1155 (m), 1118 (s).

HRMS: (ESI$^+$) m/z: [M + H]$^+$ Calcd for C$_{17}$H$_{28}$NO$_3$ $^+$: 294.2069; Found: 294.2070.

$R_f$(PE/EtOAc 8:2) = 0.38.

**Compound 133:**

yellow oil, 7.0 mg, 24% yield as an inseparable mixture of two diastereoisomers.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.87-5.67 (m, 1H, C$^9$−H), 5.24-5.03 (m, 2H, C$^{10}$−H), 4.24-4.05 (m, 2H, C$^{13}$−H), 3.24-3.06 (m, 1H, C$^8$−H), 2.44-2.22 (m, 4H, C$^{5,3}$−H), 2.15-2.00 (m, 2 H), 1.91-1.79 (m, 1 H), 1.72-1.60 (m, 2 H), 1.44-1.30 (m, 1 H), 1.29-1.21 (m, 4H, C$^{12}$−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 174.0, 173.9, 136.0, 135.9, 117.7, 117.3, 60.7, 48.1, 47.9, 47.8, 42.3, 34.6, 34.2, 31.7, 31.6, 28.2, 28.1, 25.2, 14.2.

HRMS: (ESI$^+$) m/z: [M + H]$^+$ Calcd for C$_{13}$H$_{21}$O$_3$ $^+$: 225.1491; Found: 225.1495.

$R_f$(PE/EtOAc 8:2) = 0.67.

**Compound 134:**

slightly yellow oil, 8.0 mg, 20% yield (calculated based on sulfonene 131).

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**1H NMR (400 MHz, CDCl₃):** δ 6.96 (m, 1H, C⁴−H), 5.88 (dd, J = 17.5, 10.7 Hz, 1H, C⁷−H), 5.15 (dd, J = 10.7, 0.5 Hz, 1H, C⁸−H), 5.11 (dd, J = 17.5, 0.5 Hz, 1H, C⁸−H), 4.24-4.10 (m, 4H, C₁¹₁,₁₄−H), 2.80 (m, 1H, C³−H), 2.40-2.28 (m, 3H, C³,₆−H), 2.07 (m, 1H, C¹−H), 1.78 (m, 1H, C¹−H), 1.31-1.21 (m, 6H, C₁₀,₁₃−H).

**13C NMR (101 MHz, CDCl₃):** δ 174.4 (C₁²), 167.0 (C⁹), 139.6 (C⁷), 136.8 (C⁴), 129.6 (C⁵), 115.1 (C⁸), 61.0 (C¹¹), 60.4 (C¹₄), 47.2 (C²), 32.2 (C³), 29.7 (C⁶), 21.7 (C¹), 14.3 (C¹₃), 14.1 (C¹₀).

**HRMS:** (ESI⁺) m/z: [M + H]⁺ Calcd for C₁₄H₂₁O₄⁺: 253.1440; Found: 253.1438.

**Rf (PE/EtOAc 8:2) = 0.67.**

**ethyl 4-azido-2-methylenebutanoate 434**

Following a known procedure, mesylate 433 (0.50 g, 2.3 mmol) was dissolved in DMF (25 mL). NaN₃ (0.22 g, 3.4 mmol, 1.5 equiv) was added and the solution was heated to 60 °C overnight. The reaction was allowed to cool down to room temperature, and saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 9:1) afforded azide 434 as a colorless oil (0.27 g, 71%). The spectroscopic data of this compound were in accord with those reported in the literature.

**1H NMR (400 MHz, CDCl₃):** δ 6.29 (s, 1H, C⁵−H), 5.69 (s, 1H, C⁵−H), 4.23 (q, J = 7.1 Hz, 2H, C⁶−H), 3.44 (t, J = 6.9 Hz, 2H, C¹−H), 2.61 (t, J = 6.9 Hz, 2H, C²−H), 1.31 (t, J = 7.2 Hz, 3H, C⁷−H).

**13C NMR (101 MHz, CDCl₃):** δ 166.5 (C⁴), 137.0 (C⁵), 127.6 (C³), 61.0 (C⁶), 50.1 (C¹), 31.9 (C²), 14.3. (C⁷).

**IR:** 2983 (w), 2935 (w), 2095 (s), 1713 (s), 1447 (w), 1299 (m), 1199 (s), 1150 (s), 1024 (m), 953 (m).

**Rf (PE/EtOAc 8:2) = 0.82.**
4-azido-2-methylenebutan-1-ol 435

To a solution of ester 434 (50 mg, 0.32 mmol) in THF (5.0 mL) was added dropwise DIBAL-H (1 M solution in toluene, 0.96 mL, 0.96 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 16 h. Saturated Rochelle’s salts was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude alcohol 435 was used directly in the next step without further purification.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.16 (s, 1H, C1−H), 4.99 (s, 1H, C1−H), 4.11 (s, 2H, C4−H), 3.44 (t, $J = 7.0$ Hz, 2H, C5−H), 2.39 (t, $J = 7.0$ Hz, 2H, C3−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 145.3 (C2), 112.7 (C1), 66.0 (C4), 50.0 (C5), 32.4 (C3).

IR: 3338 (br w), 2928 (w), 2875 (w), 2090 (s), 1263 (m), 1023 (m), 904 (m).

No HRMS could be obtained from this structure due to its instability.

$R_f$ (PE/EtOAc 7:3) = 0.33.

4-azido-2-methylenebutan-1-al 139

To a solution of alcohol 435 (40 mg, 0.31 mmol) in DMSO (2.0 mL) was added IBX (0.18 g, 0.62 mmol, 2.0 equiv) and the reaction mixture was stirred for 1 h. The mixture was filtered, saturated NaHCO$_3$ was added and the mixture was extracted with Et$_2$O. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (PE/EtOAc 7:3) afforded aldehyde 139 as a colorless oil (35 mg, 90%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.55 (s, 1H, C4−H), 6.40 (s, 1H, C1−H), 6.15 (s, 1H, C1−H), 3.41 (t, $J = 6.8$ Hz, 2H, C5−H), 2.55 (t, $J = 6.8$ Hz, 2H, C3−H).
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$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 194.0 (C$_4$), 146.3 (C$_2$), 136.4 (C$_1$), 49.3 (C$_5$), 27.9 (C$_3$).

IR: 2932 (w), 2823 (w), 2090 (s), 1686 (s), 1260 (m), 954 (m).

No HRMS could be obtained from this structure due to its instability.

$R_f$ (PE/EtOAc 7:3) = 0.59.

4-(<i>tert</i>-butyldimethylsilyloxy)-2-(2-nitrophenyl)butan-1-ol 146

To a solution of ester 145 (50 mg, 0.14 mmol) in THF (5.0 mL) was added dropwise DIBALH (1 M solution in toluene, 0.42 mL, 0.42 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 0.5 h. Saturated Rochelle's salts was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (9:1 PE/EtOAc) afforded the desired alcohol 146 as a yellow oil (32 mg, 71% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.74 (m, 1H, C$_2^–$H), 7.56-7.54 (m, 2H, C$_3^–$5$^–$H), 7.35 (m, 1H, C$_4^–$H), 3.85 (dd, $J = 4.4$ Hz, 2H, C$_{10}^–$H), 3.70 (m, 1H, C$_9^–$H), 3.60 (m, 1H, C$_9^–$H), 3.47 (m, 1H, C$_7^–$H), 2.03 (m, 1H, C$_8^–$H), 1.93 (m, 1H, C$_8^–$H), 0.88 (s, 9H, C$_{14}^–$H), 0.03 (s, 3H, C$_{12}^–$H), 0.03 (s, 3H, C$_{12}^–$H), OH peak not observed.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 150.6 (C$_1$), 137.8 (C$_6$), 132.7 (C$_3$), 129.0 (C$_5$), 127.3 (C$_4$), 124.2 (C$_2$), 66.7 (C$_{10}$), 61.7 (C$_9$), 40.2 (C$_7$), 35.9 (C$_8$), 26.0 (C$_{14}$), 18.3 (C$_{13}$), -5.4. (C$_{12}$).

IR: 3366 (br w), 2930 (m), 2857 (m), 1527 (s), 1358 (m), 1256 (w), 837 (s).

HRMS: (ESI$^+$) m/z: [M + H]$^+$ Calcd for C$_{16}$H$_{28}$NO$_4$Si$: 326.1782; Found: 326.1792.

$R_f$ (PE/EtOAc 8:2) = 0.32.
3-(2-nitrophenyl)tetrahydrofuran 147

To a solution of the alcohol 146 (63 mg, 0.19 mmol) in Et₂O (2.0 mL) was added triethylamine (60 μL, 0.43 mmol, 2.2 equiv) followed by MsCl (16 μL, 0.21 mmol, 1.1 equiv). After 1 h, the reaction was quenched with saturated NaHCO₃ and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude mesyl alcohol was dissolved in toluene (2.0 mL), and DBU (40 μL, 0.29 mmol, 1.5 equiv) was added. The reaction was stirred for 0.5 h at room temperature. Water was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (9:1 PE/EtOAc) afforded the side-product 147 as a yellow oil (33 mg, 90% yield). The desired elimination product 142 was not observed.

¹H NMR (400 MHz, CDCl₃): δ 7.77 (m, 1H, C₂−H), 7.61-7.52 (m, 2H, C₃,₅−H), 7.35 (m, 1H, C₄−H), 4.08-3.99 (m, 2H, C₉,₁₀−H), 3.96-3.81 (m, 3H, C₇,₉,₁₀−H), 2.49 (m, 1H, C₈−H), 2.04 (m, 1H, C₈−H).

¹³C NMR (101 MHz, CDCl₃): δ 150.3 (C¹), 138.4 (C⁶), 133.1 (C³), 128.2 (C⁵), 127.2 (C⁴), 124.0 (C²), 74.4 (C¹₀), 68.3 (C⁹), 39.5 (C⁷), 34.8 (C⁸).

IR: 2930 (w), 2866 (w), 1525 (s), 1355 (m).

HRMS: (ESI⁺) m/z: [M + H]⁺ Calcd for C₁₀H₁₂NO₃⁺: 194.0812; Found: 194.0811.

Rf (PE/EtOAc 8:2) = 0.26.
To a solution of the alcohol 146 (50 mg, 0.15 mmol) in pyridine (1.0 mL) at 0 °C was added tosyl chloride (44 mg, 0.23 mmol, 1.5 equiv). The solution was stirred at room temperature for 2 h. Aqueous 1 M HCl was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (9:1 PE/EtOAc) afforded the tosylate 149 as a yellow oil (58 mg, 80% yield).

$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.74 (dd, $J$ = 8.1,1.3 Hz, 1H, C$_2$−H), 7.65 (d, $J$ = 8.3 Hz, 2H, C$_{16}$−H), 7.52 (td, $J$ = 7.5,1.4 Hz, 1H, C$_4$−H), 7.42 (dd, $J$ = 7.9,1.3 Hz, 1H, C$_5$−H), 7.36 (m, 1H, C$_3$−H), 7.35-7.18 (m, 2H, C$_{17}$−H), 4.28 (d, $J$ = 5.3 Hz, 2H, C$_{10}$−H), 3.73 (m, 1H, C$_7$−H), 3.52 (m, 1H, C$_9$−H), 3.41 (m, 1H, C$_9$−H), 2.43 (s, 3H, C$_{19}$−H), 2.00-1.91 (m, 2H, C$_8$−H), 0.80 (s, 9H, C$_{14}$−H), -0.09 (s, 3H, C$_{12}$−H), -0.09 (s, 3H, C$_{12}$−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 150.5 (C$_1$), 144.8 (C$_{15}$), 134.6 (C$_6$), 132.6 (C$_4$), 132.6 (C$_{18}$), 129.8 (C$_{17}$), 129.5 (C$_5$), 127.8 (C$_{16}$), 127.3 (C$_3$), 124.5 (C$_2$), 72.6 (C$_{10}$), 60.0 (C$_9$), 35.8 (C$_7$), 34.2 (C$_8$), 25.8 (C$_{14}$), 21.7 (C$_{19}$), 18.2 (C$_{13}$), -5.6 (C$_{12}$).

IR: 2953 (w), 2930 (w), 2857 (w), 1527 (s), 1358 (s), 1177 (s), 1098 (m), 966 (m), 837 (s), 780 (s).

HRMS: (ESI$^+$) m/z: [M + Na]$^+$ Calcd for C$_{23}$H$_{33}$NNaO$_6$Si$^+$: 502.1690; Found: 502.1699.

$R_f$ (PE/EtOAc 8:2) = 0.5.
tert-butyldimethyl((3-(2-nitrophenyl)but-3-en-1-yl)oxy)silane 142

![Chemical Structure](image)

To a solution of the tosylate 149 (20 mg, 0.042 mmol) in glyme (0.50 mL) was added NaI (13 mg, 0.065 mmol, 2.0 equiv) and DBU (12 μL, 0.065 mmol, 2.0 equiv). The mixture was heated at 80 °C overnight. Saturated NaHCO₃ was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (95:5 PE/EtOAc) afforded the olefin 142 as a yellow oil (10 mg, 78% yield).

**¹H NMR (400 MHz, CDCl₃):** δ 7.88 (dd, J = 7.8, 1.1 Hz, 1H, C²−H), 7.54 (td, J = 7.8, 1.3 Hz, 1H, C³−H), 7.40 (m, 1H, C⁴−H), 7.34 (dd, J = 7.8, 1.3 Hz, 1H, C⁵−H), 5.22 (q, J = 1.2 Hz, 1H, C¹⁰−H), 5.03 (m, 1H, C¹⁰−H), 3.69 (t, J = 6.8 Hz, 2H, C⁹−H), 2.59 (td, J = 6.8, 0.8 Hz, 2H, C⁸−H), 0.85 (s, 9H, C¹⁴−H), -0.01 (s, 6H, C¹²−H).

**¹³C NMR (101 MHz, CDCl₃):** δ 148.2 (C¹), 144.5 (C⁶), 138.3, (C⁹), 132.6 (C⁵), 131.4 (C³), 128.0 (C⁴), 124.1 (C²), 116.1 (C¹⁰), 61.8 (C⁹), 40.0 (C⁸), 25.9 (C¹⁴), 18.2 (C¹³), -5.4 (C¹²).

**IR:** 2953 (w), 2929 (w), 2885 (w), 2856 (w), 1527 (s), 1471 (w), 1349 (m), 1255 (m), 1096 (s), 933 (w), 906 (w), 834 (s), 776 (s).

**HRMS:** (ESI⁺) m/z: [M + H]⁺ Calcd for C₁₆H₂₆NO₃Si⁺: 308.1676; Found: 308.1700.

**R_f** (PE/EtOAc 8:2) = 0.8.
8.3 Experimental Procedures of Chapter 3

3-ethoxycyclopent-2-en-1-one 217

Following a reported procedure,\textsuperscript{224} to a solution of 1,3-cyclopentadione (20 g, 0.20 mol) and EtOH (46 mL, 0.83 mol, 4.0 equiv) in toluene (200 mL) was added $p$-TsOH (0.3 g, 2.0 mmol, 1.0 mol%). The reaction mixture was heated at refluxing temperature for 16 h. Water was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na$_2$SO$_4$, and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 9:1) afforded pure enone 217 as a yellow oil (21 g, 80% yield). The spectroscopic data of this compound were in accord with those reported in the literature.\textsuperscript{225}

\textbf{1H NMR (400 MHz, CDCl$_3$):} $\delta$ 5.28 (s, 1H, C$_2$−H), 4.04 (q, $J = 7.1$ Hz, 2H, C$_6$−H), 2.62-2.58 (m, 2H, C$_5$−H), 2.46-2.41 (m, 2H, C$_4$−H), 1.41 (t, $J = 7.1$ Hz, 3H, C$_7$−H).

\textbf{13C NMR (101 MHz, CDCl$_3$):} $\delta$ 206.1 (C$_1$), 190.2 (C$_3$), 104.7 (C$_2$), 67.7 (C$_6$), 34.0 (C$_5$), 28.6 (C$_4$), 14.2 (C$_7$).

\textbf{R$_f$ (EtOAc) = 0.46.}

3-(3-hydroxypropyl)cyclopent-2-en-1-one 218

Following a reported procedure,\textsuperscript{22} to a solution of 3-chloropropanol (2.4 mL, 29 mmol, 2.0 equiv) in THF (45 mL) at -78 °C was added dropwise a solution of MeMgCl (3 M in THF, 9.5 mL, 29 mmol, 2.0 equiv). The solution was allowed to warm to RT. When no more gas was produced, magnesium turning (0.76 g, 31 mmol, 2.2 equiv) was added and the mixture was

\textsuperscript{224}Kikani, B. B.; McKee, J. R.; Zanger, M. \textit{Synthesis} 1991, 23, 176–176

\textsuperscript{225}Reimann, E; Poeschl, K \textit{Pharmazie} 1995, 50, 589–592
heated at reflux for 3 h. To the above freshly prepared Grignard reagent solution at refluxing temperature was added dropwise a solution of 3-ethoxycyclopent-2-en-1-one 217 (1.8 g, 14 mmol) in THF (45 mL) over 20 min. The reaction mixture was stirred at refluxing temperature for 2 h before being allowed to cool down to RT. The reaction was quenched by slow addition of saturated aqueous NH₄Cl. DCM and 2 M HCl was added to the reaction mixture and the biphasic reaction mixture was stirred vigorously for 3 h. The layers were separated and the aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give crude enone 218 as a yellow oil (1.4 g), which was used for the next reaction without further purification. An analytical sample was obtained by FCC (EtOAc) to give 218 as a colorless oil. The spectroscopic data of this compound were in accord with those reported in the literature.²²

¹H NMR (400 MHz, CDCl₃):  δ 5.96 (t,  J = 1.4 Hz, 1H, C₂−H), 3.70 (t,  J = 7.1 Hz, 2H, C⁸−H), 2.62-2.57 (m, 2H, C⁵−H), 2.52 (t,  J = 7.1 Hz, 2H, C⁶−H), 2.43-2.38 (m, 2H, C⁴−H), 1.92 (br s, 1H, C⁸−OH), 1.85 (quintet,  J = 7.1 Hz, 2H, C⁷−H).

¹³C NMR (101 MHz, CDCl₃): δ 210.3 (C¹), 182.7 (C³), 129.6 (C²), 62.1 (C⁸), 35.4 (C⁵), 31.8 (C⁶), 30.1 (C⁷ or C⁴), 30.0 (C⁷ or C⁴).

IR: 3402 (br w), 2936 (w), 2867 (w), 1703 (s), 1673 (s), 1611 (s), 1437 (w), 1190 (w), 1056 (m), HRMS: (ESI⁺) m/z: [M + H]⁺ Calcd for C₉H₁₃O₂⁺: 141.0910; Found: 141.0909.

Rf (EtOAc) = 0.23.

3-(3-((tert-butyldimethylsilyl)oxy)propyl)cyclopent-2-en-1-one 220

Following a reported procedure,²² to a solution of crude 218 (obtained from 14 mmol of 3-ethoxycyclopent-2-en-1-one) in DMF (100 mL) at 0 °C were added imidazole (1.5 g, 22 mmol, 1.5 equiv) and TBSCI (2.4 g, 16 mmol, 1.1 equiv). The solution was stirred at RT for 3 h. Saturated aqueous NaHCO₃ was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 4:1) afforded compound 220 as a slightly yellow oil (2.2 g, 60% yield over two steps). The spectroscopic data of this compound were in accord with those reported in the literature.²²
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\[ ^1\text{H NMR (400 MHz, CDCl}_3\text{)}: \delta \ 5.95 \text{ (s, 1H, C}^2\text{−H), 3.66 (t, } J = 6.1 \text{ Hz, 2H, C}^8\text{−H), 2.62-2.57 (m, 2H, C}^5\text{−H), 2.48 (t, } J = 7.5 \text{ Hz, 2H, C}^6\text{−H), 2.43-2.38 (m, 2H, C}^4\text{−H), 1.80 (tt, } J = 7.5, 6.1 \text{ Hz, 2H, C}^7\text{−H), 0.89 (s, 9H, C}^{11}\text{−H), 0.05 (s, 6H, C}^9\text{−H).} \]

\[ ^{13}\text{C NMR (101 MHz, CDCl}_3\text{): } \delta \ 210.2 \ (C^1), 183.0 \ (C^3), 129.6 \ (C^2), 62.4 \ (C^8), 35.5 \ (C^5), 31.8 \ (C^6), 30.3 \ (C^7 \text{ or C}^4), 30.2 \ (C^7 \text{ or C}^4), 26.1 \ (C^{11}), 18.5 \ (C^{10}), -5.2 \ (C^9). \]

\( R_f \) (EtOAc) = 0.87.

3-(3-((triethylsilyl)oxy)propyl)cyclopent-2-en-1-one 219

![Chemical Structure]

To a solution of crude 218 (obtained from 14 mmol of 3-ethoxycyclopent-2-en-1-one) in DMF (100 mL) at 0°C were added imidazole (1.5 g, 22 mmol, 1.5 equiv) and TESCl (2.6 mL, 16 mmol, 1.1 equiv) were added. The solution was stirred at RT for 3 h. Saturated aqueous NaHCO\textsubscript{3} was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 8:2) afforded compound 219 as a yellow oil (2.2 g, 61% yield over two steps).

\[ ^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta \ 5.94 \text{ (t, } J = 1.4 \text{ Hz, 1H, C}^2\text{−H), 3.65 (t, } J = 6.4 \text{ Hz, 2H, C}^8\text{−H), 2.62-2.56 (m, 2H, C}^5\text{−H), 2.48 (t, } J = 8.0 \text{ Hz, 2H, C}^6\text{−H), 2.42-2.37 (m, 2H, C}^4\text{−H), 1.80 (tt, } J = 8.0, 6.4 \text{ Hz, 2H, C}^7\text{−H), 0.95 (t, } J = 7.9 \text{ Hz, 9H, C}^{10}\text{−H), 0.59 (q, } J = 7.9 \text{ Hz, 6H, C}^9\text{−H).} \]

\[ ^{13}\text{C NMR (101 MHz, CDCl}_3\text{): } \delta \ 210.2 \ (C^1), 183.0 \ (C^3), 129.6 \ (C^2), 62.0 \ (C^8), 35.5 \ (C^5), 31.8 \ (C^6), 30.3 \ (C^7 \text{ or C}^4), 30.2 \ (C^7 \text{ or C}^4), 6.9 \ (C^{10}), 4.5 \ (C^9). \]

IR: 2953 (w), 2912 (w), 2876 (w), 1708 (s), 1676 (w), 1617 (w), 1097 (s), 1009 (w), 732 (s).

HRMS: (ESI\textsuperscript{+}) m/z: [M + H]\textsuperscript{+} Calcd for C\textsubscript{14}H\textsubscript{27}O\textsubscript{2}Si\textsuperscript{+}: 255.1775; Found: 255.1781.

\( R_f \) (PE/EtOAc 1:1) = 0.5.
3-(1-ethyl-3-oxocyclopentyl)propyl benzoate 223

Following a reported procedure, to a solution of Cu(OTf)$_2$ (1.6 mg, 0.0045 mmol, 0.75 mol%) and the ligand (2.4 mg, 0.0060 mmol, 1.0 mol%) in Et$_2$O (2.0 mL) at -30 °C was added dropwise a solution of EtMgBr (3.0 M in Et$_2$O, 0.24 mL, 1.2 equiv). The mixture was stirred for 40 min at -30 °C. Then, a solution of 220 (0.15 g, 0.60 mmol) in Et$_2$O (6.0 mL) was added dropwise to the mixture via an automatic syringe pump over 30 min, and the mixture was stirred for 2 h. The reaction mixture was quenched by dropwise addition of a saturated NH$_4$Cl solution at -30 °C, and the reaction mixture was allowed to warm up to RT. The mixture was extracted with Et$_2$O. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude compound 222 thus obtained was used for the next step without further purification.

To a solution of the crude ketone 222 (obtained from 0.60 mmol of enone 220) in MeOH (7.0 mL) was added acetyl chloride (8.0 μL, 20 mol%) at 0 °C. The reaction mixture was stirred at RT for 2 h. The solution was concentrated in vacuo. The crude alcohol thus obtained was used for the next step without further purification.

The crude alcohol was dissolved in DCM (10 mL) and stirred at 0 °C. Pyridine (95 μL, 1.4 mmol, 2.0 equiv) and benzoyl chloride (0.11 mL, 0.90 mmol, 1.5 equiv) were added. The reaction mixture was stirred for 2 h. Aqueous 1 M HCl was added. The mixture was extracted with DCM. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification by FCC (9:1 PE/EtOAc) afforded benzoyl ester 223 as a colorless oil (0.12 g, 75%, ee=5%).

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.03 (dd, $J = 8.2, 1.4$ Hz, 2H, C$_{13,17}$–H), 7.56 (m, 1H, C$_{15}$–H), 7.45 (dd, $J = 8.2, 1.4$ Hz, 2H, C$_{14,16}$–H), 4.32 (t, $J = 6.5$ Hz, 2H, C$_{10}$–H), 2.28 (t, $J = 8.0$ Hz, 2H, C$_5$–H), 2.13 (d, $J = 18.0$ Hz, 1H, C$_2$–H), 2.08 (d, $J = 18.0$ Hz, 1H, C$_2$–H), 1.90–1.78 (m, 2H, C$_4$–H), 1.78–1.74 (m, 2H, C$_3$–H), 1.57–1.49 (m, 2H, C$_8$–H), 1.46 (q, $J = 7.3$ Hz, 2H, C$_6$–H), 0.88 (t, $J = 7.3$ Hz, 3H, C$_7$–H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 220.0 (C$_{11}$), 167.1 (C$_1$), 133.4 (C$_{15}$), 130.7 (C$_{12}$), 130.0 (C$_{13}$),

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The chiral ligand used for enantioselective 1,4 additions on cyclopentenone was kindly provided by Professor Alexakis (Geneva University).
128.9 (C\textsuperscript{14}), 65.7 (C\textsuperscript{10}), 51.1 (C\textsuperscript{2}), 42.8 (C\textsuperscript{3}), 36.9 (C\textsuperscript{5}), 33.9 (C\textsuperscript{8}), 33.2 (C\textsuperscript{4}), 30.1 (C\textsuperscript{6}), 24.3 (C\textsuperscript{9}), 9.0 (C\textsuperscript{7}).

IR: 2957 (w), 1737 (s), 1718 (s), 1281 (s), 1069 (m), 1028 (m), 714 (m).

HRMS: (ESI\textsuperscript{+}) m/z: [M + H]\textsuperscript{+} Calcd for C\textsubscript{17}H\textsubscript{23}O\textsubscript{3}: 275.1647; Found: 275.1644.

\(R_f\) (PE/E\textsubscript{2}O/E\textsubscript{3}N 8:2) = 0.6.
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3-allylcyclopent-2-en-1-one 224

Following a known procedure, a solution of cyclopent-2-en-1-one (1.2 mL, 15 mmol) in THF (2.4 mL) was added dropwise to a stirred solution of allylmagnesium bromide (1 M in Et₂O, 18 mL, 18 mmol, 1.2 equiv) at 0 °C. The mixture was allowed to warm to RT and stirred for 2 h. The reaction mixture was cooled to 0 °C, 15 mL of a saturated solution of NH₄Cl were added and the mixture was stirred at RT for 15 min. The aqueous layer was extracted with Et₂O and the combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by Kugelrohr distillation (Bp = 120-130 °C/1.2 mmHg) afforded product 436 as a colorless oil (1.1 g, 60% yield). The spectroscopic data of this compound were in accord with those reported in the literature.
Pyridium dichromate (5.5 g, 15 mmol, 2.0 equiv) was added in one portion to a stirred solution of 436 (0.90 g, 7.2 mmol, 1.0 equiv) in DCM (9.0 mL) at RT. The resulting brown suspension was stirred for 6 h. Et₂O was added and the solid residue was removed by filtration through a plug of silica gel, and washed with Et₂O. The filtrate was concentrated in vacuo.

Purification by Kugelrohr distillation (Bp= 118-128 °C/1.2 mmHg) afforded product 224 as a colorless oil (0.73 g, 83% yield). The spectroscopic data of this compound were in accord with those reported in the literature. 94

Compound 436

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\]:} \ δ 5.91-5.80 (m, 2H, C\(^{7,2}\)-H), 5.70 (dt, \(J = 5.6, 2.2\) Hz, 1H, C\(^1\)-H), 5.22-5.01 (m, 2H, C\(^8\)-H), 2.50 (dddt, \(J = 17.0, 8.7, 4.6, 2.3\) Hz, 1H, C\(^5\)-H), 2.41 (dt, \(J = 7.4, 1.2\) Hz, 2H, C\(^6\)-H), 2.29 (dddt, \(J = 17.0, 8.7, 4.6, 2.3\) Hz, 1H, C\(^3\)-H), 2.04 (dddt, \(J = 13.4, 8.7, 4.6\) Hz, 1H, C\(^4\)-H), 1.83 (dddt, \(J = 13.4, 8.7, 4.6\) Hz, 1H, C\(^4\)-H), OH peak not observed.

\(R_f\) (PE/EtOAc 1:1) = 0.67.

Compound 224

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\]:} \ δ 5.94 (s, 1H, C\(^2\)-H), 5.91-5.77 (m, 1H, C\(^7\)-H), 5.19 (m, 1H, C\(^8\)-H), 5.13 (m, 1H, C\(^8\)-H), 3.13 (d, \(J = 6.9\) Hz, 2H, C\(^6\)-H), 2.62-2.55 (m, 2H, C\(^4\)-H), 2.42-2.38 (m, 2H, C\(^5\)-H).

\[ ^{13}C \text{ NMR (101 MHz, CDCl}_3\]:} \ δ 210.0 (C\(^1\), 180.6 (C\(^3\)), 132.9 (C\(^7\)), 130.2 (C\(^2\)), 118.4 (C\(^8\)), 38.0 (C\(^6\)), 35.5 (C\(^5\)), 31.4 (C\(^4\)).

\(R_f\) (PE/EtOAc 1:1) = 0.44.

Enantioselective synthesis of 3-allyl-3-ethylcyclopentan-1-one 226

Following a reported procedure,93 to a solution of Cu(OTf)\(_2\) (1.6 mg, 0.0045 mmol, 0.75 mol%) and the ligand (2.4 mg, 0.0060 mmol, 1.0 mol%) in Et\(_2\)O (2.0 mL) at -30 °C was added dropwise
a solution of EtMgBr (3 M in Et₂O, 0.24 mL, 1.2 equiv). The mixture was stirred for 40 min at -30 °C. Then, a solution of 224 (73 mg, 0.60 mmol) in Et₂O (6.0 mL) was added dropwise to the mixture via an automatic syringe pump over 30 min, and the mixture was stirred for 2 h. The reaction mixture was quenched by dropwise addition of a saturated NH₄Cl solution at -30 °C, and the reaction mixture was allowed to warm up to RT. The mixture was extracted with Et₂O. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by FCC (9:1 PE/Et₂O) afforded product 225 as a colorless oil (55 mg, 60% yield).

To a solution of compound 225 (27 mg, 0.18 mmol) and styrene (84 μL, 0.36 mmol, 2.0 equiv) in DCM (18 mL) was added Grubbs II catalyst (30 mg, 0.036 mmol, 0.20 equiv). The reaction mixture was stirred at RT overnight. It was then heated at 30 °C for 4 h. Aqueous 1 M HCl was added, and the mixture was extracted with DCM. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by FCC (PE/Et₂O 10:0 to 9:1) afforded 226 as a colorless oil (16 mg, 40%, ee = 10%).

### Compound 225

**¹H NMR (400 MHz, CDCl₃):** δ 5.77 (ddt, J = 16.7, 10.5, 7.4 Hz, 1H, C⁷−H), 5.13-5.01 (m, 2H, C⁸−H), 2.26 (t, J = 8.0 Hz, 2H, C⁵−H), 2.14 (d, J = 7.4 Hz, 2H, C⁶−H), 2.12 (d, J = 7.8 Hz, 1H, C²−H), 2.03 (d, J = 7.8 Hz, 1H, C²−H), 1.89-1.72 (m, 2H, C⁴−H), 1.44 (q, J = 7.4 Hz, 2H, C²−H), 0.89 (t, J = 7.4 Hz, 3H, C₁₀−H).

**¹³C NMR (101 MHz, CDCl₃):** δ 219.5 (C¹), 134.3 (C⁷), 118.0 (C⁸), 49.9 (C²), 42.7 (C⁶), 41.4 (C³), 36.6 (C⁵), 32.2 (C¹), 30.6 (C⁹), 8.5 (C¹⁰).

**IR:** 2963 (w), 2921 (w), 1741 (s), 1462 (w), 1405 (w), 1166 (w), 915 (w).

**HRMS:** (ESI⁺) m/z: [M + H]⁺ Calcd for C₁₀H₁₇O⁺: 153.1279; Found: 153.1361.

**Rf** (PE/Et₂O 3:2) = 0.50.

### Compound 226

**¹H NMR (400 MHz, CDCl₃):** δ 7.38-7.28 (4H, m, C¹²,¹³−H), 7.23 (m, 1H, C¹⁴−H), 6.43 (dt, J = 15.8, 1.3 Hz, 1H, C⁸−H), 6.17 (dt, J = 15.4, 7.5 Hz, 1H, C⁷−H), 2.30 (t, J = 5.2 Hz, 2H, C³−H), 2.28 (dd, J = 2.6, 4.1 Hz, 2H, C⁶−H), 2.19 (d, J = 18.1 Hz, 1H, C²−H), 2.09 (d, J = 18.1 Hz, 1H, C²−H), 1.89-1.71 (m, 2H, C⁴−H), 1.49 (q, J = 7.4 Hz, 2H, C⁹−H), 0.93 (t, J = 7.4 Hz, 3H, C¹⁰−H).
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$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 219.9 (C$^1$), 137.1 (C$^{11}$), 132.9 (C$^8$), 128.4 (C$^{13}$), 127.1 (C$^{14}$), 125.9 (C$^{12}$), 125.8 (C$^7$), 49.8 (C$^2$), 43.2 (C$^3$), 40.3 (C$^5$), 36.5 (C$^6$), 32.1 (C$^4$), 30.7 (C$^9$), 8.5 (C$^{10}$).

IR: 2961 (w), 2923 (w), 1739 (s), 1450 (w), 1160 (w), 967 (m), 737 (m).

HRMS: (ESI$^+$) m/z: [M + H]$^+$ Calcd for C$_{16}$H$_{21}$O$: 229.1592; Found: 229.1585.

$R_f$ (PE/Et$_2$O 9:1) = 0.16.
8.3. Experimental Procedures of Chapter 3

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Following a reported procedure,\textsuperscript{94} to a suspension of magnesium turning (0.92 g, 38 mmol, 2.0 equiv) in THF (50 mL) at RT was added I\textsubscript{2} (one crystal), and the solution was heated to 60°C. 4-bromo-1-butene (2.2 mL, 22 mmol, 1.2 equiv) was added dropwise, keeping a gentle reflux. After addition, the mixture was heated to refluxing temperature for 1 h. Then, a solution of 3-ethoxycyclopent-2-en-1-one \textsuperscript{217} (2.4 g, 18 mmol) in THF (10 mL) was added dropwise, and the mixture was stirred for 30 min at reflux. The reaction mixture was cooled down to RT. The reaction was quenched with aqueous NH\textsubscript{4}Cl. 2 M HCl was then added, followed by DCM. The biphasic mixture was stirred for 30 min. The mixture was extracted with DCM. The combined organic phases were washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. Purification by FCC (PE/Et\textsubscript{2}O 1:1) afforded the pure product \textsuperscript{228} as colorless oil (2.2 g,
91% yield). The spectroscopic data of this compound were in accord with those reported in the literature.\textsuperscript{94}

\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})}: \(\delta\) 5.96 (quint, \(J = 1.4\) Hz, 1H, C\textsuperscript{2}H), 5.80 (ddt, \(J = 17.0,10.3,6.5\) Hz, 1H, C\textsuperscript{8}H), 5.06 (dq, \(J = 17.0,1.5\) Hz, 1H, C\textsuperscript{9}H), 5.02 (dq, \(J = 10.3,1.5\) Hz, 1H, C\textsuperscript{9}H), 2.60-2.56 (m, 2H, C\textsuperscript{4}H), 2.51 (t, \(J = 7.4\) Hz, 2H, C\textsuperscript{6}H), 2.41-2.38 (m, 2H, C\textsuperscript{5}H), 2.38-2.31 (m, 2H, C\textsuperscript{7}H).

\textbf{\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})}: \(\delta\) 210.1 (C\textsubscript{1}), 182.1 (C\textsubscript{3}), 136.9 (C\textsubscript{8}), 129.9 (C\textsubscript{2}), 115.9 (C\textsubscript{9}), 35.4 (C\textsubscript{5}), 32.8 (C\textsubscript{6}), 31.7 (C\textsubscript{4}), 31.1 (C\textsubscript{7}).

\(R_f\) (PE/Ether 1:1) = 0.30

methyl 3-(3-oxocyclopent-1-en-1-yl)propanoate 227

\begin{center}
\includegraphics[width=0.8\textwidth]{methyl_3-(3-oxocyclopent-1-en-1-yl)propanoate}
\end{center}

To a solution of the enone 228 (1.0 g, 7.3 mmol) in DCM/MeOH (2:1, 15 mL) was added NaHCO\textsubscript{3} (0.12 g, 15 mmol, 2.0 equiv). The reaction mixture was cooled down to -78 °C, and ozone was bubbled through the solution. When the blue color persisted, argon was bubbled through the solution for 10 min. Triethylamine (2.0 mL, 14 mmol, 2.0 equiv), and Ac\textsubscript{2}O (1.3 mL, 14 mmol, 1.9 equiv) were added, and the mixture was stirred at RT for 2 h. Water was added. The mixture was extracted with Et\textsubscript{2}O. The combined organic phases were washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. Purification by FCC (PE/Et\textsubscript{2}O 1:9) afforded product 227 as a colorless oil (0.77 g, 63% yield).

\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})}: \(\delta\) 5.94 (m, 1H, C\textsuperscript{2}H), 3.70 (s, 3H, C\textsuperscript{9}H), 2.73 (m, 2H, C\textsuperscript{7}H), 2.66-2.59 (m, 4H, C\textsuperscript{5,6}H), 2.42 (m, 2H, C\textsuperscript{4}H).

\textbf{\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})}: \(\delta\) 209.7 (C\textsubscript{1}), 180.4 (C\textsubscript{3}), 172.7 (C\textsubscript{8}), 129.6 (C\textsubscript{2}), 52.1 (C\textsubscript{9}), 35.4 (C\textsubscript{5}), 31.8 (C\textsubscript{6o7}), 31.5 (C\textsubscript{6o7}), 28.6 (C\textsubscript{4}).

\textbf{IR}: 2955 (w), 2924 (w), 2852 (w), 1737 (s), 1703 (s), 1616 (m), 1437 (m), 1175 (m).

\textbf{HRMS}: (ESI\textsuperscript{+}) m/z: [M + H]\textsuperscript{+} Calcd for C\textsubscript{9}H\textsubscript{13}O\textsubscript{3}: 169.0859; Found: 169.0858.

\(R_f\) (Ether) = 0.4
3-ethyl-3-(3-((triethylsilyl)oxy)propyl)cyclopent-1-en-1-yl trifluoromethane-sulfonate 214

To a suspension of CuBr·Me₂S (5.7 g, 28 mmol, 2.0 equiv) in THF (85 mL) at -78 °C was added dropwise EtMgBr (3 M in THF, 18 mL, 55 mmol, 4.0 equiv). The reaction mixture was stirred at -78 °C for 1 h and then warmed to -40 °C. To the above prepared cuprate solution was added dropwise a solution of the ketone 219 (3.5 g, 14 mmol) in THF (30 mL) while keeping the solution below -40 °C. The reaction mixture was stirred at -40 °C for 3 h. A solution of Comins’ reagent (10.8 g, 28 mmol, 2.0 equiv) in THF (30 mL) was added to the reaction mixture. The reaction mixture was allowed to warm to RT, and stirred for 24 h. The reaction was quenched with NH₄Cl. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 20:1) afforded compound 214 as a colorless oil (4.7 g, 82% yield).

¹H NMR (400 MHz, CDCl₃): δ 5.42 (t, J = 1.6 Hz, 1H, C²−H), 3.58 (t, J = 5.9 Hz, 2H, C¹¹−H), 2.57 (td, J = 7.9, 1.6, 2H, C⁵−H), 1.81-1.76 (m, 2H, C⁴−H), 1.49-1.40 (m, 6H, C⁷,⁹,¹⁰−H), 0.95 (t, J = 7.9 Hz, 9H, C¹³−H), 0.84 (t, J = 7.4 Hz, 3H, C⁸−H), 0.59 (t, J = 7.9 Hz, 6H, C¹²−H).

¹³C NMR (101 MHz, CDCl₃): δ 148.0 (C¹), 124.7 (C²), 118.7 (q, J = 320.3 Hz, C⁶), 63.6 (C¹¹), 48.9 (C³), 35.6 (C⁵), 32.4 (C⁷), 31.5 (C⁴), 31.1 (C⁵), 28.0 (C¹⁰), 8.8 (C⁸), 6.9 (C¹³), 4.6 (C¹²).

IR: 2957 (w), 2878 (w), 1421 (w), 1214 (w), 1141 (w), 1089 (w), 906 (s), 729 (s).

HRMS: (ESI⁺) m/z: [M + H]⁺ Calcd for C₁₇H₃₂F₃O₄SSi⁺: 417.1737; Found: 417.1728.

Rᶠ (PE/EtOAc 95:5) = 0.48.
3-ethyl-3-(3-((dimethyl tert butylsilyl)oxy)propyl)cyclopent-1-en-1-yl trifluoromethanesulfonate 58

To a suspension of CuBr-Me₂S (5.7 g, 28 mmol, 2.0 equiv) in THF (85 mL) at -78 °C was added dropwise EtMgBr (3 M in THF, 18 mL, 55 mmol, 4.0 equiv). The reaction mixture was stirred at -78 °C for 1 h and then warmed to -40 °C. To the above prepared cuprate solution was added dropwise a solution of the ketone 220 (3.5 g, 14 mmol) in THF (30 mL) while keeping the solution below -40 °C. The reaction mixture was stirred at -40 °C for 3 h. A solution of Comins’ reagent (11 g, 28 mmol, 2.0 equiv) in THF (30 mL) was added. The reaction mixture was allowed to warm to RT, and stirred for 24 h. The reaction was quenched with NH₄Cl. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 40:1) afforded compound 58 as a colorless oil (4.7 g, 82% yield). The spectroscopic data of this compound were in accord with those reported in the literature.¹²

¹H NMR (400 MHz, CDCl₃): δ 5.42 (t, J = 1.4 Hz, 1H, C₂−H), 3.58 (t, J = 5.4 Hz, 2H, C₁₁−H), 2.57 (td, J = 7.9, 1.4 Hz, 2H, C₅−H), 1.83-1.77 (m, 2H, C₄−H), 1.49-1.39 (m, 6H, C₇,₉,₁₀−H), 0.89 (s, 9H, C₁₄−H), 0.84 (t, J = 7.4 Hz, 3H, C₈−H), 0.04 (s, 6H, C₁₂−H).

¹³C NMR (101 MHz, CDCl₃): δ 148.0 (C₁), 124.8 (C₂), 118.7 (q, J = 322.2 Hz, C₆), 63.6 (C₁₁), 48.9 (C₃), 35.6 (C₉), 32.4 (C₇), 31.5 (C₄), 31.1 (C₅), 28.0 (C₁₀), 26.1 (C₁₄), 18.5 (C₁₃), 8.8 (C₈), -5.2 (C₁₂).

Rₚ (PE/EtOAc 10:1) = 0.8.

3-ethyl-3-(3-hydroxypropyl)cyclopent-1-en-1-yl trifluoromethanesulfonate 221

To a solution of 58 (14 g, 33 mmol) in MeOH (100 mL) at 0 °C was added acetyl chloride
8.3. Experimental Procedures of Chapter 3

(0.23 mL, 3.3 mmol, 0.10 equiv). After stirring at RT for 1 h, the reaction mixture was concentrated in vacuo to afford 221 as a yellowish oil (10 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature. The product thus obtained was used for the next step without further purification.

$^1\text{H} \text{NMR (400 MHz, CDCl}_3\text{): } \delta$ 5.41 (s, 1H, C$_2$−H), 3.62 (t, $J$ = 6.0 Hz, 2H, C$_{11}$−H), 2.57 (td, $J$ = 7.3, 1.1 Hz, 2H, C$_3$−H), 1.82-1.75 (m, 2H, C$_4$−H), 1.54 (s, 1H, C$_{11}$−OH), 1.55-1.40 (m, 6H, C$_{7,9,10}$−H), 0.84 (t, $J$ = 7.5 Hz, 3H, C$_8$−H).

$^{13}\text{C} \text{NMR (101 MHz, CDCl}_3\text{): } \delta$ 148.1 (C$_1$), 124.6 (C$_2$), 118.7 (q, $J$ = 319.4 Hz, C$_6$), 63.4 (C$_{11}$), 48.9 (C$_3$), 35.6 (C$_9$), 32.4 (C$_7$), 31.4 (C$_4$), 31.1 (C$_5$), 27.9 (C$_{10}$), 8.8 (C$_8$).

$R_f$ (PE/EtOAc 1:1) = 0.56.

**tert-butyl(2-iodoethoxy)dimethylsilane 144**

Following a reported procedure, ethylene glycol (3.0 mL, 54 mmol) was added dropwise to a suspension of NaH (60% in mineral oil, 2.2 g, 54 mmol, 1.0 equiv) in THF (100 mL) at 0 °C. The reaction mixture was stirred at RT for 1 h. TBSCl (7.2 g, 54 mmol, 1.0 equiv) was added at 0 °C and the mixture was stirred for 1 h at RT. The reaction was quenched with saturated NH$_4$Cl and the reaction mixture was extracted with EtOAc. The combined organic phases were washed with saturated NaHCO$_3$, brine, dried over Na$_2$SO$_4$ and concentrated in vacuo to afford the crude monoprotected diol as a colorless oil.

To a solution of the crude monoprotected diol in THF (300 mL) were added imidazole (5.5 g, 81 mmol, 1.5 equiv) and PPh$_3$ (18 g, 70 mmol, 1.3 equiv). The solution was cooled down to 0 °C and iodine (16 g, 65 mmol, 1.2 equiv) was added slowly. The resulting mixture was stirred at RT for 1 h, quenched with saturated Na$_2$S$_2$O$_3$, diluted with saturated NH$_4$Cl and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (PE) afforded compound 144 as a colorless oil (13 g, 85% yield). The spectroscopic data of this compound were in accord with those reported in the literature.

$^1\text{H} \text{NMR (400 MHz, CDCl}_3\text{): } \delta$ 3.83 (t, $J$ = 7.0 Hz, 2H, C$_2$−H), 3.20 (t, $J$ = 7.0 Hz, 2H, C$_1$−H),

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0.90 (s, 9H, C5−H), 0.08 (s, 6H, C3−H).

\[^{13}C\text{ NMR (101 MHz, CDCl}_3\text{): } \delta 64.4 (C^2), 26.0 (C^5), 16.4 (C^4), 7.2 (C^1), -5.1 (C^3).\]

\(R_f\) (PE) = 0.26.

methyl 4-((tert-butyldimethylsilyl)oxy)-2-(2-nitrophenyl)butanoate 145

To a solution of the ester 96 (10 g, 51 mmol) and the iodide 144 (16 g, 56 mmol, 1.1 equiv) in DMF (300 mL) was added Cs₂CO₃ (25 g, 77 mmol, 1.5 equiv). The reaction mixture was stirred at 60 °C for 18 h. The reaction mixture was allowed to cool down to RT. Water was added and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 95:5) afforded compound 145 as a yellow wax (17 g, 95% yield). The spectroscopic data of this compound were in accord with those reported in the literature.\(^{22}\)

\[^{1}H\text{ NMR (400 MHz, CDCl}_3\text{): } \delta 7.91 (dd, J = 7.7, 1.3 Hz, 1H, C^2−H), 7.57 (td, J = 7.7, 1.3 Hz, 1H, C^1−H), 7.51 (dd, J = 7.7, 1.5 Hz, 1H, C^5−H), 7.41 (td, J = 7.7, 1.5 Hz, 1H, C^3−H), 4.40 (t, J = 7.2 Hz, 1H, C^7−H), 3.70-3.63 (m, 1H, C^{11}−H), 3.66 (s, 3H, C^9−H), 3.52 (ddd, J = 10.3, 7.4, 5.3 Hz, 1H, C^{11}−H), 2.45 (dt, d, J = 13.9, 7.2, 5.5 Hz, 1H, C^{10}−H), 2.00 (dt, d, J = 13.9, 7.2, 5.7 Hz, 1H, C^{10}−H), 0.87 (s, 9H, C^{14}−H), 0.01 (s, 3H, C^{12}−H), 0.00 (s, 3H, C^{12}−H).

\[^{13}C\text{ NMR (101 MHz, CDCl}_3\text{): } \delta 173.2 (C^8), 149.4 (C^1), 133.8 (C^6), 133.1 (C^4), 130.9 (C^5), 128.2 (C^3), 125.0 (C^2), 60.5 (C^{11}), 52.4 (C^9), 43.3 (C^7), 35.6 (C^{10}), 26.0 (C^{14}), 18.4 (C^{13}), -5.4 (C^{12}).\]

\(R_f\) (PE/EtOAc 9:1) = 0.43.
4-((tert-butyldimethylsilyl)oxy)-2-(2-nitrophenyl)butanoic acid 216

To a solution of the ester 145 (2.0 g, 5.7 mmol) in THF (50 mL) was added a solution of aqueous 10% KOH (10 mL). The reaction mixture was stirred until complete consumption of the ester. Water was added and the reaction mixture was acidified to pH 5-6 with 1 M HCl. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo to afford carboxylic acid 216 as a yellow oil (1.9 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature. The compound was used for the next step without further purification.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.78 (br s, 1H, O9−H), 7.95 (dd, $J$ = 7.8, 1.4 Hz, 1H, C2−H), 7.58 (td, $J$ = 7.8, 1.4 Hz, 1H, C4−H), 7.50 (dd, $J$ = 7.8, 1.5 Hz, 1H, C5−H), 7.43 (td, $J$ = 7.8, 1.5 Hz, 1H, C3−H), 4.41 (t, $J$ = 7.0 Hz, 1H, C7−H), 3.69 (dt, $J$ = 10.4, 5.3 Hz, 1H, C11−H), 3.51 (ddd, $J$ = 10.4, 8.0, 5.3 Hz, 1H, C11−H), 2.47 (dddd, $J$ = 14.0, 8.1, 7.0, 5.3 Hz, 1H, C10−H), 2.01 (dddt, $J$ = 14.0, 7.0, 5.3 Hz, 1H, C10−H), 0.86 (s, 9H, C14−H), 0.00 (two s, 6H, C12−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 178.7 (C8), 149.1 (C1), 133.3 (C6), 133.2 (C4), 131.2 (C5), 128.4 (C3), 125.1 (C2), 60.5 (C11), 43.9 (C7), 35.1 (C10), 25.9 (C14), 18.3 (C13), -5.4 (C12).

$R_f$ (PE/EtOAc 8:2) = 0.24.

potassium 4-((tert-butyldimethylsilyl)oxy)-2-(2-nitrophenyl)butanoate 215

Following a reported procedure, to a solution of crude acid 216 (1.9 g, 5.7 mmol) in EtOH (50 mL) was added dropwise a solution of t-BuOK (0.64 g, 5.7 mmol, 1.0 equiv) in EtOH (5.0 mL). The reaction mixture was stirred for 1 h, then concentrated in vacuo and coevaporated with toluene to afford the crude carboxylate 215 as a white amorphous solid (2.2 g,
quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature. This compound was used for the next step without further purification.

$^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 7.79 (dd, $J = 8.2, 1.4$ Hz, 1H, C$_2^\text{2}$−H), 7.68 (dd, $J = 7.7, 1.6$ Hz, 1H, C$_4^\text{4}$−H), 7.58 (td, $J = 7.7, 1.4$ Hz, 1H, C$_5^\text{5}$−H), 7.38 (ddd, $J = 8.1, 7.3, 1.5$ Hz, 1H, C$_3^\text{3}$−H), 4.41 (t, $J = 7.2$ Hz, 1H, C$_7^\text{7}$−H), 3.65 (ddd, $J = 10.0, 4.6, 6.1$ Hz, 1H, C$_1^\text{11}$−H), 3.60 (ddd, $J = 10.0, 7.0, 6.8$ Hz, 1H, C$_1^\text{10}$−H), 2.38 (dq, $J = 13.5, 7.2$ Hz, 1H, C$_1^\text{10}$−H), 0.87 (s, 9H, C$_1^\text{14}$−H), 0.00 (two s, 6H, C$_1^\text{12}$−H).

$^{13}$C NMR (101 MHz, CD$_3$OD): $\delta$ 179.8 (C$_8^\text{8}$), 151.7 (C$_1^\text{1}$), 138.1 (C$_6^\text{6}$), 133.6 (C$_4^\text{4}$), 131.6 (C$_5^\text{5}$), 128.2 (C$_3^\text{3}$), 125.2 (C$_2^\text{2}$), 62.9 (C$_1^\text{11}$), 47.5 (C$_7^\text{7}$), 38.2 (C$_1^\text{10}$), 26.6 (C$_1^\text{14}$), 19.2 (C$_1^\text{13}$), -5.1 (C$_1^\text{12}$).

3-(3-(3-(tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl)-1-ethylcyclopent-2-en-1-yl)propan-1-ol 213

From free alcohol 221

An oven-dried flask was charged with salt 215 (2.0 g, 5.3 mmol, 1.2 equiv), X-Phos (0.32 g, 0.66 mmol, 15 mol%) and allylpalladium chloride dimer (40 mg, 0.11 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (30 mL) was added, and the reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate 221 (1.3 g, 4.4 mmol) in diglyme (30 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was allowed to cool down to RT, and saturated aqueous NaHCO$_3$ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. The two diastereoisomers were separated by FCC (PE/EtOAc 8:2), giving 213a and 213b as yellow oils (0.89 g, 45% yield, dr 1:1).
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From TES-protected alcohol 214

An oven-dried flask was charged with salt 215 (2.0 g, 5.3 mmol, 1.2 equiv), X-Phos (0.32 g, 0.66 mmol, 15 mol%) and allylpalladium chloride dimer (40 mg, 0.11 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (30 mL) was added, and the reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate 214 (1.8 g, 4.4 mmol) in diglyme (30 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was cooled down to 0 °C, and TBAF (1 M solution in THF, 5 mL, 5 mmol, 1.1 equiv) was added dropwise. The reaction was monitored by TLC until total conversion. Saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The two diastereoisomers were separated by FCC (PE/EtOAc 8:2), giving 213a and 213b as yellow oils (1.1 g, 57% yield, dr 1:1).

**Compound 213a**

**¹H NMR (400 MHz, CDCl₃):** δ 7.68 (dd, J = 7.8, 1.5 Hz, 1H, C₁²–H), 7.49 (td, J = 7.8, 1.5 Hz, 1H, C₁⁰–H), 7.38 (dd, J = 7.8, 1.5 Hz, 1H, C⁹–H), 7.30 (td, J = 7.8, 1.5 Hz, 1H, C¹¹–H), 5.25 (d, J = 1.7 Hz, 1H, C₂¹–H), 4.07 (t, J = 7.4 Hz, 1H, C⁷–H), 3.59 (t, J = 6.4 Hz, 2H, C₃–H), 3.53 (t, J = 6.8 Hz, 2H, C₅–H), 2.18-1.89 (m, 4H, C₆,₁₅–H), 1.70 (br s, 1H, O⁴–H), 1.66-1.53 (m, 2H, C₁₇–H), 1.49-1.41 (m, 2H, C¹⁴–H), 1.40-1.31 (m, 4H, C₁₆,₁₉–H), 0.85 (s, 9H, C₂₄–H), 0.78 (t, J = 7.5 Hz, 3H, C₁₈–H), -0.02 (s, 6H, C₂₂–H).

**¹³C NMR (101 MHz, CDCl₃):** δ 150.7 (C₁₃), 144.1 (C²), 137.8 (C⁶), 133.0 (C₂¹), 132.3 (C¹⁰), 129.2 (C⁹), 127.0 (C¹¹), 124.0 (C₁²), 63.8 (C³), 61.2 (C⁵), 51.8 (C₂⁰), 37.4 (C⁷), 37.1 (C⁶), 35.3 (C₁⁵), 33.6 (C₁₆), 33.5 (C₁₇), 32.1 (C₁₉), 28.3 (C₁₄), 26.0 (C₂⁴), 18.4 (C₂₃), 9.1 (C₁₈), -5.3 (C₂₂).

**IR:** 3378 (br w), 2930 (w), 2856 (w), 1527 (s), 1462 (w), 1356 (m), 1254 (m), 1099 (s), 1061 (m), 834 (s), 777 (s).

**HRMS:** (ESI⁺) m/z: [M + H]⁺ Calcd for C₂₅H₄₂NO₄Si+: 448.2878; Found: 448.2885.

**Rf** (PE/EtOAc 6:4) = 0.43.
Compound 213b

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.67 (dd, $J = 7.7, 1.5$ Hz, 1H, C$_{12}$–H), 7.48 (td, $J = 7.7, 1.5$ Hz, 1H, C$_{10}$–H), 7.38 (dd, $J = 7.7, 1.6$ Hz, 1H, C$_9$–H), 7.29 (td, $J = 7.7, 1.6$ Hz, 1H, C$_{11}$–H), 5.26 (d, $J = 1.9$ Hz, 1H, C$_{21}$–H), 4.11 (t, $J = 7.3$ Hz, 1H, C$_7$–H), 3.58 (t, $J = 6.5$ Hz, 2H, C$_3$–H), 3.52 (t, $J = 6.8$ Hz, 2H, C$_5$–H), 2.16–2.00 (m, 3H, C$_{6,15}$–H), 1.95 (dq, $J = 13.6, 6.8$ Hz, 1H, C$_6$–H), 1.73 (br s, 1H, O$_4$–H), 1.57 (t, $J = 7.4$ Hz, 2H, C$_{17}$–H), 1.50–1.40 (m, 2H, C$_{14}$–H), 1.40–1.30 (m, 4H, C$_{16,19}$–H), 0.84 (s, 9H, C$_{24}$–H), 0.77 (t, $J = 7.3$ Hz, 3H, C$_{18}$–H), -0.03 (s, 6H, C$_{22}$–H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 150.7 (C$_{13}$), 143.9 (C$_2$), 137.7 (C$_8$), 133.2 (C$_{21}$), 132.2 (C$_{10}$), 129.1 (C$_9$), 127.0 (C$_{11}$), 124.0 (C$_{12}$), 63.7 (C$_3$), 61.1 (C$_5$), 51.8 (C$_{20}$), 37.3 (C$_7$), 36.9 (C$_6$), 35.3 (C$_{15}$), 33.4 (C$_{16}$), 33.3 (C$_{17}$), 32.1 (C$_{19}$), 28.3 (C$_{14}$), 26.0 (C$_{24}$), 18.4 (C$_{23}$), 9.1 (C$_{18}$), -5.3 (C$_{22}$).

IR: 3362 (br w), 2934 (w), 2856 (w), 1527 (s), 1463 (w), 1356 (m), 1254 (m), 1099 (s), 1062 (m), 834 (s), 778 (s).

HRMS: (ESI$^+$) m/z: [M + H]$^+$ Calcd for C$_{25}$H$_{42}$NO$_4$Si$: 448.2878; Found: 448.2876.

$R_f$ (PE/EtOAc 6:4) = 0.57.

3-(3-(3-(hydroxy)-1-(2-nitrophenyl)propyl)-1-ethylcyclopent-2-en-1-yl)propan-1-ol 229

From 213

To a solution of compounds 213a/213b (dr 1:1, 2.7 g, 6.0 mmol) in MeOH (50 mL) at 0°C was added dropwise acetyl chloride (40 μL, 0.60 mmol, 10 mol%). The reaction was stirred at RT for 1 h, then concentrated in vacuo. The crude alcohols 229a/229b (2.0 g, quantitative yield, no change in dr) thus obtained was used for the next step without further purification.
An oven-dried flask was charged with salt 215 (dr 1:1, 2.0 g, 5.3 mmol, 1.2 equiv), X-Phos (0.32 g, 0.66 mmol, 15 mol%) and allylpalladium chloride dimer (40 mg, 0.11 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (30 mL) was added, and the reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate 58 (1.8 g, 4.4 mmol) in diglyme (30 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was cooled down to RT, and TBAF (1 M solution in THF, 13 mL, 13 mmol, 3.0 equiv) was added dropwise. The reaction was monitored by TLC until total conversion. Saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo.

Purification by FCC (PE/EtOAc 8:2) afforded the two diastereoisomers 229a and 229b as yellow oils (0.81 g, 55% yield, dr 1:1).

**Compound 229a**

**¹H NMR (400 MHz, CDCl₃):** δ 7.67 (dd, J = 7.7, 1.4 Hz, 1H, C₁₂−H), 7.51 (td, J = 7.7, 1.4 Hz, 1H, C₁₀−H), 7.38 (dd, J = 7.7, 1.6 Hz, 1H, C⁹−H), 7.31 (td, J = 7.7, 1.6 Hz, 1H, C¹¹−H), 5.29 (d, J = 1.7 Hz, 1H, C²¹−H), 4.06 (t, J = 7.4 Hz, 1H, C⁷−H), 3.61-3.48 (m, 4H, C³,⁵−H), 2.46 (br s, 2H, O⁴,²₂−H), 2.20 (ddt, J = 13.2, 6.6, 6.6 Hz, 1H, C⁶−H), 2.14-2.04 (m, 1H, C¹⁵−H), 2.04-1.92 (m, 2H, C⁵,¹⁵−H), 1.65-1.50 (m, 2H, C¹⁷−H), 1.49-1.39 (m, 2H, C¹⁴−H), 1.40-1.30 (m, 4H, C¹⁶,¹⁹−H), 0.76 (t, J = 7.4 Hz, 3H, C₁₈−H).

**¹³C NMR (101 MHz, CDCl₃):** δ 150.8 (C¹³), 143.9 (C²), 137.3 (C⁸), 133.3 (C²¹), 132.5 (C¹⁰), 129.2 (C⁹), 127.2 (C¹¹), 124.0 (C¹²), 63.7 (C⁵), 60.8 (C⁵), 51.9 (C²⁰), 37.5 (C⁷), 36.9 (C⁶), 35.2 (C¹⁵), 33.5 (C¹⁶), 33.5 (C¹⁷), 32.1 (C¹⁹), 28.2 (C¹⁴), 9.1 (C¹₈).

**IR:** 3343 (br w), 2937 (w), 2875 (w), 1525 (s), 1451 (w), 1355 (m), 1052 (m), 909 (m), 731 (s).


**Rf** (PE/EtOAc 4:6) = 0.22.
Compound 229b

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.67 (dd, $J = 7.7, 1.7$ Hz, 1H, C$^{12}$−H), 7.50 (td, $J = 7.7, 1.6$ Hz, 1H, C$^9$−H), 7.38 (dd, $J = 7.7, 1.6$ Hz, 1H, C$^{11}$−H), 5.31 (d, $J = 1.8$ Hz, 1H, C$^{21}$−H), 4.03 (t, $J = 7.5$ Hz, 1H, C$^7$−H), 3.61-3.48 (m, 4H, C$^3,5$−H), 2.50 (br s, 2H, O$^4,22$−H), 2.19 (ddt, $J = 13.5, 13.0, 6.7$ Hz, 1H, C$^6$−H), 2.14-2.04 (m, 1H, C$^{15}$−H), 1.59-1.53 (m, 2H, C$^{17}$−H), 1.50-1.41 (m, 2H, C$^{14}$−H), 1.40-1.30 (m, 4H, C$^{16,19}$−H), 0.77 (t, $J = 7.4$ Hz, 3H, C$^{18}$−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 150.7 (C$^{13}$), 143.9 (C$^2$), 137.4 (C$^8$), 133.2 (C$^{21}$), 132.5 (C$^{10}$), 129.2 (C$^9$), 127.2 (C$^{11}$), 123.9 (C$^{12}$), 63.7 (C$^3$), 60.7 (C$^5$), 51.9 (C$^{20}$), 37.5 (C$^7$), 37.0 (C$^6$), 35.3 (C$^{15}$), 33.7 (C$^{16}$), 33.3 (C$^{17}$), 32.2 (C$^{19}$), 28.2 (C$^{14}$), 9.2 (C$^{18}$).

IR: 3330 (br w), 2937 (w), 2875 (w), 1525 (s), 1461 (w), 1355 (m), 1052 (m), 910 (w), 855 (w), 784 (m), 732 (s).


$R_f$ (PE/EtOAc 4:6) = 0.22.

3-(-1-ethyl-3-(-3-((methylsulfonyl)oxy)-1-(2-nitrophenyl)propyl)cyclopent-2-en-1-yl)propyl methanesulfonate 233

To a solution of diols 229a/229b (dr 1:1, 50 mg, 0.15 mmol) in DCM (15 mL) at 0°C was added Et$_3$N (63 $\mu$L, 0.50 mmol, 3.0 equiv) and MsCl (29 $\mu$L, 0.37 mmol, 2.5 equiv). The reaction mixture was stirred at RT until complete consumption of the starting material. The reaction mixture was poured into water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded the pure compounds 233a/233b as a mixture of two diastereoisomers (yellow oils, 54 mg, 74% yield, no change in dr).
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**Compound 233a**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.75 (dd, $J = 7.9, 1.3$ Hz, 1H, C$_{12}^{12}$−H), 7.58 (td, $J = 7.9, 1.3$ Hz, 1H, C$_{10}^{10}$−H), 7.41-7.35 (m, 2H, C$_{9,11}^{9,11}$−H), 5.31 (d, $J = 1.4$ Hz, 1H, C$_{21}^{21}$−H), 4.25-4.05 (m, 5H, C$_{5,7,14}^{5,7,14}$−H), 3.00 (s, 3H, C$_{23}^{23}$−H), 2.97 (s, 3H, C$_{22}^{22}$−H), 2.41 (dq, $J = 14.3, 6.9$ Hz, 1H, C$_{6}^{6}$−H), 2.23 (dq, $J = 14.3, 7.3$ Hz, 1H, C$_{6}^{6}$−H), 2.15 (m, 1H, C$_{15}^{15}$−H), 2.02 (m, 1H, C$_{15}^{15}$−H), 1.72-1.62 (m, 3H, C$_{17}^{17}$, C$_{14}^{14}$−H), 1.55 (m, 1H, C$_{14}^{14}$−H), 1.45-1.34 (m, 4H, C$_{16}, C_{19}^{16}, C_{19}^{19}$−H), 0.80 (t, $J = 7.5$ Hz, 3H, C$_{18}^{18}$−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 150.6 (C$_{13}^{13}$), 143.7 (C$_{2}^{2}$), 136.0 (C$_{8}^{8}$), 133.2 (C$_{21}^{21}$), 133.0 (C$_{10}^{10}$), 129.0 (C$_{9}^{9}$), 127.9 (C$_{11}^{11}$), 124.4 (C$_{12}^{12}$), 71.0 (C$_{3}^{3}$), 67.5 (C$_{5}^{5}$), 51.9 (C$_{20}^{20}$), 37.6 (C$_{7}^{7}$), 37.5 (C$_{22}^{22}$), 37.5 (C$_{23}^{23}$), 34.8 (C$_{6}^{6}$, C$_{15}^{15}$), 33.6 (C$_{6}^{6}$, C$_{15}^{15}$), 33.4 (C$_{17}^{17}$), 32.1 (C$_{19}^{19}$), 25.0 (C$_{14}^{14}$), 9.1 (C$_{18}^{18}$).

IR: 2959 (w), 2941 (w), 2851 (w), 1526 (m), 1350 (s), 1172 (s), 958 (m), 918 (m), 815 (m).

HRMS: (ESI$^+$) m/z: [M + H]$^+$ Calcd for C$_{21}^{21}$H$_{32}^{32}$NO$_{8}^{8}$S$_{2}^{2}$: 490.1564; Found: 490.1508.

$R_f$ (PE/EtOAc 4:6) = 0.58.

**Compound 233b**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.74 (dd, $J = 7.6, 1.4$ Hz, 1H, C$_{12}^{12}$−H), 7.56 (td, $J = 7.6, 1.4$ Hz, 1H, C$_{10}^{10}$−H), 7.31 (td, $J = 7.6, 1.5$ Hz, 2H, C$_{9,11}^{9,11}$−H), 5.33 (d, $J = 1.3$ Hz, 1H, C$_{21}^{21}$−H), 4.28-4.05 (m, 5H, C$_{5,7,14}^{5,7,14}$−H), 3.01 (s, 3H, C$_{23}^{23}$−H), 2.97 (s, 3H, C$_{22}^{22}$−H), 2.39 (dq, $J = 14.1, 7.0$ Hz, 1H, C$_{6}^{6}$−H), 2.23 (dq, $J = 14.1, 7.0$ Hz, 1H, C$_{6}^{6}$−H), 2.13 (ddd, $J = 16.1, 7.8, 7.2$ Hz, 1H, C$_{15}^{15}$−H), 2.02 (ddd, $J = 16.1, 7.8, 7.2$ Hz, 1H, C$_{15}^{15}$−H), 1.70-1.55 (m, 4H, C$_{14}^{14}, C_{17}^{17}$−H), 1.46-1.35 (m, 4H, C$_{16}, C_{19}^{16}, C_{19}^{19}$−H), 0.8 (t, $J = 7.0$ Hz, 3H, C$_{18}^{18}$−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 150.6 (C$_{13}^{13}$), 143.5 (C$_{2}^{2}$), 136.1 (C$_{8}^{8}$), 133.3 (C$_{21}^{21}$), 132.8 (C$_{10}^{10}$), 129.0 (C$_{9}^{9}$), 127.8 (C$_{11}^{11}$), 124.4 (C$_{12}^{12}$), 70.9 (C$_{3}^{3}$), 67.5 (C$_{5}^{5}$), 51.9 (C$_{20}^{20}$), 37.6 (C$_{7}^{7}$), 37.5 (C$_{22}^{22}$), 37.4 (C$_{22}^{22}$, C$_{15}^{15}$), 35.0 (C$_{15}^{15}$), 33.6 (C$_{6}^{6}$, C$_{15}^{15}$), 33.6 (C$_{6}^{6}$, C$_{15}^{15}$), 33.2 (C$_{17}^{17}$), 33.1 (C$_{19}^{19}$), 24.9 (C$_{14}^{14}$), 9.2 (C$_{18}^{18}$).

IR: 2960 (w), 2942 (w), 2850 (w), 1527 (m), 1351 (s), 1173 (s), 967 (m), 919 (m), 815 (m).

HRMS: (ESI$^+$) m/z: [M + H]$^+$ Calcd for C$_{21}^{21}$H$_{32}^{32}$NO$_{8}^{8}$S$_{2}^{2}$: 490.1564; Found: 490.1563.

$R_f$ (PE/EtOAc 4:6) = 0.58.
To a solution of diols 229a/229b (dr 1:1, 50 mg, 0.15 mmol) in THF (15 mL) at 0 °C was added imidazole (34 mg, 0.50 mmol, 3.0 equiv) and PPh₃ (97 mg, 0.37 mmol, 2.5 equiv), followed by portionwise addition of iodine (84 mg, 0.33 mmol, 2.2 equiv). The reaction mixture was stirred at RT until complete consumption of the starting material. The reaction mixture was poured into saturated aqueous NH₄Cl, and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded the pure compounds 232a/232b as a mixture of two diastereoisomers (yellow oils, 80 mg, 96% yield, no change in dr).

**Compound 232a**

**¹H NMR (400 MHz, CDCl₃):** δ 7.74 (dd, J = 8.0, 1.5 Hz, 1H, C¹²−H), 7.56 (td, J = 8.0, 1.5 Hz, 1H, C¹⁰−H), 7.40-7.34 (m, 2H, C⁹,¹¹−H), 5.30 (d, J = 1.9 Hz, 1H, C²¹−H), 4.04 (t, J = 7.4 Hz, 1H, C⁷−H), 3.19-3.12 (m, 2H, C⁵−H), 3.04 (ddd, J = 9.7, 9.6, 6.1 Hz, 1H, C⁵−H), 2.47 (dq, J = 14.1, 6.9 Hz, 1H, C⁶−H), 2.33 (ddt, J = 13.9, 9.3, 6.6 Hz, 1H, C⁵−H), 2.15 (ddd, J = 15.8, 7.7, 7.7 Hz, 1H, C¹⁶−H), 2.02 (ddd, J = 15.8, 7.7, 7.7 Hz, 1H, C¹⁶−H), 1.73 (quint, J = 7.16 Hz, 2H, C¹⁴−H), 1.69-1.50 (m, 2H, C¹⁷−H), 1.42 (q, J = 7.8 Hz, 2H, C¹⁸−H), 1.41-1.34 (m, 2H, C¹⁵−H), 0.80 (t, J = 7.5 Hz, 3H, C¹⁸−H).

**¹³C NMR (101 MHz, CDCl₃):** δ 150.7 (C¹³), 143.3 (C⁵), 136.2 (C⁸), 133.3 (C²¹), 132.8 (C¹⁰), 129.0 (C⁹), 127.6 (C¹¹), 124.4 (C¹²), 52.0 (C²⁰), 42.5 (C⁷), 40.3 (C¹⁵), 38.4 (C⁶), 33.7 (C¹⁶°r¹⁷), 33.5 (C¹⁶°r¹⁷), 32.3 (C¹⁹), 29.6 (C¹⁴), 9.1 (C¹⁸), 8.1 (C³), 2.8 (C²).

**IR:** 2933 (w), 2918 (w), 2848 (w), 1526 (s), 1458 (w), 1353 (m), 1230 (w), 1172 (w), 786 (w), 746 (w).

**HRMS:** (ESI⁺) m/z: [M + Na]⁺ Calcd for C₁₉H₂₅I₂NNaO₂⁺: 575.9867; Found: 575.9861.

**Rf** (PE/EtOAc 8:2) = 0.42.
8.3. Experimental Procedures of Chapter 3

Compound 232b

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.74 (dd, $J = 8.4, 1.4$ Hz, 1H, C$^{12}$–H), 7.54 (td, $J = 7.5, 1.4$ Hz, 1H, C$^{10}$–H), 7.39-7.34 (m, 2H, C$^{9,11}$–H), 5.30 (d, $J = 1.7$ Hz, 1H, C$^{21}$–H), 4.06 (t, $J = 7.4$ Hz, 1H, C$^{7}$–H), 3.16 (t, $J = 6.6$ Hz, 2H, C$^{3}$–H), 3.10 (ddd, $J = 9.5, 9.4, 6.1$ Hz, 1H, C$^{5}$–H), 3.03 (ddd, $J = 9.5, 9.4, 6.1$ Hz, 1H, C$^{5}$–H), 2.46 (m, 1H, C$^{6}$–H), 2.32 (m, 1H, C$^{6}$–H), 2.14 (ddd, $J = 15.8, 7.7, 7.4$ Hz, 1H, C$^{16}$–H), 2.02 (ddd, $J = 15.8, 7.7, 7.4$ Hz, 1H, C$^{16}$–H), 1.60 (t, $J = 7.4$ Hz, 2H, C$^{17}$–H), 1.46-1.33 (m, 2H, C$^{15}$–H), 1.36 (q, $J = 7.5$ Hz, 2H, C$^{19}$–H), 0.80 (t, $J = 7.5$ Hz, 3H, C$^{18}$–H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 150.8 (C$^{13}$), 143.2 (C$^2$), 136.2 (C$^8$), 133.6 (C$^{21}$), 128.9 (C$^9$), 127.6 (C$^{11}$), 124.4 (C$^{12}$), 51.9 (C$^{20}$), 42.5 (C$^7$), 40.3 (C$^{15}$), 38.3 (C$^6$), 33.5 (C$^{16or17}$), 33.4 (C$^{16or17}$), 32.1 (C$^{19}$), 29.4 (C$^{14}$), 9.2 (C$^3$), 8.1 (C$^3$), 2.8 (C$^5$).

IR: 2956 (w), 2932 (w), 2847 (w), 1525 (s), 1447 (w), 1353 (m), 1230 (w), 1170 (w), 909 (w), 855 (w), 783 (w), 733 (m).

HRMS: (ESI$^+$) m/z: [M + Na]$^+$ Calcd for C$_{19}$H$_{25}$I$_2$NNaO$_2$: 575.9867; Found: 575.9870.

$R_f$ (PE/EtOAc 8:2) = 0.42.

N-(3-(3-((tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl)-1-ethyl-cyclopent-2-en-1-yl)propyl)-2-nitrobenzenesulfonamide 437

To a solution of alcohols 213a/213b (dr 1:1, 60 mg, 0.13 mmol), neopentyl alcohol (5.8 mg, 0.060 mmol, 0.40 equiv), o-nitrophenylsulfonamide (53 mg, 0.27 mmol, 2.0 equiv) and PPh$_3$ (35 mg, 0.13 mmol, 1.0 equiv) in toluene (4.0 mL) at RT was added DEAD (40 wt.% in toluene, 60 $\mu$L, 0.13 mmol, 1.0 equiv). After stirring for 1 h at RT, additional PPh$_3$ (35 mg, 0.13 mmol, 1.0 equiv) and DEAD (40 wt.% in toluene, 60 $\mu$L, 0.13 mmol, 1.0 equiv) were added. The reaction mixture was stirred for one more hour. Saturated aqueous NaHCO$_3$ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine,
dried over Na$_2$SO$_4$ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded the two diastereoisomers 437a and 437b as yellow oils (67 mg, 81% yield, no change in dr).

**Compound 437a**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.13 (m, 1H, C$_{30}$−H), 7.84 (m, 1H, C$_{27}$−H), 7.76-7.71 (m, 2H, C$_{28,29}$−H), 7.70 (d, $J = 7.8$ Hz, 1H, C$_{12}$−H), 7.54 (t, $J = 7.8$ Hz, 1H, C$_{10}$−H), 7.36 (d, $J = 7.8$ Hz, 1H, C$_9$−H), 7.33 (t, $J = 7.8$ Hz, 1H, C$_{11}$−H), 5.24 (t, $J = 5.8$ Hz, 1H, C$_4$−H), 5.14 (d, $J = 1.4$ Hz, 1H, C$_{21}$−H), 4.05 (t, $J = 7.2$ Hz, 1H, C$_7$−H), 3.56-3.46 (m, 2H, C$_5$−H), 3.07 (q, $J = 6.6$ Hz, 2H, C$_3$−H), 2.20-2.06 (m, 2H, C$_{6,16}$−H), 2.02-1.88 (m, 2H, C$_{6,16}$−H), 1.58 (m, 1H, C$_{17}$−H), 1.46-1.35 (m, 3H, C$_{14,17}$−H), 1.32-1.23 (m, 4H, C$_{15,19}$−H), 0.85 (s, 9H, C$_{24}$−H), 0.73 (t, $J = 7.4$ Hz, 3H, C$_{18}$−H), -0.02 (s, 6H, C$_{22}$−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 150.7 (C$_{13}$), 148.3 (C$_{26}$), 144.8 (C$_2$), 137.6 (C$_8$), 134.1 (C$_{25}$), 133.6 (C$_{28}$), 132.9 (C$_{29}$), 132.5 (C$_{10}$), 132.3 (C$_{21}$), 131.2 (C$_{30}$), 129.2 (C$_9$), 127.2 (C$_{11}$), 125.5 (C$_{27}$), 124.1 (C$_{12}$), 61.1 (C$_5$), 51.8 (C$_7$), 37.5 (C$_7$), 37.1 (C$_6$), 36.2 (C$_{15}$), 33.8 (C$_{16}$), 33.4 (C$_{17}$), 32.2 (C$_{19}$), 26.1 (C$_{24}$), 25.3 (C$_{14}$), 18.4 (C$_{23}$), 9.1 (C$_{18}$), -5.3 (C$_{22}$).

IR: 3353 (br w), 2950 (m), 2932 (m), 2856 (m), 1721 (w), 1529 (s), 1358 (s), 1256 (m), 1169 (s), 1100 (s), 836 (s), 781 (s).

HRMS: (ESI$^+$) m/z: [M+H]$^+$ Calcd for C$_{31}$H$_{46}$N$_3$O$_7$SSi+: 632.2820; Found: 632.2820.

$R_f$ (PE/EtOAc 6:4) = 0.57.

**Compound 437b**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.14 (m, 1H, C$_{30}$−H), 7.86 (m, 1H, C$_{27}$−H), 7.77-7.72 (m, 2H, C$_{28,29}$−H), 7.69 (dd, $J = 7.9,1.1$ Hz, 1H, C$_{12}$−H), 7.51 (t, $J = 7.9$ Hz, 1H, C$_{10}$−H), 7.36 (d, $J = 7.9$ Hz, 1H, C$_9$−H), 7.32 (t, $J = 7.9$ Hz, 1H, C$_{11}$−H), 5.26 (t, $J = 6.0$ Hz, 1H, C$_4$−H), 5.16 (s, 1H, C$_{21}$−H), 4.13 (t, $J = 7.3$ Hz, 1H, C$_7$−H), 3.54-3.46 (m, 2H, C$_3$−H), 3.11-3.03 (m, 2H, C$_{6,16}$−H), 2.08 (dq, $J = 13.9,7.0$ Hz, 1H, C$_{6}$−H), 2.01 (t, $J = 7.2$ Hz, 2H, C$_{16}$−H), 1.95 (dq, $J = 14.0,7.0$ Hz, 1H, C$_{6}$−H), 1.53 (dd, $J = 14.3,8.2$ Hz, 1H, C$_{17}$−H), 1.44 (dd, $J = 14.3,7.6$ Hz, 1H, C$_{17}$−H), 1.42-1.35 (m, 2H, C$_{14}$−H), 1.31-1.22 (m, 4H, C$_{15,19}$−H), 0.86 (s, 9H, C$_{24}$−H), 0.73 (t, $J = 7.4$ Hz, 3H, C$_{18}$−H), 0.02 (s, 6H, C$_{22}$−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 150.8 (C$_{13}$), 148.2 (C$_{26}$), 144.4 (C$_2$), 137.4 (C$_8$), 134.1 (C$_{25}$), 133.6 (C$_{28}$), 132.9 (C$_{29}$), 132.3 (C$_{19}$), 131.2 (C$_{30}$), 129.0 (C$_9$), 127.1 (C$_{11}$), 125.5 (C$_{27}$), 124.2 (C$_{12}$), 61.1 (C$_5$), 51.8 (C$_7$), 37.3 (C$_5$), 36.6 (C$_{15}$), 36.3 (C$_7$), 33.3 (C$_{16}$), 32.9 (C$_{17}$), 32.2 (C$_{19}$), 26.1 (C$_{24}$), 25.2 (C$_{14}$), 18.4 (C$_{23}$), 9.2 (C$_{18}$), -5.3 (C$_{22}$).
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IR: 3329 (br w), 2953 (w), 2934 (w), 2856 (w), 1723 (s), 1528 (s), 1353 (s), 1249 (s), 1168 (s), 1097 (s), 1063 (s), 836 (s), 779 (s), 740 (s).

HRMS: (ESI⁺) m/z: [M + H]⁺ Calcd for C₃₁H₄₆N₃O₇SSi⁺: 632.2820; Found: 632.2806.

Rf (PE/EtOAc 6:4) = 0.57.

N-(3-(1-ethyl-3-(3-hydroxy-1-(2-nitrophenyl)propyl)cyclopent-2-en-1-yl)-propyl)-2-nitrobenzenesulfonamide 239

From TBS-protected alcohol 437

![Chemical Structure](image)

To a solution of compounds 437a/437b (dr 1:1, 3.2 g, 5.0 mmol) in MeOH (50 mL) at 0 °C was added dropwise acetyl chloride (30 μL, 0.50 mmol, 10 mol%). After stirring for 1 h at RT, the reaction mixture was concentrated in vacuo. The crude compounds 239a/239b thus obtained was used for the next step without further purification (2.6 g, quantitative yield, no change in dr).

From monoprotected diol 213

![Chemical Structure](image)

To a solution of alcohols 213a/213b (dr 1:1, 60 mg, 0.13 mmol), neopentyl alcohol (5.8 mg, 0.060 mmol, 0.40 equiv), o-nitrophenylsulfonamide (53 mg, 0.27 mmol, 2.0 equiv) and PPh₃...
(35 mg, 0.13 mmol, 1.0 equiv) in toluene (4.0 mL) at RT was added DEAD (40 wt.% in toluene, 60 μL, 0.13 mmol, 1.0 equiv). After stirring for 1 h at RT, additional PPh₃ (35 mg, 0.13 mmol, 1.0 equiv) and DEAD (40 wt.% in toluene, 60 μL, 0.13 mmol, 1.0 equiv) were added. The reaction mixture was stirred for one more hour. TBAF (1 M solution in THF, 0.39 mL, 0.39 mmol, 3.0 equiv) was added and the reaction mixture was stirred at RT for 3 h. Saturated aqueous NaHCO₃ was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded the two diastereoisomers 239a and 239b as a mixture (yellow oil, 50 mg, 75% yield, no change in dr).

Compound 239a

1H NMR (400 MHz, CDCl₃): δ 8.13 (m, 1H, C₂₈−H), 7.85 (m, 1H, C₂₅−H), 7.77-7.71 (m, 2H, C⁹,₁₁−H), 7.69 (d, J = 7.5 Hz, 1H, C₁₂−H), 7.56 (t, J = 7.0 Hz, 1H, C₁₀−H), 7.40-7.31 (m, 2H, C₉,₁₁−H), 5.27 (br s, 1H, N₄−H), 5.21 (s, 1H, C₂₁−H), 4.05 (t, J = 6.9 Hz, 1H, C₇−H), 3.61 (m, 1H, C₅−H), 3.52 (m, 1H, C₅−H), 3.07 (q, J = 6.4 Hz, 2H, C₃−H), 2.04-1.88 (m, 2H, C₆,₁₆−H), 1.58 (m, 1H, C₁₇−H), 1.47-1.36 (m, 3H, C₁₄,₁₇−H), 1.35-1.22 (m, 4H, C₁₅,₁₉−H), 0.73 (t, J = 7.4 Hz, 3H, C₁₈−H), OH peak not observed.

13C NMR (101 MHz, CDCl₃): δ 150.9 (C₁₃), 148.2 (C²⁴), 144.7 (C²), 137.1 (C₈), 134.0 (C₂₃), 133.7 (C²₆), 132.9 (C²¹), 132.7 (C²⁷), 132.5 (C₁₀), 131.2 (C₂₈), 129.2 (C₉), 127.4 (C₁₁), 125.5 (C₂₅), 124.0 (C₁₂), 60.8 (C₅), 51.8 (C²⁹), 44.8 (C³), 37.5 (C⁷), 37.0 (C₆), 36.2 (C₁₅), 33.7 (C₁₆), 33.4 (C₁₇), 32.2 (C¹⁹), 25.4 (C₁₄), 9.1 (C₁₈).

IR: 3565 (br w), 3354 (br w), 2937 (w), 2852 (w), 1525 (m), 1352 (m), 1165 (m), 1051 (w), 909 (m), 730 (s).


Rf (PE/EtOAc 4:6) = 0.48.

Compound 239b

1H NMR (400 MHz, CDCl₃): δ 8.14 (m, 1H, C₂₈−H), 7.87 (m, 1H, C₂₅−H), 7.78-7.72 (m, 2H, C₂₆,₂₇−H), 7.69 (dd, J = 8.0, 1.6 Hz, 1H, C₁₂−H), 7.52 (td, J = 7.6, 1.6 Hz, 1H, C₁₀−H), 7.38-7.31 (m, 2H, C⁹,₁₁−H), 5.28 (t, J = 6.2 Hz, 1H, N₄−H), 5.22 (d, J = 1.8 Hz, 1H, C₂¹−H), 4.07 (t, J = 7.1 Hz, 1H, C₇−H), 3.61 (m, 1H, C₅−H), 3.52 (m, 1H, C₅−H), 3.07 (q, J = 6.7 Hz, 2H, C³−H), 2.19 (m, 1H, C₆−H), 2.02-1.91 (m, 3H, C₆,₁₆−H), 2.55-1.35 (m, 4H, C₁₄,₁₇−H), 1.35-1.23 (m, 4H, C₁₅,₁₉−H), 0.74 (t, J = 7.5 Hz, 3H, C₁₈−H), OH peak not observed.
8.3. Experimental Procedures of Chapter 3

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 150.9 (C$_{13}$), 148.2 (C$_{24}$), 144.5 (C$_{2}$), 137.0 (C$_{8}$), 134.1 (C$_{23}$), 133.7 (C$_{26}$), 132.9 (C$_{21}$), 132.7 (C$_{27}$), 132.6 (C$_{10}$), 131.2 (C$_{28}$), 129.2 (C$_{9}$), 127.4 (C$_{11}$), 125.5 (C$_{25}$), 124.1 (C$_{12}$), 60.8 (C$_{5}$), 51.8 (C$_{20}$), 44.7 (C$_{3}$), 37.4 (C$_{6}$), 36.8 (C$_{15}$), 36.2 (C$_{7}$), 33.4 (C$_{16}$), 33.2 (C$_{17}$), 32.2 (C$_{19}$), 25.2 (C$_{14}$), 9.1 (C$_{18}$).

IR: 3566 (br w), 3341 (br w), 2935 (w), 2853 (w), 1526 (s), 1358 (s), 1166 (s), 1061 (w), 741 (m).

HRMS: (ESI$^+$) m/z: [M + Na]$^+$ Calcd for C$_{25}$H$_{31}$N$_3$NaO$_7$S$: 540.1775; Found: 540.1786.

$R_f$ (PE/EtOAc 4:6) = 0.48.

3-(3-ethyl-3-(2-nitrophenyl)sulfonamido)propyl)cyclopent-1-en-1-yl)-3-(2-nitrophenyl)propyl methanesulfonate 438

To a solution of alcohols 239a/239b (dr 1:1, 20 mg, 0.040 mmol) in DCM (1.0 mL) at RT was added triethylamine (8.0 μL, 0.060 mmol, 1.5 equiv) and MsCl (3.7 μL, 0.050 mmol, 1.2 equiv) dropwise. The reaction mixture was stirred for 0.5 h. Saturated aqueous NaHCO$_3$ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product thus obtained was used for the next step without further purification (24 mg, quantitative yield, no change in dr). An analytical sample was obtained by FCC (PE/EtOAc 4:6) to afford 438a and 438b (yellow oils).

Compound 438a

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.13 (m, 1H, C$_{28}^-H$), 7.85 (m, 1H, C$_{25}^-H$), 7.77-7.71 (m, 3H, C$_{12,26,27}^-H$), 7.59 (t, J = 7.8 Hz, 1H, C$_{10}^-H$), 7.39 (t, J = 7.8 Hz, 1H, C$_{11}^-H$), 7.36 (d, J = 7.8 Hz, 1H, C$_{9}^-H$), 5.32 (t, J = 6.4 Hz, 1H, N$^4^-H$), 5.26 (m, 1H, C$_{21}^-H$), 4.21 (dt, J = 9.9,6.5 Hz, 1H, C$_{5}^-H$), 4.13 (dt, J = 9.9,6.5 Hz, 1H, C$_{3}^-H$), 4.09 (t, J = 7.4 Hz, 1H, C$_{7}^-H$), 3.07 (q, J = 7.4 Hz, 2H, C$_{3}^-H$), 2.99 (s, 3H, C$_{22}^-H$), 2.38 (dddd, J = 14.2,7.1,7.1,7.0 Hz, 1H, C$_{6}^-H$), 2.22 (ddddd,
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\[ J = 14.2, 7.1, 7.1, 7.0 \text{ Hz}, 1\text{H}, \text{C}^6-\text{H}), 2.10 \text{ (m, 1H, C}^{16}-\text{H}), 1.96 \text{ (m, 1H, C}^{16}-\text{H}), 1.64-1.54 \text{ (m, 2H, C}^{17}-\text{H}), 1.49-1.40 \text{ (m, 2H, C}^{14}-\text{H}), 1.35-1.27 \text{ (m, 4H, C}^{15,19}-\text{H}), 0.74 \text{ (t, } J = 7.3 \text{ Hz, 3H, C}^{18}-\text{H}).

^{13}\text{C NMR (101 MHz, CDCl}_3)\): \[ \delta 150.6 \text{ (C}^{13}), 148.2 \text{ (C}^{24}), 143.3 \text{ (C}^2), 136.0 \text{ (C}^8), 134.0 \text{ (C}^{23}), 133.7 \text{ (C}^{26}), 133.6 \text{ (C}^{21}), 133.0 \text{ (C}^{10or27}), 132.9 \text{ (C}^{10or27}), 131.2 \text{ (C}^{28}), 129.0 \text{ (C}^9), 127.9 \text{ (C}^{11}), 125.5 \text{ (C}^{25}), 124.4 \text{ (C}^{12}), 67.5 \text{ (C}^5), 51.9 \text{ (C}^{20}), 44.7 \text{ (C}^3), 37.6 \text{ (C}^{22}), 37.5 \text{ (C}^7), 36.0 \text{ (C}^{15}), 33.4 \text{ (C}^9), 33.4 \text{ (C}^{16}), 33.4 \text{ (C}^{17}), 32.1 \text{ (C}^{19}), 25.4 \text{ (C}^{14}), 9.1 \text{ (C}^{18}).

\text{IR:} 3343 \text{ (br w), 2930 \text{ (w), 2853 \text{ (w), 1529 \text{ (s), 1355 \text{ (s), 1172 \text{ (s), 976 \text{ (m).}}}})

\text{HRMS: (ESI}^+\text{) m/z: [M} + \text{H}]^+ \text{ Calcd for C}_{26}\text{H}_{34}\text{N}_3\text{O}_9\text{S}_2^+: 596.1731; \text{ Found: 596.1722.}

R_f \text{ (PE/EtOAc 6:4) = 0.48.}

\text{Compound 438b}

\text{^1H NMR (400 MHz, CDCl}_3): \[ \delta 8.14 \text{ (m, 1H, C}^{28}-\text{H}), 7.86 \text{ (m, 1H, C}^{25}-\text{H}), 7.78-7.71 \text{ (m, 3H, C}^{12,26,27}-\text{H}), 7.55 \text{ (t, } J = 7.7 \text{ Hz, 1H, C}^{10}-\text{H}), 7.41-7.34 \text{ (m, 2H, C}^{9,11}-\text{H}), 5.35 \text{ (t, } J = 5.7 \text{ Hz, 1H, N}^4-\text{H}), 5.28 \text{ (s, 1H, C}^{21}-\text{H}), 4.23 \text{ (dt, } J = 10.0, 7.0 \text{ Hz, 1H, C}^5-\text{H}), 4.15 \text{ (dt, } J = 10.0, 7.0 \text{ Hz, 1H, C}^5-\text{H}), 4.06 \text{ (t, } J = 7.4 \text{ Hz, 1H, C}^7-\text{H}), 3.11-3.04 \text{ (m, 2H, C}^3-\text{H}), 3.00 \text{ (s, 3H, C}^{22}-\text{H}), 2.35 \text{ (m, 1H, C}^6-\text{H}), 2.22 \text{ (m, 1H, C}^6-\text{H}), 2.09-1.94 \text{ (m, 2H, C}^{16}-\text{H}), 1.55-1.48 \text{ (m, 2H, C}^{17}-\text{H}), 1.47-1.39 \text{ (m, 2H, C}^{14}-\text{H}), 1.36-1.28 \text{ (m, 4H, C}^{15,19}-\text{H}), 0.76 \text{ (t, } J = 7.4 \text{ Hz, 3H, C}^{18}-\text{H}).

\text{IR:} 3329 \text{ (br w), 2938 \text{ (w), 2852 \text{ (w), 1528 \text{ (s), 1353 \text{ (s), 1171 \text{ (s), 970 \text{ (w), 921 \text{ (w), 786 \text{ (w), 743 \text{ (w).}})}})

\text{HRMS: (ESI}^+\text{) m/z: [M} + \text{Na}]^+ \text{ Calcd for C}_{26}\text{H}_{33}\text{N}_3\text{NaO}_9\text{S}_2^+: 618.1550; \text{ Found: 618.1541.}

R_f \text{ (PE/EtOAc 6:4) = 0.48.}
8.3. Experimental Procedures of Chapter 3

1-ethyl-8-(2-nitrophenyl)-5-((2-nitrophenyl)sulfonyl)-5-azabicyclo[7.2.1]dodec-9(12)-ene 212

![Diagram of the compounds](image)

To a solution of alcohols 239a/239b (dr 1:1, 68 mg, 0.13 mmol), neopentyl alcohol (5.8 mg, 0.060 mmol, 0.40 equiv) and PPh₃ (35 mg, 0.13 mmol, 1.0 equiv) in toluene (4.5 mL) at RT was added DEAD (40 wt.% in toluene, 60 μL, 0.13 mmol, 1.0 equiv). After stirring for 1 h at RT, additional PPh₃ (35 mg, 0.13 mmol, 1.0 equiv) and DEAD (40 wt.% in toluene, 60 μL, 0.13 mmol, 1.0 equiv) were added. The reaction mixture was stirred for one more hour. Saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded the two diastereoisomers 212a and 212b as yellow prism and yellow oil, respectively (53 mg, 81% yield, no change in dr).

Compound 212a

mp = 188.6-189 °C (CHCl₃ / C₇H₁₆).

**¹H NMR (400 MHz, CDCl₃):** δ 7.91 (dd, J = 7.4,2.0 Hz, 1H, C27−H), 7.74-7.65 (m, 3H, C12,25,26−H), 7.59 (dd, J = 7.3,1.9 Hz, 1H, C24−H), 7.55 (td, J = 7.7,1.3 Hz, 1H, C10−H), 7.47 (dd, J = 7.7,1.4 Hz, 1H, C9−H), 7.35 (td, J = 7.7,1.4 Hz, 1H, C11−H), 5.47 (s, 1H, C21−H), 4.33 (dd, J = 12.3,3.2 Hz, 1H, C7−H), 4.03 (dd, J = 15.6,7.2 Hz, 1H, C3−H), 3.73 (ddd, J = 15.3,10.3,4.9 Hz, 1H, C5−H), 3.03 (dd, J = 15.6,8.6 Hz, 1H, C5−H), 2.72 (ddd, J = 15.0,6.7,2.4 Hz, 1H, C5−H), 2.68-2.54 (m, 2H, C6,16−H), 2.13 (ddd, J = 14.5,7.2,3.2 Hz, 1H, C8−H), 2.03 (m, 1H, C14−H), 1.82-1.63 (m, 3H, C16,17−H), 1.53 (dd, J = 14.6,6.7 Hz, 1H, C15−H), 1.42-1.20 (m, 4H, C14,15,19−H), 0.75 (t, J = 7.5 Hz, 3H, C18−H).

**¹³C NMR (101 MHz, CDCl₃):** δ 150.3 (C13), 149.1 (C23), 141.9 (C2), 136.8 (C21), 136.1 (C8), 133.7 (C25), 132.3 (C10), 131.4 (C26), 131.2 (C22), 130.6 (C27), 128.6 (C9), 127.2 (C11), 124.4 (C12), 124.1 (C24), 56.6 (C3), 54.8 (C5), 53.5 (C20), 43.0 (C7), 40.3 (C15), 35.7 (C6), 33.9 (C19), 32.6 (C17), 31.4 (C16), 28.2 (C14), 9.4 (C18).
Chapter 8: Experimental Section

IR: 2960 (w), 2934 (w), 2849 (w), 1544 (s), 1529 (s), 1465 (w), 1355 (s), 1164 (m), 784 (m), 755 (m).

HRMS: (ESI+) m/z: [M + H]+ Calcd for C_{25}H_{30}N_{3}O_{6}S+: 500.1850; Found: 500.1860.

*RF* (PE/EtOAc 4:6) = 0.59.

**Compound 212b**

**1H NMR (400 MHz, CDCl₃):** δ 7.91 (dd, *J* = 7.5, 1.9 Hz, 1H, C_{27}−H), 7.78 (dd, *J* = 7.8, 1.4 Hz, 1H, C_{12}−H), 7.70 (td, *J* = 7.5, 1.9 Hz, 1H, C_{25}−H), 7.66 (td, *J* = 7.5, 1.8 Hz, 1H, C_{26}−H), 7.60 (dd, *J* = 7.8, 1.5 Hz, 1H, C_{3}−H), 7.57 (dd, *J* = 7.5, 1.8 Hz, 1H, C_{24}−H), 7.54 (td, *J* = 7.8, 1.4 Hz, 1H, C_{10}−H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H, C_{11}−H), 5.63 (s, 1H, C_{21}−H), 3.85 (dd, *J* = 11.5, 3.4 Hz, 1H, C_{7}−H), 3.54 (ddd, *J* = 15.4, 7.5, 2.1 Hz, 1H, C_{5}−H), 3.27 (m, 1H, C_{3}−H), 3.07 (m, 1H, C_{3}−H), 2.94 (ddd, *J* = 15.4, 7.2, 2.6 Hz, 1H, C_{5}−H), 2.54 (ddtd, *J* = 15.2, 11.4, 7.2, 2.1 Hz, 1H, C_{6}−H), 2.44-2.36 (m, 2H, C_{16}−H), 2.17 (ddt, *J* = 15.3, 7.9, 3.3 Hz, 1H, C_{6}−H), 1.80-1.63 (m, 3H, C_{14,15,17}−H), 1.58 (ddd, *J* = 13.6, 8.4, 3.7 Hz, 1H, C_{17}−H), 1.53-1.43 (m, 2H, C_{19}−H), 1.42-1.38 (m, 2H, C_{14,15}−H), 0.85 (t, *J* = 7.5 Hz, 3H, C_{18}−H).

**13C NMR (101 MHz, CDCl₃):** δ 149.7 (C_{13}), 149.0 (C_{23}), 140.7 (C_{2}), 137.6 (C_{21}), 137.4 (C_{6}), 133.7 (C_{2}), 132.9 (C_{10}), 131.4 (C_{26}), 131.2 (C_{22}), 131.0 (C_{27}), 129.6 (C_{9}), 127.4 (C_{11}), 124.5 (C_{12}), 124.0 (C_{24}), 54.5 (C_{20}), 52.5 (C_{5}), 48.7 (C_{3}), 42.1 (C_{7}), 39.2 (C_{16}), 38.3 (C_{15}), 35.6 (C_{6}), 33.3 (C_{19}), 32.1 (C_{17}), 22.3 (C_{14}), 9.8 (C_{18}).

IR: 2958 (w), 2932 (w), 2850 (w), 1545 (s), 1526 (s), 1462 (w), 1354 (s), 1165 (m), 782 (m), 734 (m).

HRMS: (ESI+) m/z: [M + H]+ Calcd for C_{25}H_{30}N_{3}O_{6}S+: 500.1850; Found: 500.1843.

*RF* (PE/EtOAc 4:6) = 0.59.
8.3. Experimental Procedures of Chapter 3

5-ethyl-9-(2-nitrophenyl)-1-((2-nitrophenyl)sulfonyl)-8-oxazacycloundecane-5-carbaldehyde 211

A solution of the macrocycle 212 (dr 1:1, 10 mg, 0.020 mmol) in DCM (0.50 mL) was stirred at -78 °C. Ozone was bubbled through the solution until a blue color appears (approximately 15 s). Argon was then bubbled through the solution for 10 min. Me₂S (0.10 mL) was added and the reaction mixture was stirred overnight at RT. The reaction mixture was concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 4:6) afforded the compound 211 as a yellow oil (8.6 mg, 81% yield, no change in dr).

\textbf{Compound 211a}

\begin{align*}
^1\text{H NMR (400 MHz, CDCl}_3\text{)}: &\delta 9.45 (s, 1H, C_{21}^-H), 7.89 (dd, J = 7.7, 1.4 Hz, 1H, C_{12}^-H), 7.83 (dd, J = 8.1, 0.9 Hz, 1H, C_{27}^-H), 7.71 (td, J = 7.5, 1.5 Hz, 1H, C_{23}^-H), 7.67 (td, J = 7.5, 1.6 Hz, 1H, C_{26}^-H), 7.55 (dd, J = 7.6, 1.5 Hz, 1H, C_{24}^-H), 7.50 (td, J = 7.7, 1.4 Hz, 1H, C_{10}^-H), 7.41 (td, J = 7.7, 1.0 Hz, 1H, C_{11}^-H), 7.22 (dd, J = 7.7, 1.0 Hz, 1H, C_{10}^-H), 5.25 (dd, J = 11.4, 2.1 Hz, 1H, C_{2}^-H), 3.70-3.54 (m, 1H, C_{3}^-H), 3.27 (dd, J = 15.1, 5.5 Hz, 1H, C_{5}^-H), 3.12 (m, 1H, C_{5}^-H), 2.82 (dt, J = 13.1, 2.6 Hz, 1H, C_{16}^-H), 2.69 (m, 1H, C_{16}^-H), 2.29 (m, 1H, C_{6}^-H), 2.14 (m, 1H, C_{6}^-H), 2.04-1.92 (m, 3H, C_{15},17^-H), 1.88 (m, 1H, C_{16}^-H), 1.71 (td, J = 13.7, 5.9 Hz, 1H, C_{17}^-H), 1.63-1.43 (m, 2H, C_{19}^-H), 0.95-0.70 (m, 2H, C_{14}^-H), 0.79 (t, J = 7.5 Hz, 3H, C_{18}^-H).

^13\text{C NMR (101 MHz, CDCl}_3\text{)}: &\delta 211.6 (C_{2}), 206.0 (C_{21}), 150.5 (C_{13}), 149.2 (C_{23}), 134.0 (C_{10}), 132.9 (C_{25}), 131.8 (C_{8}), 131.5 (C_{26}or27), 131.4 (C_{26}or27), 130.1 (C_{22}), 130.0 (C_{8}), 128.7 (C_{11}), 125.3 (C_{12}), 124.0 (C_{24}), 53.0 (C_{20}), 51.5 (C_{3}), 49.3 (C_{7}), 46.0 (C_{5}), 36.9 (C_{16}), 32.1 (C_{6}), 27.9 (C_{15}), 27.4 (C_{19}), 25.4 (C_{17}), 20.5 (C_{14}), 8.6 (C_{18}).

\text{IR}: 2961 (w), 2878 (w), 1711 (m), 1545 (s), 1529 (s), 1465 (w), 1373 (s), 1354 (s), 1171 (m), 785 (m), 745 (m), 731 (m).

\text{HRMS}: (ESI\textsuperscript{+}) m/z: [M + H]\textsuperscript{+} Calcd for C_{25}H_{30}N_{3}O_{8}S\textsuperscript{+}: 532.1748; Found: 532.1754.

\text{RF} (PE/EtOAc 4:6) = 0.47.
Compound 211b

\[ \text{^1H NMR (400 MHz, CDCl}_3\text{): } \delta 9.41 (s, 1H, C}_21\text{−H}), 7.86 (dd, } J = 7.8, 1.4 \text{ Hz, 1H, C}_12\text{−H}), 7.85 \text{ (dd, } J = 7.7, 1.3 \text{ Hz, 1H, C}_27\text{−H}), 7.54 (dd, } J = 7.7, 1.4 \text{ Hz, 1H, C}_12\text{−H}), 7.53 (td, } J = 7.8, 1.3 \text{ Hz, 1H, C}_10\text{−H}), 7.43 \text{ (td, } J = 7.8, 1.0 \text{ Hz, 1H, C}_11\text{−H}), 7.22 \text{ (dd, } J = 7.8, 1.0 \text{ Hz, 1H, C}_9\text{−H}), 3.61 \text{ (td, } J = 13.1, 3.1 \text{ Hz, 1H, C}_3\text{−H}), 3.26 \text{ (dd, } J = 15.0, 5.3 \text{ Hz, 1H, C}_7\text{−H}), 3.06 \text{ (dd, } J = 15.2,12.5,4.8 \text{ Hz, 1H, C}_8\text{−H}), 2.87 \text{ (dd, } J = 14.7,10.9 \text{ Hz, 1H, C}_16\text{−H}), 2.71 \text{ (dt, } J = 13.3,2.7 \text{ Hz, 1H, C}_3\text{−H}), 2.26 \text{ (m, 2H, C}_6\text{−H}), 2.12 \text{ (m, 1H, C}_6\text{−H}), 2.00 \text{ (dd, } J = 14.7,10.3 \text{ Hz, 1H, C}_16\text{−H}),1.92-1.70 \text{ (m, 3H, C}_15\text{−H}), 1.77 \text{ (q, } J = 7.7 \text{ Hz, 2H, C}_9\text{−H}), 1.31-1.12 \text{ (m, 2H, C}_14\text{−H}), 0.76 \text{ (t, } J = 7.5 \text{ Hz, 3H, C}_18\text{−H}). \]

\[ \text{^13C NMR (101 MHz, CDCl}_3\text{): } \delta 212.7 \text{ (C}_2\text{), 205.9 \text{ (C}_21\text{), 150.5 \text{ (C}_13\text{), 149.1 \text{ (C}_23\text{), 134.0 \text{ (C}_10\text{), 133.0 \text{ (C}_25\text{), 131.8 \text{ (C}_8\text{), 131.3 \text{ (C}_25\text{or27\text{), 131.3 \text{ (C}_25\text{or27\text{, 130.0 \text{ (C}_22\text{), 128.7 \text{ (C}_11\text{), 125.3 \text{ (C}_12\text{, 124.0 \text{ (C}_24\text{, 53.0 \text{ (C}_7\text{, 51.4 \text{ (C}_3\text{, 48.9 \text{ (C}_7\text{, 46.0 \text{ (C}_5\text{, 34.4 \text{ (C}_16\text{, 32.3 \text{ (C}_6\text{, 30.5 \text{ (C}_15\text{, 27.3 \text{ (C}_19\text{, 23.3 \text{ (C}_17\text{, 21.7 \text{ (C}_14\text{, 8.7 \text{ (C}_18\text{. \]

IR: \(2963 \text{ (w), 2932 \text{ (w), 2878 \text{ (w), 1713 \text{ (m), 1544 \text{ (s), 1528 \text{ (s), 1465 \text{ (w), 1352 \text{ (s), 1168 \text{ (m), 912 \text{ (w), 852 \text{ (w), 782 \text{ (m), 733 \text{ (m), 674 \text{ (m). \]

HRMS: (ESI\(^+\)) m/z: \([\text{M + H\(^+\)}] \text{ Calcd for C}_25\text{H}_30\text{N}_3\text{O}_8\text{S}^+: 532.1748; \text{ Found: 532.1754. \]

\[ \text{Rf (PE/EtOAc 4:6) = 0.47.} \]

\((\pm)-1,2\text{-dehydroaspidospermidine 2} \]

A solution of the macrocycles 212a/212b (dr 1:1, 10 mg, 0.020 mmol) in DCM (0.50 mL) was stirred at -78 °C. Ozone was bubbled through the solution until a blue color appeared (approximately 15 s). Argon was then bubbled through the solution for 10 min. Me\(_2\)S (50 \(\mu\)L) was added and the reaction mixture was stirred overnight at RT. Cesium carbonate (20 mg, 0.060 mmol, 3.0 equiv) and thiophenol (6.0 \(\mu\)L, 0.060 mmol, 3.0 equiv) were added. The reaction mixture was stirred at RT for 24 h. Methanol (0.20 mL) was then added, followed by aqueous NH\(_4\)OAc (2.5 M solution in H\(_2\)O, 0.30 mL). A mixture of TiCl\(_3\) (20% in aqueous 3%
8.3. Experimental Procedures of Chapter 3

HCl, 60 μL, 0.10 mmol, 5.0 equiv) and aqueous NH₄OAc (2.5 M solution in H₂O, 0.3.0 mL) was then added dropwise. The dark purple solution was stirred at RT for 30 min. The reaction mixture was then poured into saturated aqueous NaHCO₃. The mixture turned black. EtOAc was added and, after vigorous shaking, the mixture turned to white. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc/Et₃N 90:10:2) afforded (+)-1,2-dehydroaspidospermidine 2 as a colorless oil (2.8 mg, 50% yield, single diastereoisomer). The spectroscopic data of this compound were in accord with those reported in the literature. 66

1H NMR (400 MHz, CDCl₃): δ 7.51 (d, J = 7.3 Hz, 1H, C₁₂−H), 7.33 (d, J = 7.3 Hz, 1H, C₉−H), 7.29 (td, J = 7.3,1.3 Hz, 1H, C₁₁−H), 7.16 (td, J = 7.3,1.0 Hz, 1H, C₁⁰−H), 3.18 (t, J = 7.5 Hz, 2H, C₃,₅−H), 3.11 (ddd, J = 14.4,11.8,5.3 Hz, 1H, C₁₆−H), 2.76 (ddd, J = 14.4,10.5,3.6 Hz, 1H, C₁⁰−H), 2.59 (ddd, J = 11.5,8.4,5.7 Hz, 1H, C₅−H), 2.46 (td, J = 12.8,3.3 Hz, 1H, C₁⁷−H), 2.40 (s, 1H, C₂¹−H), 2.14-2.06 (m, 2H, C₃₆−H), 1.85 (qt, J = 13.4,4.7 Hz, 1H, C₁⁴−H), 1.65 (dd, J = 12.2,5.4 Hz, 1H, C₅−H), 1.61-1.52 (m, 2H, C₁₄,₁₇−H), 1.47 (dd, J = 13.7,2.7 Hz, 1H, C₁₅−H), 1.00 (td, J = 13.6,5.0 Hz, 1H, C₁⁵−H), 0.70 (dq, J = 14.5,7.4 Hz, 1H, C₁₉−H), 0.64 (dq, J = 14.5,7.4 Hz, 1H, C₁⁹−H), 0.49 (t, J = 7.4 Hz, 3H, C₁₈−H).

13C NMR (101 MHz, CDCl₃): δ 192.5 (C₂), 154.7 (C₁₃), 147.3 (C₈), 127.6 (C₁¹), 125.3 (C₁⁰), 121.1 (C₉), 120.3 (C₁²), 79.2 (C₂¹), 61.5 (C₇), 54.7 (C₅), 52.2 (C₃), 36.7 (C₂⁰), 35.3 (C₆), 33.4 (C₁₅), 29.9 (C₁₉), 27.4 (C₁₇), 23.9 (C₁₆), 22.2 (C₁₄), 7.4 (C₁₈).

IR: 2933 (m), 2773 (m), 1575 (m), 1456 (m), 1324 (w), 1251 (w), 1194 (w), 1123 (w), 1014 (w), 751 (w), 615 (s).


Rf (PE/EtOAc/Et₃N 4:4:0.5) = 0.54 (red to blue with molybdenate stain).

(±)-aspidospermidine 3

A solution of the macrocycles 2₁²a/2₁²b (dr 1:1, 10 mg, 0.020 mmol) in DCM (0.50 mL) was
stirred at -78 °C. Ozone was bubbled through the solution until a blue color appeared (approximately 15 s). Argon was then bubbled through the solution for 10 min. Me₂S (0.050 mL) was added and the reaction mixture was stirred overnight at RT. Cesium carbonate (20 mg, 0.060 mmol, 3.0 equiv) and thiophenol (6.0 μL, 0.060 mmol, 3.0 equiv) were added. The reaction mixture was stirred at RT for 24 h. Methanol (0.20 mL) was then added, followed by aqueous NH₄OAc (2.5 M solution in H₂O, 0.30 mL). A mixture of TiCl₃ (20% in aqueous 3% HCl, 60 μL, 0.10 mmol, 5.0 equiv) and aqueous NH₄OAc (2.5 M solution in H₂O, 0.30 mL) was then added dropwise. The dark purple solution was stirred at RT for 30 min. Saturated aqueous NaHCO₃ (1.0 mL) was then added. The mixture turned black, and after vigorous stirring for 15 min, the mixture turned to white. NaBH₄ (7.6 mg, 0.20 mmol, 10 equiv) was then added, and the mixture was stirred for 2 h. EtOAc was added. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc/Et₃N 90:10:2) afforded (+)-aspidospermidine 3 as a colorless oil (2.9 mg, 51% yield, single diastereoisomer). The spectroscopic data of this compound were in accord with those reported in the literature.⁷⁰

**1H NMR (800 MHz, CDCl₃):** δ 7.08 (d, J = 7.5 Hz, 1H, C⁹−H), 7.02 (td, J = 7.6,1.0 Hz, 1H, C¹¹−H), 6.73 (td, J = 7.2,0.7 Hz, 1H, C¹⁰−H), 6.64 (d, J = 7.8 Hz, 1H, C¹²−H), 3.51 (dd, J = 11.1,6.2 Hz, 1H, C²−H), 3.12 (td, J = 8.9,2.7 Hz, 1H, C³−H), 3.06 (m, 1H, C³−H), 2.29 (dt, J = 13.0,8.6 Hz, 1H, C⁹−H), 2.24 (dt, J = 10.1,8.6 Hz, 1H, C⁵−H), 2.21 (s, 1H, C²¹−H), 2.01-1.90 (m, 2H, C³¹⁶−H), 1.74 (qt, J = 13.1,3.9 Hz, 1H, C¹⁴−H), 1.66-1.61 (m, 2H, C¹⁵¹⁷−H), 1.51 (m, 1H, C¹⁴−H), 1.50-1.45 (m, 2H, C⁶¹⁹−H), 1.39 (dt, J = 13.9,2.7 Hz, 1H, C¹⁷−H), 1.11 (td, J = 13.4,4.8 Hz, 1H, C¹⁵−H), 1.05 (dt, J = 13.7,2.9 Hz, 1H, C¹⁶−H), 0.87 (dq, J = 14.4,7.9 Hz, 1H, C¹⁹−H), 0.63 (t, J = 7.5 Hz, 3H, C¹⁸−H).

**13C NMR (101 MHz, CDCl₃):** δ 149.5 (C¹³), 135.9 (C⁸), 127.2 (C¹¹), 123.0 (C⁹), 119.1 (C¹⁰), 110.5 (C¹²), 71.4 (C²¹), 65.8 (C²), 54.0 (C³), 53.5 (C⁵), 53.2 (C³), 39.0 (C⁶), 35.8 (C²⁰), 34.6 (C¹⁵), 30.1 (C¹⁹), 28.2 (C¹⁷), 23.2 (C¹⁶), 21.9 (C¹⁴), 7.0 (C¹⁸).

**IR:** 3361 (w), 2930 (m), 2778 (w), 2772 (w), 1607 (w), 1481 (m), 1462 (m), 1332 (w), 1259 (m), 1179 (w), 1024 (m), 905 (w), 737 (s).

**HRMS:** (ESI⁺) m/z: [M + H]⁺ Calcd for C₁₉H₂₇N₂⁺: 283.2169; Found: 283.2107.

**Rf** (PE/EtOAc/Et₃N 4:4:0.5) = 0.25 (red to blue with molybdenate stain).
8.3. Experimental Procedures of Chapter 3

(±)-vincadifformine 4

To a solution of (±)-1,2-dehydroaspidospermidine 2 (10 mg, 0.036 mmol) in THF (0.50 mL) at -78 °C was added dropwise n-BuLi (1.1 M in THF, 36 μL, 0.036 mmol, 1.0 equiv). The solution was stirred for 30 min. Methyl cyanoformate (4.5 μL, 0.058 mmol, 1.6 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 30 min, and allowed to warm to 0 °C. The reaction was monitored by TLC. After complete consumption of the starting material, saturated aqueous NaHCO₃ was added slowly, and the reaction mixture was warmed up to RT. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/Et₂O/Et₃N 80:10:2) afforded (±)-vincadifformine 4 as a colorless oil (6.0 mg, 50% yield, single diastereoisomer). The spectroscopic data of this compound were in accord with those reported in the literature.⁷⁰

\[ \begin{align*}
\text{H NMR (} & \text{400 MHz, CDCl}_3\text{): } \delta 8.89 \text{ (s, 1H, } N^1-\text{H)}, 7.18 \text{ (d, } J = 7.6 \text{ Hz, 1H, } C^9-\text{H)}, 7.12 \text{ (t, } J = 7.1 \text{ Hz, 1H, } C^{11}-\text{H)}, 6.85 \text{ (t, } J = 7.4 \text{ Hz, 1H, } C^{10}-\text{H)}, 6.79 \text{ (d, } J = 7.6 \text{ Hz, 1H, } C^{12}-\text{H)}, 3.76 \text{ (s, 3H, } C^{23}-\text{H}), 3.12 \text{ (m, 1H, } C^3-\text{H}), 2.92 \text{ (t, } J = 7.4 \text{ Hz, 1H, } C^5-\text{H}), 2.72 \text{ (d, } J = 15.1 \text{ Hz, 1H, } C^{17}-\text{H}), 2.55 \text{ (ddd, } J = 11.4,8.2,4.6 \text{ Hz, 1H, } C^3-\text{H}), 2.45 \text{ (d, } J = 0.9 \text{ Hz, 1H, } C^{21}-\text{H}), 2.40 \text{ (td, } J = 10.7,3.0 \text{ Hz, 1H, } C^3-\text{H}), 2.27 \text{ (dd, } J = 15.2,1.6 \text{ Hz, 1H, } C^{17}-\text{H}), 2.05 \text{ (ddd, } J = 11.3,11.3,6.5 \text{ Hz, 1H, } C^6-\text{H}), 1.88-1.76 \text{ (m, 2H, } C^{14}-\text{H}), 1.70 \text{ (dd, } J = 11.5,4.8 \text{ Hz, 1H, } C^6-\text{H}), 1.21 \text{ (m, 1H, } C^{15}-\text{H}), 0.96 \text{ (m, 1H, } C^{19}-\text{H}), 0.88 \text{ (m, 1H, } C^{15}-\text{H}), 0.62 \text{ (m, 1H, } C^{19}-\text{H}), 0.57 \text{ (t, } J = 7.0 \text{ Hz, 3H, } C^{18}-\text{H}).
\end{align*} \]

\[ \begin{align*}
\text{C NMR (} & \text{101 MHz, CDCl}_3\text{): } \delta 169.4 \text{ (C}^{22}\text{), 168.0 \text{ (C}^2\text{), 143.5 \text{ (C}^{13}\text{), 138.1 \text{ (C}^8\text{), 127.6 \text{ (C}^{11}\text{), 121.1 \text{ (C}^9\text{), 120.6 \text{ (C}^{10}\text{), 109.5 \text{ (C}^{12}\text{), 92.8 \text{ (C}^{16}\text{), 72.9 \text{ (C}^{21}\text{), 55.16 \text{ (C}^7\text{), 51.9 \text{ (C}^5\text{), 51.1 \text{ (C}^3\text{), 50.9 \text{ (C}^{23}\text{), 45.4 \text{ (C}^6\text{), 38.4 \text{ (C}^{20}\text{), 33.0 \text{ (C}^{15}\text{), 29.4 \text{ (C}^{19}\text{), 25.6 \text{ (C}^{17}\text{), 22.3 \text{ (C}^{14}\text{), 7.3 \text{ (C}^{18}\text{).}}
\end{align*} \]

\[ \begin{align*}
\text{IR: } & 3378 \text{ (br m), 2927 } \text{ (s), 2854 } \text{ (m), 2776 } \text{ (w), 1736 } \text{ (w), 1676 } \text{ (s), 1609 } \text{ (s), 1464 } \text{ (w), 1437 } \text{ (w), 1252 } \text{ (m), 1159 } \text{ (s).}
\end{align*} \]

\[ \begin{align*}
\text{HRMS: (ESI\textsuperscript{+}) m/z: } [M + H]\textsuperscript{+} \text{ Calcd for } C_{21}H_{27}N_2O_2\textsuperscript{+}: 339.2067; \text{ Found: 339.2063.}
\end{align*} \]

\[ R_f \text{ (PE/Et}_2\text{O/Et}_3\text{N 8:2:0.5) = 0.4 (red to blue with molybdenate stain).} \]
8.4 Experimental Procedures of Chapter 4

3-vinyl-3-(3-((triethylsilyl)oxy)propyl)cyclopent-1-en-1-yl trifluoromethanesulfonate 295

To a suspension of CuBr·Me₂S (5.7 g, 28 mmol, 2.0 equiv) in THF (85 mL) at -78 °C was added dropwise vinylmagnesium bromide (0.8 M in THF, 69 mL, 55 mmol, 4.0 equiv). The reaction mixture was stirred at -78 °C for 1 h and then warmed to -40 °C. To the above prepared cuprate solution was added dropwise a solution of the ketone 219 (3.5 g, 14 mmol) in THF (30 mL) while keeping the solution below -40 °C. The reaction mixture was stirred at -40 °C for 3 h. A solution of Comins’ reagent (11 g, 28 mmol, 2.0 equiv) in THF (30 mL) was added to the reaction mixture. The reaction mixture was allowed to warm to RT, and stirred for 24 h. The reaction was quenched with NH₄Cl. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 20:1) afforded compound 295 as a colorless oil (4.2 g, 73% yield).

¹H NMR (400 MHz, CDCl₃): δ 5.73 (dd, J = 17.5, 10.8 Hz, 1H, C⁷−H), 5.55 (t, J = 1.6 Hz, 1H, C³−H), 5.01 (dd, J = 10.8, 1.9 Hz, 1H, C⁸a−H), 4.96 (dd, J = 17.5, 1.9 Hz, 1H, C⁸b−H), 3.58 (t, J = 5.8 Hz, 2H, C¹¹−H), 2.68-2.50 (m, 2H, C⁶−H), 1.99-1.85 (m, 2H, C⁵−H), 1.59-1.42 (m, 4H, C⁹,10−H), 0.95 (t, J = 7.8 Hz, 9H, C¹³−H), 0.59 (q, J = 7.8 Hz, 6H, C¹²−H).

¹³C NMR (101 MHz, CDCl₃): δ 149.1 (C²), 143.8 (C⁷), 122.7 (C³), 118.4 (q, J = 338.0 Hz, C¹), 112.7 (C⁸), 63.1 (C¹¹), 51.4 (C⁴), 36.6 (C⁶), 34.0 (C⁵), 30.3 (C⁹), 28.4 (C¹⁰), 6.9 (C¹³), 4.5 (C¹²).

IR: 2954 (m), 2910 (w), 2878 (w), 1661 (w), 1425 (m), 1221 (s), 11.42 (m), 1097 (m), 1006 (w), 914 (m), 839 (w), 741 (m).

HRMS: (ESI⁺) m/z: [M + Na]⁺ Calcd for C₁₇H₂₉F₃NaO₄Si+: 437.1400; Found: 437.1400.

Rf (PE/EtOAc 10:1) = 0.88

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8.4. Experimental Procedures of Chapter 4

3-((-3-((tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl)-1-vinylcyclopent-2-en-1-yl)propan-1-ol 294

An oven-dried flask was charged with salt 215 (10 g, 27 mmol, 1.2 equiv), X-Phos (1.6 g, 3.3 mmol, 15 mol%), allylpalladium chloride dimer (0.20 g, 0.55 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (150 mL) was added, and the reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate 295 (9.0 g, 22 mmol) in diglyme (150 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was cooled down to 0 °C, and TBAF (1 M solution in THF, 24 mL, 24 mmol, 1.1 equiv) was added dropwise. The reaction was monitored by TLC until total conversion. Saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The two diastereoisomers were separated by FCC (PE/EtOAc 8:2), giving 294a and 294b as yellow oils (5.7 g, 58% yield, dr 1:1).

**Compound 294a**

**¹H NMR (400 MHz, CDCl₃):** δ 7.70 (dd, J = 7.8, 1.2 Hz, 1H, C¹²−H), 7.51 (td, J = 7.8, 1.2 Hz, 1H, C¹⁰−H), 7.38 (dd, J = 7.8, 1.2 Hz, 1H, C⁹−H), 7.32 (td, J = 7.8, 1.2 Hz, 1H, C¹¹−H), 5.83 (dd, J = 17.5, 10.1 Hz, 1H, C¹⁹−H), 5.40 (m, 1H, C²¹−H), 4.92 (dd, J = 10.1, 1.6 Hz, 1H, C¹⁸−H), 4.91 (dd, J = 17.5, 1.6 Hz, 1H, C¹⁸−H), 4.17 (t, J = 7.4 Hz, 1H, C⁷−H), 3.65-3.59 (m, 2H, C³−H), 3.51-3.50 (m, 2H, C⁵−H), 2.19-2.03 (m, 3H, C⁶,¹⁵−H), 1.97 (m, 1H, C⁶−H), 1.80-1.67 (m, 2H, C¹⁷−H), 1.54-1.46 (m, 4H, C¹⁴,¹⁶−H), 0.86 (s, 9H, C³'−H), -0.09 (s, 6H, C¹'−H), OH peak not observed.

**¹³C NMR (101 MHz, CDCl₃):** δ 150.8 (C¹³), 145.5 (C¹⁹), 145.2 (C²), 137.4 (C⁸), 132.4 (C¹⁰), 131.2 (C²¹), 129.1 (C³), 127.1 (C¹¹), 124.2 (C¹²), 111.2 (C¹⁸), 63.7 (C⁷), 61.1 (C⁵), 54.5 (C²⁰), 37.4 (C⁷), 36.9 (C⁵), 36.2 (C¹⁵), 35.8 (C¹⁷), 32.6 (C¹⁶), 28.7 (C¹⁴), 26.1 (C³), 18.4 (C²), -5.3 (C¹) 175

IR: 3354 (br w), 2931 (m), 2856 (w), 1528 (s), 1357 (m), 1255 (m), 1101 (s), 1061 (m), 836 (s), 777 (s).

HRMS: (ESI⁺) m/z: [M + Na]⁺ Calcd for C₂₅H₃₉NNaO₄Si+: 468.2541; Found: 468.2549.
Chapter 8: Experimental Section

\[ R_f \text{ (PE/EtOAc 6:4)} = 0.60 \]

**Compound 294b**

\^H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 7.71 (dd, \( J = 7.8,1.5 \text{ Hz}, 1\text{H}, \text{C}^{12} - \text{H} \)), 7.51 (td, \( J = 7.8,1.5 \text{ Hz}, 1\text{H}, \text{C}^{11} - \text{H} \)), 7.39 (td, \( J = 7.8,1.5 \text{ Hz}, 1\text{H}, \text{C}^{9} - \text{H} \)), 7.33 (td, \( J = 7.8,1.5 \text{ Hz}, 1\text{H}, \text{C}^{10} - \text{H} \)), 5.83 (dd, \( J = 1.40,10.7 \text{ Hz}, 1\text{H}, \text{C}^{19} - \text{H} \)), 4.93 (dd, \( J = 1.3 \text{ Hz}, 1\text{H}, \text{C}^{18} - \text{H} \)), 4.89 (dd, \( J = 10.7,1.3 \text{ Hz}, 1\text{H}, \text{C}^{18} - \text{H} \)), 4.12 (t, \( J = 7.4 \text{ Hz}, 1\text{H}, \text{C}^{7} - \text{H} \)), 3.64-3.59 (m, 2\text{H}, \text{C}^{3} - \text{H} \)), 3.57-3.50 (m, 2\text{H}, \text{C}^{5} - \text{H} \)), 2.25-2.12 (m, 2\text{H}, \text{C}^{6,15} - \text{H} \)), 2.06 (m, 1\text{H}, \text{C}^{15} - \text{H} \)), 1.97 (m, 1\text{H}, \text{C}^{6} - \text{H} \)), 1.84-1.78 (m, 2\text{H}, C\text{C}^{17} - \text{H} and C\text{C}^{3} - \text{OH} \)), 1.68 (m, 1\text{H}, C\text{C}^{17} - \text{H} \)), 1.55-1.45 (m, 4\text{H}, \text{C}^{14,16} - \text{H} \)), 0.85 (s, 9\text{H}, \text{C}^{3'} - \text{H} \)), -0.02 (s, 6\text{H}, \text{C}^{1'} - \text{H} \)).

\^C NMR (101 MHz, CDCl\textsubscript{3}): \( \delta \) 150.7 (C\text{C}^{13}), 145.6 (C\text{C}^{2}), 145.3 (C\text{C}^{19}), 137.6 (C\text{C}^{8}), 132.4 (C\text{C}^{10}), 131.0 (C\text{C}^{21}), 129.2 (C\text{C}^{9}), 127.1 (C\text{C}^{11}), 124.2 (C\text{C}^{12}), 111.4 (C\text{C}^{3}), 64.0 (C\text{C}^{3}), 61.1 (C\text{C}^{5}), 54.6 (C\text{C}^{20}), 37.6 (C\text{C}^{7}), 37.2 (C\text{C}^{6}), 36.2 (C\text{C}^{15}), 35.9 (C\text{C}^{17}), 33.0 (C\text{C}^{16}), 28.7 (C\text{C}^{14}), 26.1 (C\text{C}^{3}), 18.4 (C\text{C}^{2}), -5.3 (C\text{C}^{1}).

IR: 3352 (br w), 2929 (m), 2857 (w), 1528 (s), 1358 (m), 1255 (m), 1102 (s), 1062 (m), 835 (s), 778 (s).

HRMS: (ESI\textsuperscript{+}) m/z: [M + Na]\textsuperscript{+} Calcd for C\textsubscript{25}H\textsubscript{39}NNaO\textsubscript{4}Si\textsuperscript{+}: 468.2541; Found: 468.2544.

\[ R_f \text{ (PE/EtOAc 6:4)} = 0.48 \]

**N-(3-(3-((tert-butyldimethylsilyl)oxy)-1-(2-nitrophenyl)propyl)-1-vinylcyclopent-2-en-1-yl)propyl)-2-nitrobenzenesulfonamide 439**

![Chemical structure of compound 439](image)

To a solution of alcohols 294a/294b (dr 1:1, 6.0 g, 13 mmol), neopentyl alcohol (0.58 g, 6.0 mmol, 0.40 equiv), o-nitrophenylsulfonamide (5.3 g, 27 mmol, 2.0 equiv) and PPh\textsubscript{3} (3.5 g, 13 mmol, 1.0 equiv) in toluene (400 mL) at RT was added DEAD (40 wt.% in toluene, 6.0 mL, 13 mmol, 1.0 equiv). After stirring for 1 h at RT, additional PPh\textsubscript{3} (3.5 g, 13 mmol, 1.0 equiv) and DEAD (40 wt.% in toluene, 6.0 mL, 13 mmol, 1.0 equiv) were added. The reaction mixture was...
stirred for one more hour. Saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (DCM) afforded the two diastereoisomers 439a and 439b as yellow oils (6.3 g, 77% yield, no change in dr).

**Compound 439a**

**¹H NMR (400 MHz, CDCl₃):** δ 8.13 (m, 1H, C₃₀−H), 7.85 (m, 1H, C₂₇−H), 7.76-7.69 (m, 3H, C¹₂,₂₈,₂₉−H), 7.54 (td, J = 7.5, 1.6 Hz, 1H, C¹⁰−H), 7.37 (d, J = 7.5 Hz, 1H, C⁹−H), 7.34 (t, J = 7.5 Hz, 1H, C¹¹−H), 5.72 (dd, J = 17.2, 10.5 Hz, 1H, C¹⁹−H), 5.28-5.22 (m, 2H, C⁴,₂¹−H), 4.88 (dd, J = 10.5, 1.4 Hz, 1H, C¹₈−H), 4.84 (dd, J = 17.2, 1.4 Hz, 1H, C¹₈−H), 4.09 (t, J = 7.5 Hz, 1H, C⁷−H), 3.75-3.45 (m, 2H, C⁵−H), 3.10-3.04 (m, 2H, C³−H), 2.23-2.09 (m, 2H, C₆,₁₇−H), 2.05-1.91 (m, 2H, C₆,₁₇−H), 1.75 (ddd, J = 13.1, 9.2, 5.0 Hz, 1H, C₁₈−H), 1.60-1.50 (m, 1H, C₁₆−H), 1.49-1.35 (m, 4H, C₁₄,₁₅−H), 0.85 (s, 9H, C₂₄−H), -0.02 (s, 6H, C₂₂−H).

**¹³C NMR (101 MHz, CDCl₃):** δ 150.7 (C¹₃), 148.3 (C²₆), 146.2 (C²), 144.8 (C¹₉), 137.3 (C⁸), 134.0 (C²₅), 133.6 (C²₈), 132.9 (C²¹), 132.5 (C²₉), 131.2 (C¹₉), 130.3 (C³₀), 129.2 (C³), 127.3 (C¹₁), 125.5 (C²₇), 124.2 (C¹₂), 111.7 (C¹₈), 61.0 (C⁵), 54.4 (C²₀), 44.6 (C³), 37.6 (C⁷), 37.1 (C₆or₁₅), 33.1 (C₁₇), 26.1 (C²₄), 25.6 (C₁₄), 18.4 (C²₃), -5.3 (C₂₂).

**IR:** 3352 (w), 2950 (w), 2930 (w), 2856 (w), 1540 (s), 1527 (s), 1413 (m), 1356 (s), 1255 (m), 1167 (s), 1100 (s), 853 (s), 836 (s), 779 (s), 742 (s).

**HRMS:** (ESI⁺) m/z: [M + Na]⁺ Calcd for C₃₁H₄₃N₃NaO₇SSi+: 652.2483; Found: 652.2482.

**Rᶠ (DCM) = 0.39**

**Compound 439b**

**¹H NMR (400 MHz, CDCl₃):** δ 8.13 (m, 1H, C₃₀−H), 7.86 (m, 1H, C₂₇−H), 7.76-7.72 (m, 2H, C₂₈,₂₉−H), 7.70 (dd, J = 8.0, 1.2 Hz, 1H, C¹₂−H), 7.51 (m, 1H, C¹₀−H), 7.40-7.30 (m, 2H, C⁹,₁₁−H), 5.71 (dd, J = 12.0, 18.4 Hz, 1H, C¹₉−H), 5.29 (m, 1H, C²¹−H), 5.25 (t, J = 5.5 Hz, 1H, N⁴−H), 4.91-4.80 (m, 2H, C¹₈−H), 4.18 (t, J = 7.4 Hz, 1H, C⁷−H), 3.56-3.47 (m, 2H, C⁵−H), 3.11-3.05 (m, 2H, C³−H), 2.10 (m, 1H, C⁶−H), 2.07-2.01 (m, 2H, C¹₇−H), 1.96 (m, 1H, C⁶−H), 1.71 (m, 1H, C¹₆−H), 1.63-1.53 (m, 1H, C¹₆−H), 1.48-1.35 (m, 4H, C₁₄,₁₅−H), 0.86 (s, 9H, C₂₄−H), -0.1 (s, 6H, C₂₂−H).

**¹³C NMR (101 MHz, CDCl₃):** δ 150.8 (C¹₃), 148.2 (C²₆), 145.6 (C²), 144.9 (C¹₉), 137.1 (C⁸), 134.1 (C²₅), 133.6 (C²₈), 132.9 (C²¹), 132.4 (C²₉), 131.3 (C¹₉), 130.8 (C³₀), 129.0 (C³), 127.2 (C¹₁), 125.5 (C²₇), 124.2 (C₁₂), 111.5 (C¹₈), 61.0 (C⁵), 54.3 (C²₀), 44.6 (C³), 37.3 (C⁷), 36.9 (C₁₅), 36.6 (C⁶), 177
35.8 (C\(^{16}\)), 32.2 (C\(^{17}\)), 26.1 (C\(^{24}\)), 25.5 (C\(^{14}\)), 18.4 (C\(^{23}\)), -5.3 (C\(^{22}\)).

**IR:** 3346 (w), 2951 (w), 2929 (w), 2855 (w), 1542 (s), 1527 (s), 1414 (w), 1357 (s), 1255 (m), 1169 (s), 1100 (s), 853 (m), 835 (s), 780 (s), 741 (m).

**HRMS:** (ESI\(^+\)) m/z: [M + Na]\(^+\) Calcd for C\(_{31}\)H\(_{43}\)N\(_3\)NaO\(_7\)SSi+: 652.2483; Found: 652.2486.

\(R_f\) (DCM) = 0.39

N-(3-(3-hydroxy-1-(2-nitrophenyl)propyl)-1-vinylcyclopent-2-en-1-yl)propyl-2-nitrobenzenesulfonamide 297

To a solution of compounds 439a/439b (dr 1:1, 6.3 g, 10 mmol) in MeOH (100 mL) at 0°C was added dropwise acetyl chloride (60 \(\mu\)L, 1.0 mmol, 10 mol%). After stirring for 1 h, the reaction mixture was concentrated \textit{in vacuo}. The crude compound 440 thus obtained (5.2 g, quantitative yield, no change in dr) was used for the next step without further purification.

**Compound 297a**

\(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.12 (m, 1H, C\(^{28}\)−H), 7.84 (m, 1H, C\(^{25}\)−H), 7.76-7.72 (m, 2H, C\(^{26,27}\)−H), 7.69 (dd, \(J = 8.0, 1.3\) Hz, 1H, C\(^{12}\)−H), 7.56 (td, \(J = 8.0, 1.3\) Hz, 1H, C\(^{10}\)−H), 7.37 (dd, \(J = 8.0, 1.3\) Hz, 1H, C\(^{9}\)−H), 7.35 (td, \(J = 8.0, 1.3\) Hz, 1H, C\(^{11}\)−H), 5.71 (dd, \(J = 17.2, 10.7\) Hz, 1H, C\(^{19}\)−H), 5.33 (m, 1H, C\(^{21}\)−H), 5.30 (m, 1H, N\(^{1}\)−H), 4.87 (dd, \(J = 10.7, 1.3\) Hz, 1H, C\(^{18}\)−H), 4.83 (dd, \(J = 17.2, 1.3\) Hz, 1H, C\(^{18}\)−H), 4.08 (t, \(J = 7.8\) Hz, 1H, C\(^{7}\)−H), 3.60 (m, 1H, C\(^{5}\)−H), 3.51 (m, 1H, C\(^{5}\)−H), 3.11-3.03 (m, 2H, C\(^{3}\)−H), 2.22 (m, 1H, C\(^{6}\)−H), 2.12 (m, 1H, C\(^{17}\)−H), 1.74 (ddd, \(J = 12.8, 8.8, 5.0\) Hz, 1H, C\(^{16}\)−H), 1.54 (ddd, \(J = 12.8, 8.8, 6.1\) Hz, 1H, C\(^{16}\)−H), 1.49-1.35 (m, 4H, C\(^{14,15}\)−H), OH peak not observed.

\(^1^C\) NMR (101 MHz, CDCl\(_3\)): \(\delta\) 150.9 (C\(^{13}\)), 148.2 (C\(^{24}\)), 146.1 (C\(^{2}\)), 144.7 (C\(^{19}\)), 136.9 (C\(^{8}\)), 134.0 (C\(^{23}\)), 133.7 (C\(^{26}\)), 132.9 (C\(^{21}\)), 132.7 (C\(^{27}\)), 131.2 (C\(^{10}\)), 130.5 (C\(^{28}\)), 129.2 (C\(^{9}\)), 127.5 (C\(^{11}\)), 127.8 (C\(^{15}\)), 125.5 (C\(^{22}\)), 124.5 (C\(^{16}\)),
125.5 (C^{25}), 124.1 (C^{12}), 111.8 (C^{18}), 60.7 (C^{5}), 54.4 (C^{20}), 44.5 (C^{3}), 37.7 (C^{7}), 37.0 (C^{6\text{or15}}), 37.0 (C^{6\text{or15}}), 35.8 (C^{16}), 33.0 (C^{17}), 25.6 (C^{14}).

IR: 3323 (w), 3081 (w), 2935 (w), 2847 (w), 2357 (w), 2323 (w), 1541 (s), 1525 (s), 1342 (s), 1165 (m), 915 (m), 854 (m), 786 (m), 733 (s).

HRMS: (ESI\textsuperscript{+}) m/z: [M + Na]\textsuperscript{+} Calcd for C\textsubscript{25}H\textsubscript{29}N\textsubscript{3}NaO\textsubscript{7}S\textsuperscript{+}: 538.1618; Found: 538.1619.

R\textsubscript{f} (PE/EtOAc 4:6) = 0.50

Compound 297b

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta 8.13 (m, 1H, C\textsubscript{28}−H), 7.86 (m, 1H, C\textsubscript{25}−H), 7.77-7.73 (m, 2H, C\textsubscript{26,27}−H), 7.69 (dd, \(J = 7.7, 1.7\) Hz, 1H, C\textsubscript{12}−H), 7.53 (td, \(J = 7.7, 1.7\) Hz, 1H, C\textsubscript{10}−H), 7.35 (d, \(J = 7.7\) Hz, 1H, C\textsubscript{9}−H), 7.34 (m, 1H, C\textsubscript{11}−H), 5.72 (dd, \(J = 17.6, 10.5\) Hz, 1H, C\textsubscript{19}−H), 5.35 (m, 1H, C\textsubscript{21}−H), 5.29 (t, \(J = 5.9\) Hz, 1H, N\textsubscript{4}−H), 4.88 (dd, \(J = 10.5, 1.4\) Hz, 1H, C\textsubscript{18}−H), 4.84 (dd, \(J = 17.6, 1.4\) Hz, 1H, C\textsubscript{18}−H), 4.12 (m, 1H, C\textsubscript{7}−H), 3.61 (m, 1H, C\textsubscript{5}−H), 3.53 (m, 1H, C\textsubscript{5}−H), 3.13-3.02 (m, 2H, C\textsubscript{3}−H), 2.20 (m, 1H, C\textsubscript{6}−H), 2.06-1.93 (m, 3H, C\textsubscript{6,17}−H), 1.70 (m, 1H, C\textsubscript{16}−H), 1.64-1.56 (m, 1H, C\textsubscript{16}−H), 1.49-1.37 (m, 4H, C\textsubscript{14,15}−H), OH peak not observed.

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): \delta 150.9 (C\textsubscript{13}), 148.2 (C\textsubscript{24}), 145.6 (C\textsubscript{2}), 144.9 (C\textsubscript{19}), 136.7 (C\textsubscript{8}), 134.0 (C\textsubscript{23}), 133.7 (C\textsubscript{26}), 132.9 (C\textsubscript{21}), 132.6 (C\textsubscript{27}), 131.2 (C\textsubscript{10}), 130.8 (C\textsubscript{28}), 129.1 (C\textsubscript{9}), 127.5 (C\textsubscript{11}), 125.5 (C\textsubscript{25}), 124.1 (C\textsubscript{12}), 111.6 (C\textsubscript{18}), 60.8 (C\textsubscript{3}), 54.4 (C\textsubscript{20}), 44.6 (C\textsubscript{3}), 37.6 (C\textsubscript{7}), 36.9 (C\textsubscript{6\text{or15}}), 36.7 (C\textsubscript{6\text{or15}}), 35.7 (C\textsubscript{16}), 32.6 (C\textsubscript{17}), 25.5 (C\textsubscript{14}).

IR: 3349 (w), 3075 (w), 2945 (w), 2877 (w), 1540 (s), 1525 (s), 1415 (w), 1358 (s), 1165 (m), 1031 (w), 913 (w), 854 (w), 783 (m), 731 (m).

HRMS: (ESI\textsuperscript{+}) m/z: [M + Na]\textsuperscript{+} Calcd for C\textsubscript{25}H\textsubscript{29}N\textsubscript{3}NaO\textsubscript{7}S\textsuperscript{+}: 538.1618; Found: 538.1620.

R\textsubscript{f} (PE/EtOAc 4:6) = 0.50
To a solution of alcohols 297a/297b (dr 1:1, 0.10 g, 0.19 mmol), neopentyl alcohol (7.5 mg, 0.078 mmol, 0.40 equiv), and PPh₃ (50 mg, 0.19 mmol, 1.0 equiv) in toluene (40 mL) at RT was added DEAD (40 wt.% in toluene, 85 μL, 0.19 mmol, 1.0 equiv). After stirring for 1 h at RT, additional PPh₃ (50 mg, 0.19 mmol, 1.0 equiv) and DEAD (40 wt.% in toluene, 85 μL, 0.19 mmol, 1.0 equiv) were added. The reaction mixture was stirred for one more hour. Saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/DCM 1:9) afforded the two diastereoisomers 298a and 298b as yellow oils (78 mg, 83% yield, no change in dr).

Compound 298a

¹H NMR (400 MHz, CDCl₃): δ 7.91 (dd, J = 7.4, 1.8 Hz, 1H, C²⁷−H), 7.75-7.65 (m, 3H, C¹²,2₅,2₆−H), 7.61-7.53 (m, 2H, C¹₀,2₄−H), 7.48 (dd, J = 7.5, 1.8 Hz, 1H, C⁹−H), 7.36 (td, J = 7.5, 1.8 Hz, 1H, C¹¹−H), 5.87 (dd, J = 17.1, 11.0 Hz, 1H, C¹⁹−H), 5.58 (m, 1H, C²₁−H), 4.96 (dd, J = 17.1, 1.7 Hz, 1H, C¹⁸−H), 4.88 (dd, J = 11.0, 1.7 Hz, 1H, C¹⁸−H), 4.36 (dd, J = 12.7, 2.8 Hz, 1H, C¹⁷−H), 4.04 (dd, J = 15.5, 7.2 Hz, 1H, C³−H), 3.77 (ddd, J = 14.9, 9.9, 5.0 Hz, 1H, C²−H), 2.84-2.61 (m, 4H, C³,⁵,⁶,¹⁷−H), 2.17-2.03 (m, 2H, C¹⁴,¹₆−H), 1.94-1.83 (m, 2H, C⁶,¹⁷−H), 1.83-1.69 (m, 2H, C¹⁴,¹₆−H), 1.69-1.61 (m, 1H, C¹⁵−H), 1.42 (m, 1H, C¹⁵−H).

¹³C NMR (101 MHz, CDCl₃): δ 150.3 (C¹³), 149.1 (C²₃), 147.2 (C¹⁹), 143.2 (C²), 135.9 (C⁸), 134.4 (C²¹), 133.8 (C²⁵), 132.4 (C¹⁰), 131.4 (C²₆), 131.0 (C²⁷), 130.6 (C²₂), 128.6 (C⁹), 127.4 (C¹¹), 124.4 (C¹₂), 124.1 (C²₄), 110.8 (C¹₈), 56.7 (C³), 55.4 (C⁵), 55.1 (C²⁰), 43.1 (C⁷), 39.4 (C¹⁵), 35.9 (C⁶), 35.4 (C¹₆), 31.4 (C¹⁷), 28.0 (C¹⁴).

IR: 2938 (w), 2913 (w), 2852 (w), 1544 (s), 1527 (s), 1465 (w), 1353 (s), 1164 (m), 1126 (w), 913 (w), 852 (w), 784 (m), 755 (m), 732 (m),
HRMS: (ESI\(^+\)) m/z: [M + Na]\(^+\) Calcd for C\(_{25}\)H\(_{27}\)N\(_3\)NaO\(_6\)S\(^+\): 520.1513; Found: 520.1512.

\(R_f\) (DCM) = 0.5

**Compound 298b**

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.91 (m, 1H, C\(_{27}\)−H), 7.79 (dd, \(J = 8.0, 1.1\) Hz, 1H, C\(_{12}\)−H), 7.73-7.65 (m, 2H, C\(_{25,26}\)−H), 7.63-7.52 (m, 3H, C\(_{9,10,24}\)−H), 7.35 (td, \(J = 8.0, 1.1\) Hz, 1H, C\(_{11}\)−H), 5.99 (dd, \(J = 17.6, 10.3\) Hz, 1H, C\(_{19}\)−H), 5.73 (m, 1H, C\(_{21}\)−H), 4.98 (dd, \(J = 17.6, 1.7\) Hz, 1H, C\(_{18}\)−H), 4.93 (dd, \(J = 10.3, 1.7\) Hz, 1H, C\(_{18}\)−H), 4.71 (m, 1H, C\(_{21}\)−H), 4.08 (dd, \(J = 10.3, 1.7\) Hz, 1H, C\(_{18}\)−H), 3.88 (dd, \(J = 11.4, 3.4\) Hz, 1H, C\(_{7}\)−H), 3.53 (ddd, \(J = 15.4, 6.8, 1.7\) Hz, 1H, C\(_{5}\)−H), 3.27 (m, 1H, C\(_{3}\)−H), 3.10 (m, 1H, C\(_{3}\)−H), 2.98 (ddd, \(J = 15.4, 6.8, 1.7\) Hz, 1H, C\(_{5}\)−H), 2.58 (m, 1H, C\(_{9}\)−H), 2.51-2.38 (m, 2H, C\(_{17}\)−H), 2.19 (m, 1H, C\(_{6}\)−H), 1.89 (m, 1H, C\(_{16}\)−H), 1.83-1.69 (m, 3H, C\(_{14,15,16}\)−H), 1.61-1.40 (m, 2H, C\(_{14,15}\)−H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 149.7 (C\(_{13}\)), 149.0 (C\(_{23}\)), 146.6 (C\(_{19}\)), 141.9 (C\(_2\)), 137.2 (C\(_8\)), 135.8 (C\(_{21}\)), 133.8 (C\(_{25}\)), 133.0 (C\(_{10}\)), 131.4 (C\(_{26}\)), 131.0 (C\(_{27,22}\)), 129.6 (C\(_8\)), 127.5 (C\(_{11}\)), 124.6 (C\(_{12}\)), 124.0 (C\(_{24}\)), 111.9 (C\(_{18}\)), 56.3 (C\(_{20}\)), 52.5 (C\(_3\)), 48.9 (C\(_7\)), 41.9 (C\(_7\)), 39.0 (C\(_7\)), 37.9 (C\(_{15}\)), 35.5 (C\(_6\)), 34.3 (C\(_{16}\)), 22.3 (C\(_{14}\)).

IR: 2929 (w), 2849 (w), 1544 (s), 1525 (s), 1373 (m), 1354 (s), 1165 (w), 1126 (w), 912 (w), 853 (w), 782 (w), 732 (w).

HRMS: (ESI\(^+\)) m/z: [M + H]\(^+\) Calcd for C\(_{25}\)H\(_{28}\)N\(_3\)O\(_6\)S\(^+\): 498.1693; Found: 498.1690.

\(R_f\) (DCM) = 0.5

**(E)-2-(8-(2-nitrophenyl)-5-((2-nitrophenyl)sulfonyl)-5-azabicyclo[7.2.1]dodec-9(12)-en-1-yl)ethan-1-ol 299**

To a solution of olefins 298a/298b (dr 1:1, 78 mg, 0.16 mmol) in THF (10 mL) at RT was added 9-BBN (0.5 M in THF, 0.32 mL, 0.32 mmol, 2.0 equiv). After stirring for 2 h at RT, EtOH (0.50 mL), NaOH (6 M in H\(_2\)O, 0.50 mL) and H\(_2\)O\(_2\) (30% in H\(_2\)O, 0.40 mL) were added at 0°C.
The reaction mixture was stirred at 0 °C for 15 minutes, and then at RT for 2 h. Saturated aqueous Na$_2$S$_2$O$_3$ was added, followed by saturated aqueous NH$_4$Cl. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (PE/EtOAc 5:5) afforded the two diastereoisomers 299a and 299b as yellow oils (65 mg, 78% yield, no change in dr).

**Compound 299a**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.91 (m, 1H, C$_{27}^-$H), 7.75-7.65 (m, 3H, C$_{12,25,26}^-$H), 7.37 (m, 1H, C$_{11}^-$H), 5.60 (m, 1H, C$_{21}^-$H), 4.28 (dd, $J$ = 13.0,3.0 Hz, 1H, C$_7^-$H), 4.04 (dd, $J$ = 16.5, 7.5 Hz, 1H, C$_5^-$H), 3.76 (dd, $J$ = 15.0, 10.0, 5.0 Hz, 1H, C$_3^-$H), 3.70-3.59 (m, 2H, C$_{18}^-$H), 2.79 (dd, $J$ = 16.5,7.5 Hz, 1H, C$_5^-$H), 2.74-2.53 (m, 3H, C$_{3,6,17}^-$H), 2.15 (m, 1H, C$_6^-$H), 2.05 (m, 1H, C$_{14}^-$H), 1.83-1.63 (m, 5H, C$_{14,16,17,19}^-$H), 1.62-1.50 (m, 2H, C$_{15,19}^-$H), 1.34 (m, 1H, C$_{15}^-$H), 1.25 (br m, 1H, O$_{28}^-$H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 150.3 (C$_{13}$), 149.1 (C$_{23}$), 142.4 (C$_2$), 135.8 (C$_8$), 135.7 (C$_{21}$), 133.8 (C$_{25}$), 132.5 (C$_{10}$), 131.4 (C$_{26}$), 131.0 (C$_{21}$), 128.5 (C$_9$), 127.4 (C$_{11}$), 124.4 (C$_{12}$), 124.1 (C$_{24}$), 60.1 (C$_{18}$), 56.6 (C$_3$), 54.8 (C$_5$), 52.0 (C$_{20}$), 44.0 (C$_{19}$), 43.0 (C$_7$), 41.6 (C$_{15}$), 35.6 (C$_6$), 33.2 (C$_{16}$), 31.2 (C$_{17}$), 28.1 (C$_{14}$).

IR: 3342 (w), 2928 (m), 2852 (w), 1544 (s), 1527 (s), 1465 (w), 1351 (s), 1164 (m), 1006 (w), 852 (w), 784 (m), 756 (m), 731 (m).

HRMS: (ESI$^+$) m/z: [M + Na]$^+$ Calcd for C$_{25}$H$_{29}$N$_3$NaO$_7$S+: 538.1618; Found: 538.1620.

$R_f$ (PE/EtOAc 4:6) = 0.2

**Compound 299b**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.90 (m, 1H, C$_{27}^-$H), 7.78 (m, 1H, C$_{12}^-$H), 7.73-7.64 (m, 2H, C$_{25,26}^-$H), 7.60-7.51 (m, 3H, C$_{9,10,24}^-$H), 7.35 (m, 1H, C$_{11}^-$H), 5.71 (s, 1H, C$_{21}^-$H), 3.87 (dd, $J$ = 11.7,2.9 Hz, 1H, C$_7^-$H), 3.77-3.65 (m, 2H, C$_{18}^-$H), 3.54 (ddd, $J$ = 16.6,7.8,2.0 Hz, 1H, C$_5^-$H), 3.26 (m, 1H, C$_3^-$H), 3.07 (m, 1H, C$_3^-$H), 2.96 (ddd, $J$ = 16.6,7.8,2.0 Hz, 1H, C$_5^-$H), 2.57 (m, 1H, C$_6^-$H), 2.47-2.34 (m, 2H, C$_{16}^-$H), 2.18 (m, 1H, C$_{5}^-$H), 1.88-1.62 (m, 6H, C$_{14,15,17,19}^-$H), 1.52-1.36 (m, 2H, C$_{14,15}^-$H), 1.25 (br s, 1H, O$_{28}^-$H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 149.7 (C$_{13}$), 149.0 (C$_{23}$), 141.3 (C$_2$), 137.3 (C$_8$), 137.0 (C$_{21}$), 133.8 (C$_{25}$), 133.0 (C$_{10}$), 131.5 (C$_{26}$), 131.1 (C$_{22}$), 131.0 (C$_{27}$), 129.5 (C$_{11}$), 127.5 (C$_9$), 124.6 (C$_{12}$), 124.1 (C$_{24}$), 60.6 (C$_{18}$), 52.6 (C$_{20}$), 52.4 (C$_3$), 48.9 (C$_5$), 43.7 (C$_{19}$), 42.0 (C$_7$), 39.0 (C$_{15or16}$), 39.0 (C$_{15or16}$), 35.4 (C$_6$), 33.1 (C$_{17}$), 22.2 (C$_{14}$).

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IR: 3362 (w), 2929 (w), 2849 (w), 1546 (s), 1525 (s), 1373 (m), 1353 (s), 1165 (m), 1043 (w), 1004 (w), 910 (w), 853 (w), 788 (w), 732 (m).

HRMS: (ESI\(^+\)) m/z: [M + Na]\(^+\) Calcd for C\(_{25}\)H\(_{29}\)N\(_3\)NaO\(_7\)S\(^+\): 538.1618; Found: 538.1623.

\(R_f\) (PE/EtOAc 4:6) = 0.2


A suspension of macrocycles 299a/299b (dr 1:1, 50 mg, 0.10 mmol) and NaHCO\(_3\) (17 mg, 0.20 mmol, 2.0 equiv) in DCM (0.50 mL) was stirred at -78 °C. Ozone was bubbled through the solution until full conversion was observed by TLC. Argon was then bubbled through the mixture for 10 min. The mixture was then stirred at 0 °C for 15 min. Ca(OCl)\(_2\) (29 mg, 0.20 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 24 h at RT. The reaction mixture was filtered through Celite and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 4:6) afforded the two diastereoisomers 303a and 303b as yellow foams (38 mg, 70% yield, no change in dr).

**Compound 303a**

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.91 (dd, \(J = 7.1, 1.6\) Hz, 1H, C\(_{27}\)H), 7.86 (dd, \(J = 7.6, 1.1\) Hz, 1H, C\(_{12}\)H), 7.71 (td, \(J = 7.1, 1.6\) Hz, 1H, C\(_{25}\)H), 7.42 (td, \(J = 7.6, 1.1\) Hz, 1H, C\(_{11}\)H), 7.31 (dd, \(J = 7.6, 1.1\) Hz, 1H, C\(_{9}\)H), 5.25 (dd, \(J = 11.7, 2.3\) Hz, 1H, C\(_{7}\)H), 4.31-4.20 (m, 2H, C\(_{18}\)H), 3.41-3.15 (m, 3H, C\(_{5},\)C\(_{16}\)H), 2.86 (m, 1H, C\(_{3}\)H), 2.40 (m, 1H, C\(_{6}\)H), 2.31-2.11 (m, 4H, C\(_{6},\)C\(_{15},\)C\(_{17},\)C\(_{19}\)H), 1.55-1.20 (m, 3H, C\(_{14},\)C\(_{17}\)H).

\(^13\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 211.3 (C\(_2\)), 180.0 (C\(_{21}\)), 150.3 (C\(_{13}\)), 149.2 (C\(_{23}\)), 134.1 (C\(_{10}\)), 133.1 (C\(_{25}\)), 131.8 (C\(_8\)), 131.5 (C\(_{26}\)), 131.4 (C\(_{27}\)), 130.5 (C\(_{22}\)), 130.0 (C\(_3\)), 128.7 (C\(_{11}\)), 125.3 (C\(_{12}\)), 124.0 (C\(_{24}\)), 64.9 (C\(_{18}\)), 51.1 (C\(_3\)), 50.3 (C\(_7\)), 46.4 (C\(_5\)), 44.3 (C\(_{20}\)), 35.8 (C\(_{19}\)), 35.3 (C\(_{16}\)), 32.1 (C\(_6\)).
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29.5 (C^{15}or^{17}), 29.3 (C^{15}or^{17}), 22.0 (C^{14}).

IR: 2930 (w), 2863 (w), 1764 (m), 1711 (w), 1545 (s), 1456 (w), 1360 (s), 1356 (s), 1169 (m), 1028 (w), 849 (w), 780 (w), 742 (m), 733 (m).

HRMS: (ESI^+) m/z: [M + Na]^+ Calcd for C_{25}H_{27}N_{3}NaO_{9}S^+: 568.1360; Found: 568.1366.

R_f (PE/EtOAc 1:9) = 0.44

Compound 303b

^{1}H NMR (400 MHz, CDCl_3): δ 7.86 (dd, J = 7.6, 1.6 Hz, 1H, C^{12}−H), 7.83 (dd, J = 7.5, 1.7 Hz, 1H, C^{27}−H), 7.71 (td, J = 7.5, 1.7 Hz, 1H, C^{25}−H), 7.65 (td, J = 7.5, 1.7 Hz, 1H, C^{26}−H), 7.54 (dd, J = 7.5, 1.7 Hz, 1H, C^{24}−H), 7.53 (td, J = 7.6, 1.6 Hz, 1H, C^{10}−H), 7.44 (td, J = 7.6, 1.6 Hz, 1H, C^{11}−H), 7.22 (dd, J = 7.6, 1.6 Hz, 1H, C^{9}−H), 5.36 (dd, J = 11.4, 2.6 Hz, 1H, C^{7}−H), 4.38-4.30 (m, 2H, C^{18}−H), 3.59 (td, J = 13.0, 2.9 Hz, 1H, C^{3}−H), 3.30 (dd, J = 15.0, 5.0 Hz, 1H, C^{5}−H), 3.10 (m, 1H, C^{5}−H), 2.88 (dd, J = 15.0, 10.0 Hz, 1H, C^{16}−H), 2.78-2.64 (m, 2H, C^{3,17}−H), 2.42 (ddd, J = 12.9, 5.9, 3.2 Hz, 1H, C^{19}−H), 2.30 (td, J = 12.9, 3.7 Hz, 1H, C^{6}−H), 2.22-1.99 (m, 4H, C^{6,15,16,19}−H), 1.77 (td, J = 12.9, 3.7 Hz, 1H, C^{15}−H), 1.67 (dd, J = 11.2, 15.4 Hz, 1H, C^{17}−H), 1.62-1.52 (m, 1H, C^{14}−H), 1.45 (m, 1H, C^{14}−H).

^{13}C NMR (101 MHz, CDCl_3): δ 210.9 (C^{2}), 179.9 (C^{21}), 150.6 (C^{13}), 149.1 (C^{23}), 134.0 (C^{10}), 133.1 (C^{25}), 131.7 (C^{8}), 131.4 (C^{26}), 131.1 (C^{27}), 129.8 (C^{9} and C^{22} superimposed), 128.8 (C^{11}), 125.3 (C^{12}), 124.0 (C^{24}), 65.3 (C^{18}), 51.3 (C^{3}), 48.5 (C^{7}), 46.0 (C^{5}), 45.9 (C^{20}), 36.7 (C^{19}), 36.2 (C^{16}), 32.1 (C^{6}), 30.8 (C^{17}), 30.3 (C^{15}), 21.5 (C^{14}).

IR: 2923 (w), 2852 (w), 1761 (m), 1715 (w), 1543 (s), 1530 (s), 1456 (w), 1374 (s), 1359 (s), 1164 (w), 1027 (w), 915 (w), 748 (w).

HRMS: (ESI^+) m/z: [M + Na]^+ Calcd for C_{25}H_{27}N_{3}NaO_{9}S^+: 568.1360; Found: 568.1373.

R_f (PE/EtOAc 1:9) = 0.65
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(E)-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-8-(2-nitrophenyl)-5-((2-nitrophenyl)sulfonyl)-5-azabicyclo[7.2.1]dodec-9(12)-ene 293

To a solution of macrocycles 299a/299b (dr 1:1, 50 mg, 0.10 mmol) and Imidazole (14 mg, 0.20 mmol, 2.0 equiv) in THF (0.50 mL) at RT was added TBSCI (23 mg, 0.15 mmol, 1.5 equiv). The reaction mixture was stirred for 2 h. Water was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded the two diastereoisomers 293a and 293b as colorless oils (57 mg, 90% yield, no change in dr).

**Compound 293a**

**¹H NMR (400 MHz, CDCl₃)**: δ 7.91 (dd, J = 7.8, 1.7 Hz, 1H, C²⁷−H), 7.74-7.65 (m, 3H, C¹₂,₂₅,₂₆−H), 7.59 (dd, J = 7.8, 1.7 Hz, 1H, C²⁴−H), 7.55 (td, J = 7.8, 1.2 Hz, 1H, C¹₀−H), 7.46 (dd, J = 7.8, 1.2 Hz, 1H, C³−H), 7.35 (td, J = 7.8, 1.2 Hz, 1H, C¹¹−H), 5.51 (s, 1H, C²¹−H), 4.30 (dd, J = 12.4, 3.4 Hz, 1H, C⁷−H), 4.03 (dd, J = 15.1, 6.6 Hz, 1H, C⁵−H), 3.74 (ddd, J = 15.0, 10.0, 5.0 Hz, 1H, C³−H), 3.59 (t, J = 7.0 Hz, 2H, C¹⁸−H), 2.78 (dd, J = 15.1, 8.5 Hz, 1H, C³−H), 2.70 (m, 1H, C³−H), 2.65-2.52 (m, 2H, C⁶,₁₇−H), 2.12 (ddd, J = 15.3, 7.6, 3.4 Hz, 1H, C⁶−H), 2.02 (m, 1H, C¹⁴−H), 1.83-1.73 (m, 3H, C₁₆,₁₇−H), 1.71-1.53 (m, 4H, C¹₄,₁₅,₁₉−H), 1.30 (m, 1H, C¹₅−H), 0.87 (s, 9H (C₃₀), 0.04 (s, 3H, C²₈−H), 0.02 (s, 3H, C²₈−H).

**¹³C NMR (101 MHz, CDCl₃)**: δ 150.3 (C¹₃), 149.1 (C²₃), 142.1 (C²), 136.0 (C⁸), 135.8 (C²¹), 133.8 (C²⁵), 132.3 (C¹₀), 131.4 (C²₈), 131.1 (C²⁷), 130.6 (C²₂), 128.6 (C⁹), 127.3 (C¹¹), 124.4 (C₁₂), 124.1 (C²₄), 60.6 (C¹₈), 56.6 (C³), 54.8 (C⁵), 51.7 (C²₉), 44.2 (C¹₉), 43.0 (C⁷), 40.8 (C¹₅), 35.8 (C⁶), 33.6 (C¹₆), 31.3 (C¹₇), 28.0 (C¹₄), 26.1 (C³₀), 18.4 (C²₉), -5.2 (C²₈), -5.2 (C²₈).

**IR**: 2929 (w), 2851 (w), 1545 (s), 1529 (s), 1465 (w), 1357 (s), 1254 (m), 1090 (m), 852 (m), 837 (s), 779 (s), 754 (m).

**HRMS** (ESI⁺) m/z: [M + Na]⁺ Calcd for C₃₁H₄₃N₃NaO₇SSi+: 652.2483; Found: 652.2491.
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\( R_f \) (PE/EtOAc 6:4) = 0.55

**Compound 293b**

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.88 (dd, \( J = 7.3,2.0 \) Hz, 1H, C\(^{27}\)−H), 7.74 (dd, \( J = 7.3,2.0 \) Hz, 1H, C\(^{12}\)−H), 7.66 (td, \( J = 7.3,2.0 \) Hz, 1H, C\(^{25}\)−H), 7.63 (td, \( J = 7.3,2.0 \) Hz, 1H, C\(^{26}\)−H), 7.55 (dd, \( J = 7.3,2.0 \) Hz, 1H, C\(^{24}\)−H), 7.53 (dd, \( J = 7.3,2.0 \) Hz, 1H, C\(^{9}\)−H), 7.49 (td, \( J = 7.3,2.0 \) Hz, 1H, C\(^{10}\)−H), 7.31 (td, \( J = 7.3,2.0 \) Hz, 1H, C\(^{11}\)−H), 5.65 (s, 1H, C\(^{21}\)−H), 3.81 (dd, \( J = 10.1,4.3 \) Hz, 1H, C\(^{7}\)−H), 3.70-3.57 (m, 2H, C\(^{18}\)−H), 3.50 (dd, \( J = 15.8,7.2 \) Hz, 1H, C\(^{5}\)−H), 3.21 (m, 1H, C\(^{3}\)−H), 3.05 (m, 1H, C\(^{3}\)−H), 2.90 (dd, \( J = 15.8,7.2 \) Hz, 1H, C\(^{5}\)−H), 2.48 (m, 1H, C\(^{6}\)−H), 2.41-2.29 (m, 2H, C\(^{16}\)−H), 2.14 (m, 1H, C\(^{6}\)−H), 1.81 (m, 1H, C\(^{17}\)−H), 1.75-1.57 (m, 5H, C\(^{14,15,17,19}\)−H), 1.44-1.33 (m, 2H, C\(^{14,15}\)−H), 0.84 (s, 9H, C\(^{30}\)−H), 0.00 (s, 6H, C\(^{28}\)−H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \) 149.6 (C\(^{13}\)), 148.9 (C\(^{23}\)), 140.7 (C\(^{2}\)), 137.3 (C\(^{21}\)), 137.2 (C\(^{8}\)), 133.6 (C\(^{25}\)), 132.8 (C\(^{10}\)), 131.3 (C\(^{26}\)), 131.1 (C\(^{22}\)), 130.9 (C\(^{27}\)), 129.4 (C\(^{11}\)), 127.3 (C\(^{9}\)), 124.4 (C\(^{12}\)), 123.9 (C\(^{24}\)), 60.8 (C\(^{18}\)), 52.4 (C\(^{3}\)), 52.1 (C\(^{20}\)), 48.4 (C\(^{5}\)), 43.6 (C\(^{19}\)), 41.7 (C\(^{7}\)), 39.1 (C\(^{16}\)), 38.6 (C\(^{15}\)), 35.4 (C\(^{6}\)), 33.1 (C\(^{17}\)), 26.0 (C\(^{30}\)), 22.0 (C\(^{14}\)), 18.3 (C\(^{29}\)), -5.2 (C\(^{28}\)).

**IR:** 2929 (w), 2855 (w), 1545 (s), 1526 (s), 1460 (w), 1373 (m), 1356 (m), 1254 (w), 1167 (m), 1125 (w), 1090 (m), 852 (m), 837 (s), 777 (s), 744 (m).

**HRMS:** (ESI\(^+\)) m/z: [M + Na]\(^+\) Calcd for C\(_{31}\)H\(_{43}\)N\(_3\)O\(_7\)SSi+: 652.2483; Found: 652.2500.

\( R_f \) (PE/EtOAc 6:4) = 0.55
To a solution of 2-(2-nitrophenyl)acetic acid (10 g, 55 mmol) in EtOH (100 mL) was added dropwise a solution of t-BuOK (6.2 g, 55 mmol, 1.0 equiv) in EtOH (20 mL). The reaction mixture was stirred for 1 h, and then concentrated in vacuo. The crude salt 345 thus obtained was used for the next step without further purification (white solid, 12 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.22

$^1$H NMR (400 MHz, MeOD): δ 7.98 (dd, $J=8.6, 1.5$ Hz, 1H, C$^2$−H), 7.57 (td, $J=7.5, 1.5$ Hz, 1H, C$^4$−H), 7.44-7.38 (m, 2H, C$^3,5$−H), 3.88 (s, 2H, C$^7$−H).

$^{13}$C NMR (101 MHz, MeOD): δ 177.6 (C$^8$), 155.1 (C$^1$), 135.0 (C$^6$), 134.5 (C$^4$), 134.2 (C$^5$), 128.5 (C$^3$), 125.7 (C$^2$), 43.9 (C$^7$).

3-(but-3-en-1-yl)-3-(3-((tert-butyldimethylsilyl)oxy)propyl)cyclopent-1-en-1-yl trifluoromethanesulfonate 344

To a solution of 4-bromobut-1-ene (2.4 mL, 24 mmol, 4.0 equiv) in THF (100 mL) was added magnesium turning (0.57 g, 24 mmol, 4.0 equiv) and the mixture was heated to reflux for 3 h. The mixture was then cooled down to -78 °C, CuBr-Me$_2$S (2.4 g, 12 mmol, 2.0 equiv) was added and the mixture was stirred for 1 h. The reaction mixture was then warmed up to -40 °C, and a solution of the enone 220 (1.5 g, 5.9 mmol) in THF (20 mL) was added dropwise. The reaction mixture was then stirred for 3 h. A solution of Comins’ reagent (4.6 g, 12 mmol, 2.0 equiv) in THF (20 mL) was added, and the reaction mixture was stirred at RT for 24 h. Saturated NaHCO$_3$ was added, and the mixture was extracted with EtOAc. The combined organic
phases were dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (PE/EtOAc 95:5) afforded the vinyl triflate 344 as a colorless oil (2.4 g, 91% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.80 (ddt, $J = 17.2, 10.1, 6.6$ Hz, 1H, C$^9$−H), 5.44 (s, 1H, C$^3$−H), 5.01 (dd, $J = 17.2, 1.9$ Hz, 1H, C$^{10}$−H), 4.94 (dd, $J = 10.1, 1.9$ Hz, 1H, C$^{10}$−H), 3.61-3.53 (m, 2H, C$^{13}$−H), 2.61-2.55 (m, 2H, C$^6$−H), 2.05-1.95 (m, 2H, C$^8$−H), 1.82 (t, $J = 7.6$ Hz, 2H, C$^5$−H), 1.53-1.47 (m, 2H, C$^7$−H), 1.47-1.43 (m, 4H, C$^{11,12}$−H), 0.89 (s, 9H, C$^{16}$−H), 0.04 (s, 6H, C$^{14}$−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 148.1 (C$^2$), 138.8 (C$^9$), 124.7 (C$^3$), 118.7 (q, $J = 319.9$ Hz, C$^1$), 114.6 (C$^{10}$), 63.5 (C$^{13}$), 48.5 (C$^4$), 39.1 (C$^7$), 36.0 (C$^{11}$), 32.0 (C$^5$), 31.0 (C$^6$), 29.0 (C$^8$), 28.0 (C$^{12}$), 26.1 (C$^{16}$), 18.5 (C$^{15}$), -5.2 (C$^{14}$).

IR: 2941 (w), 2931 (w), 2858 (w), 1660 (w), 1643 (w), 1424 (m), 1251 (m), 1210 (s), 1141 (s), 1096 (s), 912 (s), 835 (s), 776 (m).

HRMS: (ESI$^+$) m/z: [M + H]$^+$ Calcd for C$_{19}$H$_{34}$F$_3$O$_4$Si+: 443.1894; Found: 443.1893.

$R_f$ (PE/EtOAc 95:5) = 0.72.

methyl 3-((1-(3-((tert-butyldimethylsilyl)oxy)propyl)-3-(((trifluoromethyl)sulfonyl)oxy)cyclopent-2-en-1-yl)propanoate 350 and 3-((2-(1,2,4-trioxolan-3-yl)ethyl)-3-((tert-butyldimethylsilyl)oxy)propyl)cyclopent-1-en-1-yl trifluoromethanesulfonate 351

To a solution of the olefin 344 (50 mg, 0.11 mmol) in DCM (1.0 mL) was added a solution of NaOH (23 mg, 0.56 mmol, 5.0 equiv) in MeOH (0.25 mL). The mixture was cooled to -78 °C, and ozone was bubbled through the reaction mixture. The reaction mixture turned yellow, followed by decoloration and subsequent blue coloration. When the blue color appeared, argon was bubbled through the solution, and the mixture was warmed up to 0 °C. Water and ether were added, and the biphasic mixture was stirred for 1 h. The two layers were separated and the aqueous layer was extracted with ether. The combined organic phases were dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (PE/EtOAc 95:5) afforded prod-
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uct 350 (colorless oil, 31 mg, 60% yield) along with the side product 351 (colorless oil, mixture of 2 diastereoisomers, dr 1:1, 19 mg, 35% yield).

**Compound 350**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.39 (t, $J = 1.6$ Hz, 1H, C$^3$−H), 3.66 (s, 3H, C$^{10}$−H), 3.60-3.55 (m, 2H, C$^{13}$−H), 2.58 (td, $J = 7.6$, 1.5 Hz, 2H, C$^6$−H), 2.26 (t, $J = 8.3$ Hz, 2H, C$^8$−H), 1.89-1.69 (m, 4H, C$^{5,7}$−H), 1.49-1.42 (m, 4H, C$^{11,12}$−H), 0.87 (s, 9H, C$^{16}$−H), 0.03 (s, 6H, C$^{14}$−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 174.1 (C$^9$), 148.5 (C$^2$), 123.9 (C$^3$), 118.7 (d, $J = 321.0$ Hz, C$^1$), 63.3 (C$^{13}$), 51.8 (C$^{10}$), 48.2 (C$^4$), 36.2 (C$^{11}$), 34.7 (C$^7$), 31.5 (C$^5$), 31.0 (C$^6$), 29.6 (C$^8$), 27.9 (C$^{12}$), 26.0 (C$^{16}$), 18.4 (C$^{15}$), -5.2 (C$^{14}$).

IR: 2952 (w), 2932 (w), 2858 (w), 1740 (m), 1423 (m), 1209 (s), 1141 (s), 1098 (m), 914 (m), 835 (s), 776 (m).

HRMS: ([M+H]$^+$) m/z: Calcd for C$_{19}$H$_{34}$F$_3$O$_6$SSi$: 475.1792; Found: 475.1792.

$R_f$ (PE/EtOAc 95:5) = 0.36.

**Compound 351 (mixture of diastereoisomers, dr 1:1)**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.42 (m, 1H, C$^3$−H), 5.17 (s, 1H, C$^{10}$−H), 5.13 (td, $J = 4.07$, 0.8 Hz, 1H, C$^9$−H), 5.04 (s, 1H, C$^{10}$−H), 3.61-3.55 (m, 2H, C$^{13}$−H), 2.59 (td, $J = 7.7$, 2.0 Hz, 2H, C$^6$−H), 1.87-1.77 (m, 2H, C$^5$−H), 1.72-1.64 (m, 2H, C$^8$−H), 1.58-1.51 (m, 2H, C$^7$−H), 1.48-1.42 (m, 4H, C$^{11,12}$−H), 0.88 (s, 9H, C$^{16}$−H), 0.04 (s, 6H, C$^{14}$−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 148.4 (C$^2$), 124.1 (C$^3$), 118.7 (d, $J = 320.5$ Hz, C$^1$), 103.7 (C$^9$), 94.2 (C$^{10}$), 63.3 (C$^{13}$), 48.1 (C$^4$), 36.1 (C$^{11}$), 36.0 (C$^{11}$), 33.4 (C$^7$), 31.7 (C$^5$), 31.7 (C$^5$), 31.0 (C$^6$), 27.9 (C$^{12}$), 26.8 (C$^8$), 26.1 (C$^{16}$), 18.5 (C$^{15}$), -5.2 (C$^{14}$).

IR: 2958 (w), 2933 (w), 2890 (w), 2859 (w), 1663 (w), 1422 (m), 1251 (w), 1210 (s), 1141 (s), 1099 (m), 1055 (m), 1014 (m), 835 (s), 777 (m).

HRMS: ([M+Na]$^+$) m/z: Calcd for C$_{19}$H$_{34}$F$_3$NaO$_7$SSi$: 513.1561; Found: 513.1553.

$R_f$ (PE/EtOAc 95:5) = 0.30.
methyl 3-(1-(3-((tert-butyldimethylsilyl)oxy)propyl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)propanoate 352

An oven-dried flask was charged with salt 345 (0.12 g, 0.53 mmol, 1.2 equiv), X-Phos (32 mg, 0.066 mmol, 15 mol%), allylpalladium chloride dimer (4.0 mg, 0.011 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (3.0 mL) was added, and the reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate 350 (0.21 g, 0.44 mmol) in diglyme (3.0 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was allowed to cool down to RT, and TBAF (1 M in THF, 1.3 mL, 1.3 mmol, 3.0 equiv) was added. The reaction mixture was stirred for 2 h. Saturated aqueous NaHCO₃ was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 95:5) afforded the pure product 352 as a yellow oil (0.13 g, 62% yield).

**¹H NMR (400 MHz, CDCl₃):** δ 7.88 (dd, *J* = 1.0, 7.8 Hz, 1H, C₁₂−H), 7.53 (td, *J* = 1.1, 7.8 Hz, 1H, C¹₀−H), 7.37 (td, *J* = 1.3, 7.8 Hz, 1H, C¹¹−H), 7.32 (dd, *J* = 7.6, 1.8 Hz, 1H, C⁹−H), 4.84 (s, 1H, C²¹−H), 3.67 (s, 2H, C⁷−H), 3.63 (s, 3H, C²²−H), 3.58 (t, *J* = 6.1 Hz, 2H, C³−H), 2.25 (t, *J* = 7.2 Hz, 2H, C₁⁶−H), 2.22-2.16 (m, 2H, C₁⁸−H), 1.76-1.64 (m, 4H, C₁⁷,₁⁹−H), 1.49-1.22 (m, 4H, C₁⁴,₁₅−H), OH peak not observed.

**¹³C NMR (101 MHz, CDCl₃):** δ 174.8 (C⁶), 149.6 (C¹₃), 141.8 (C²), 134.7 (C⁸), 133.0 (C¹₀), 132.6 (C⁹), 132.4 (C²¹), 127.5 (C¹¹), 124.9 (C¹₂), 63.7 (C³), 51.7 (C²₀), 51.5 (C²²), 36.0 (C¹⁵), 35.1 (C₁⁸), 35.0 (C⁷), 34.7 (C¹⁷), 33.9 (C¹⁹), 30.0 (C₁⁶), 28.1 (C¹⁴).

**IR:** 3397 (br w), 2940 (w), 2847 (w), 1735 (m), 1526 (s), 1436 (w), 1353 (m), 1199 (w), 1172 (w), 1055 (w).

**HRMS:** (ESI⁺) *m/z*: [M + H]⁺ Calcd for C₁⁹H₂₆NO₅⁺: 348.1806; Found: 348.1807.

**Rf** (PE/EtOAc 6:4) = 0.11.
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(3-(1-oxaspiro[4.4]non-6-en-7-yl)propoxy)(tert-butyl)dimethylsilane 342

To a solution of 3-chloropropan-1-ol (2.0 mL, 24 mmol, 4.0 equiv) in THF (100 mL) at 0 °C was added MeMgBr (1.2 M in THF, 20 mL, 24 mmol, 4.0 equiv). The mixture was then warmed up to RT, and magnesium turning (0.57 g, 24 mmol, 4.0 equiv) was added. The mixture was heated to reflux for 3 h. The solution was then cooled down to -78 °C, CuBr·Me2S (2.4 g, 12 mmol, 2.0 equiv) was added and the solution was stirred for 1 h. The reaction mixture was then warmed up to -40 °C, and a solution of enone 220 (1.5 g, 5.9 mmol) in THF (20 mL) was added dropwise. The reaction mixture was then stirred for 3 h at -40 °C for 3 h. Saturated NaHCO3 was added, and the mixture was extracted with EtOAc. The combined organic phases were dried over Na2SO4 and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded compound 342 as a colorless oil (0.75 g, 43% yield).

1H NMR (400 MHz, CDCl3): δ 5.33 (s, 1H, C8−H), 3.81 (t, J = 6.8 Hz, 2H, C3−H), 3.61 (t, J = 6.4 Hz, 2H, C11−H), 2.40 (m, 1H, C5−H), 2.19 (m, 1H, C5−H), 2.14-2.08 (m, 2H, C9−H), 2.01 (ddd, J = 13.5, 8.9, 4.6 Hz, 1H, C6−H), 1.94 (t, J = 6.8 Hz, 2H, C2−H), 1.91 (m, 1H, C6−H), 1.85-1.78 (m, 2H, C1−H), 1.73-1.64 (m, 2H, C10−H), 0.89 (s, 9H, C14−H), 0.04 (s, 6H, C12−H).

13C NMR (101 MHz, CDCl3): δ 148.3 (C7), 128.0 (C8), 94.5 (C4), 67.0 (C3), 63.0 (C11), 37.5 (C6), 36.8 (C1), 33.8 (C3), 30.8 (C10), 27.7 (C9), 26.5 (C2), 26.1 (C14), 18.5 (C13), -5.1 (C12).

IR: 2953 (m), 2930 (m), 2856 (m), 1471 (w), 1254 (w), 1096 (m), 1046 (w), 835 (s), 775 (s).

HRMS: (ESI+) m/z: [M + Na]+ Calcd for C17H32NaO2Si+: 319.2069; Found: 319.2068.

Rf (PE/EtOAc 1:1) = 0.48.

methyl 3-iodopropionate 441

1H NMR (400 MHz, CDCl3): δ 5.33 (s, 1H, C8−H), 3.81 (t, J = 6.8 Hz, 2H, C3−H), 3.61 (t, J = 6.4 Hz, 2H, C11−H), 2.40 (m, 1H, C5−H), 2.19 (m, 1H, C5−H), 2.14-2.08 (m, 2H, C9−H), 2.01 (ddd, J = 13.5, 8.9, 4.6 Hz, 1H, C6−H), 1.94 (t, J = 6.8 Hz, 2H, C2−H), 1.91 (m, 1H, C6−H), 1.85-1.78 (m, 2H, C1−H), 1.73-1.64 (m, 2H, C10−H), 0.89 (s, 9H, C14−H), 0.04 (s, 6H, C12−H).

IR: 2953 (m), 2930 (m), 2856 (m), 1471 (w), 1254 (w), 1096 (m), 1046 (w), 835 (s), 775 (s).

HRMS: (ESI+) m/z: [M + Na]+ Calcd for C17H32NaO2Si+: 319.2069; Found: 319.2068.

Rf (PE/EtOAc 1:1) = 0.48.
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Following a known procedure, a suspension of sodium iodide (5.4 g, 36 mmol, 1.3 equiv) in acetone (20 mL) was heated to reflux. Ethyl bromopropionate (3.0 mL, 28 mmol) was added dropwise over 30 min. The reaction mixture was heated for 4 h. The mixture was allowed to cool down to RT, diluted with diethyl ether (20 mL), and filtered. The filtrate was washed with 2% NaOH, water, brine, dried over Na₂SO₄ and concentrated in vacuo. The crude compound 441 thus obtained was used for the next step without further purification (colourless oil, 5.8 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.²²⁸

¹H NMR (400 MHz, CDCl₃): δ 3.71 (s, 3H, C⁴−H), 3.31 (t, J = 7.1 Hz, 2H, C¹−H), 2.97 (t, J = 7.1 Hz, 2H, C²−H).

¹³C NMR (101 MHz, CDCl₃): δ 171.6 (C³), 52.1 (C⁴), 38.5 (C²), -3.8 (C¹).

(3-(1-(but-3-en-1-yl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)propoxy)(tert-butyl)-dimethylsilane 442

An oven-dried flask was charged with salt 345 (1.2 g, 5.3 mmol, 1.2 equiv), X-Phos (0.32 g, 0.66 mmol, 15 mol%), allylpalladium chloride dimer (40 mg, 0.11 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (30 mL) was added. The reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate 344 (2.0 g, 4.4 mmol) in diglyme (30 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was allowed to cool down to RT, and saturated aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 95:5) afforded the pure product 442 as a yellow oil (1.6 g, 87% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.87 (d, J = 7.8 Hz, 1H, C¹²−H), 7.51 (td, J = 7.8, 1.4 Hz, 1H, C¹⁰−H), 7.36 (t, J = 7.8 Hz, 1H, C¹¹−H), 7.33 (d, J = 7.8 Hz, 1H, C⁹−H), 5.79 (ddt, J = 16.0, 10.1, 6.5 Hz, 1H, C⁶−H), 4.97 (dd, J = 16.0, 1.6 Hz, 1H, C²²−H), 4.96 (s, 1H, C²¹−H), 3.71 (s, 3H, C⁴−H), 3.31 (t, J = 7.1 Hz, 2H, C¹−H), 2.97 (t, J = 7.1 Hz, 2H, C²−H).

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4.89 (d, $J = 10.1$ Hz, 1H, C$_{22}^-$H), 3.67 (s, 2H, C$_7^-$H), 3.55 (t, $J = 6.4$ Hz, 2H, C$_3^-$H), 2.22 (t, $J = 7.2$ Hz, 2H, C$_{18}^-$H), 2.01-1.88 (m, 2H, C$_{16}^-$H), 1.68 (t, $J = 7.2$ Hz, 2H, C$_{19}^-$H), 1.47-1.24 (m, 6H, C$_{14,15,17}^-$H), 0.88 (s, 9H, C$_{25}^-$H), 0.04 (s, 6H, C$_{23}^-$H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 149.7 (C$_{13}$), 140.5 (C$_2$), 139.8 (C$_6$), 135.0 (C$_8$), 134.2 (C$_{21}$), 132.8 (C$_{10}$), 132.3 (C$_9$), 127.3 (C$_{11}$), 124.8 (C$_{12}$), 113.9 (C$_{22}$), 64.1 (C$_3$), 51.7 (C$_{20}$), 39.1 (C$_{17}$), 35.8 (C$_{18}$), 34.9 (C$_{19}$), 34.8 (C$_7$), 34.5 (C$_{15}$), 29.3 (C$_{16}$), 28.4 (C$_{14}$), 26.1 (C$_{25}$), 18.5 (C$_{24}$), -5.1 (C$_{23}$).

IR: 2929 (m), 2854 (w), 1528 (s), 1462 (w), 1353 (m), 1255 (m), 1095 (s), 835 (s), 776 (s).

HRMS: (ESI$^+$) m/z: [M + H]$^+$ Calcd for C$_{25}$H$_{40}$NO$_3$Si+: 430.2772; Found: 430.2771.

$R_f$ (PE/EtOAc 9:1) = 0.61.

3-(1-(but-3-en-1-yl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)propan-1-ol 346

An oven-dried flask was charged with salt 345 (1.2 g, 5.3 mmol, 1.2 equiv), X-Phos (0.32 g, 0.66 mmol, 15 mol%), allylpalladium chloride dimer (40 mg, 0.11 mmol, 5.0 mol%) and flushed with nitrogen. Degassed and dry diglyme (30 mL) was added. The reaction mixture was stirred for 5 minutes. A solution of the vinyl triflate 344 (2.0 g, 4.4 mmol) in diglyme (30 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was allowed to cool down to RT, and TBAF (1 M in THF, 14 mL, 14 mmol, 3.0 equiv) was added. The reaction mixture was then stirred until complete consumption of intermediate 442. Saturated aqueous NaHCO$_3$ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, and concentrated $\text{in vacuo}$. Purification by FCC (PE/EtOAc 95:5) afforded the pure product 346 as a yellow oil (1.2 g, 88% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.88 (dd, $J = 7.8,1.5$ Hz, 1H, C$_{12}^-$H), 7.52 (td, $J = 7.8,1.5$ Hz, 1H, C$_{10}^-$H), 7.37 (td, $J = 7.8,1.5$ Hz, 1H, C$_{11}^-$H), 7.33 (d, $J = 7.8$ Hz, 1H, C$_9^-$H), 5.78 (ddt, $J = 17.5,10.2,6.6$ Hz, 1H, C$_6^-$H), 4.97 (dd, $J = 17.5,2.1$ Hz, 1H, C$_{22}^-$H), 4.92-4.86 (m, 2H, C$_{21,22}^-$H), 3.68 (s, 2H, C$_7^-$H), 3.58 (t, $J = 6.3$ Hz, 2H, C$_3^-$H), 2.23 (t, $J = 7.3$ Hz, 2H, C$_{18}^-$H), 2.02-1.87 (m, 2H, C$_{16}^-$H), 1.74-1.63 (m, 2H, C$_{19}^-$H), 1.49-1.22 (m, 6H, C$_{14,15,17}^-$H), OH peak not observed.
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$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 149.7 (C$^{13}$), 140.8 (C$^{2}$), 139.7 (C$^{6}$), 134.9 (C$^{8}$), 133.7 (C$^{21}$), 132.9 (C$^{10}$), 132.4 (C$^{9}$), 127.4 (C$^{11}$), 124.8 (C$^{12}$), 113.9 (C$^{22}$), 63.8 (C$^{3}$), 51.7 (C$^{20}$), 39.2 (C$^{17}$), 35.8 (C$^{18}$), 35.0 (C$^{19}$), 34.9 (C$^7$), 34.4 (C$^{15}$), 29.3 (C$^{16}$), 28.2 (C$^{14}$).

IR: 3354 (br w), 2934 (w), 2848 (w), 1526 (s), 1450 (w), 1353 (w), 1054 (w), 908 (s), 730 (s).

HRMS: (ESI$^+$) m/z: [M + Na]$^+$ Calcd for C$_{19}$H$_{25}$NNaO$_3$: 338.1727; Found: 338.1716.

$R_f$ (PE/EtOAc 6:4) = 0.39.

1-((3-(3-azidopropyl)-3-(but-3-en-1-yl)cyclopent-1-en-1-yl)methyl)-2-nitrobenzene 347

Stepwise preparation of 347

To a solution of the alcohol 346 (1.0 g, 3.2 mmol) and Et$_3$N (0.60 mL, 4.8 mmol, 1.5 equiv) in DMF (60 mL) at 0 °C was added MsCl (0.27 mL, 3.5 mmol, 1.1 equiv). The reaction mixture was stirred at RT for 30 min, and then water was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded the pure product 443 as a yellow oil (1.1 g, 88% yield).

To a refluxing solution of the mesylate 443 (1.0 g, 2.5 mmol) in DCM (50 mL) was added NaN$_3$ (0.50 g, 7.6 mmol, 3.0 equiv). The reaction mixture was stirred for 3 h, and then water was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded the azide 347 as a yellow oil (0.76 g, 89% yield).
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One-pot preparation of 347

To a solution of the alcohol 346 (1.0 g, 3.2 mmol) and Et₃N (0.60 mL, 4.8 mmol, 1.5 equiv) in DMF (60 mL) at 0 °C was added MsCl (0.27 mL, 3.5 mmol, 1.1 equiv). The reaction mixture was then stirred at RT for 30 min. NaN₃ (0.62 g, 9.5 mmol, 3.0 equiv) was added and the reaction mixture was stirred at 40 °C for 3 h. Water was added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded the azide 347 as a yellow oil (0.96 g, 89% yield).

Mesyl alcohol 443

1H NMR (400 MHz, CDCl₃): δ 7.88 (dd, J = 7.8, 1.3 Hz, 1H, C₁₂−H), 7.53 (td, J = 7.8, 1.3 Hz, 1H, C₁₀−H), 7.38 (td, J = 7.8, 1.4 Hz, 1H, C₁₁−H), 7.33 (dd, J = 7.8, 1.4 Hz, 1H, C₉−H), 5.78 (ddt, J = 17.1, 10.2, 6.6 Hz, 1H, C₆−H), 4.97 (dd, J = 17.1, 1.9 Hz, 1H, C₂₂−H), 4.93-4.85 (m, 2H, C₂₁,₂₂−H), 4.37 (td, J = 6.5, 0.9 Hz, 2H, C₃−H), 3.86 (s, 2H, C₇−H), 3.00 (s, 3H, C₂₃−H), 2.25 (t, J = 7.1 Hz, 2H, C₁₈−H), 1.97-1.87 (m, 2H, C₁₆−H), 1.72 (ddt, J = 13.6, 8.5, 6.6 Hz, 1H, C₁₉−H), 1.66 (ddt, J = 13.6, 8.5, 6.6 Hz, 1H, C₁₉−H), 1.66-1.58 (m, 2H, C₁₄−H), 1.47-1.30 (m, 4H, C₁₅,₁₇−H).

13C NMR (101 MHz, CDCl₃): δ 149.7 (C₁₃), 141.5 (C₂), 139.4 (C₆), 134.7 (C₈), 133.0 (C₂₁), 132.9 (C₁₀), 132.4 (C₉), 127.5 (C₁₁), 124.9 (C₁₂), 71.0 (C₃), 51.6 (C₂₀), 39.2 (C₁₇), 37.5 (C₂₃), 35.6 (C₁₈), 35.1 (C₁₉), 35.0 (C₇), 34.2 (C₁₅), 29.2 (C₁₆), 24.8 (C₁₄).

IR: 2933 (w), 2848 (w), 1526 (s), 1353 (s), 1175 (s), 953 (m), 917 (m).

HRMS: (ESI⁺) m/z: [M + Na]⁺ Calcd for C₂₀H₂₇NNaO₅S⁺: 416.1502; Found: 416.1495.

Rf (PE/EtOAc 6:4) = 0.60.

Azide 347

1H NMR (400 MHz, CDCl₃): δ 7.89 (dd, J = 7.8, 1.4 Hz, 1H, C₁₂−H), 7.53 (td, J = 7.8, 1.4 Hz, 1H, C₁₀−H), 7.37 (td, J = 7.8, 1.5 Hz, 1H, C₁₁−H), 7.33 (dd, J = 7.8, 1.5 Hz, 1H, C₉−H), 5.79 (ddt, J = 17.2, 10.2, 6.6 Hz, 1H, C₆−H), 4.98 (dd, J = 17.2, 1.9 Hz, 1H, C₂₂−H), 4.93-4.88 (m, 2H, C₂₁,₂₂−H), 3.68 (s, 2H, C₇−H), 3.22 (t, J = 6.8 Hz, 2H, C₃−H), 2.25 (td, J = 7.4, 2.0 Hz, 2H, C₁₈−H), 1.96-1.88 (m, 2H, C₁₆−H), 1.72 (ddt, J = 13.7, 7.8, 6.6 Hz, 1H, C₁₉−H), 1.66 (ddt, J = 13.7, 7.8, 6.6 Hz, 1H, C₁₉−H), 1.50-1.30 (m, 6H, C₁₄,₁₅,₁₇−H).

13C NMR (101 MHz, CDCl₃): δ 149.7 (C₁₃), 141.3 (C₂), 139.5 (C₆), 134.8 (C₈), 133.3 (C₂₁), 132.9
(C\textsuperscript{10}), 132.3 (C\textsuperscript{9}), 127.5 (C\textsuperscript{11}), 124.9 (C\textsuperscript{12}), 114.1 (C\textsuperscript{22}), 52.3 (C\textsuperscript{3}), 51.8 (C\textsuperscript{20}), 39.2 (C\textsuperscript{17}), 37.0 (C\textsuperscript{18}), 35.0 (C\textsuperscript{19}), 34.9 (C\textsuperscript{7}), 34.3 (C\textsuperscript{15}), 29.2 (C\textsuperscript{16}), 24.4 (C\textsuperscript{14}).

**IR**

2934 (w), 2847 (w), 2093 (s), 1526 (s), 1352 (m), 910 (m), 736 (m).

**Anal.** Calcd for C\textsubscript{19}H\textsubscript{24}N\textsubscript{4}O\textsubscript{2}: C, 67.04; H 7.11; N 16.46. Found: C 66.74; H 7.10; N 16.15.

**R\textsubscript{f}** (PE/EtOAc 6:4) = 0.88.

4-(1-(3-azidopropyl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)-1-hydroxybutan-2-one 348 and 3-(1-(3-azidopropyl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)propanoic acid 340

**Stepwise preparation of 340**

To a solution of the olefin 347 (20 mg, 0.059 mmol) in acetone/water/AcOH (5:1:0.1, 1.5 mL) at RT was added a solution of KMnO\textsubscript{4} (14 mg, 0.088 mmol, 1.5 equiv) in a mixture of acetone/water (5:1, 1.0 mL). After 15 seconds of vigorous stirring, the reaction mixture was poured into an ice-cooled saturated Na\textsubscript{2}SO\textsubscript{3} solution, and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated in vacuo.

The crude hydroxyketone 348 (13 mg, 60%, 91% BRSM) thus obtained was used for the next step without further purification. An analytical sample was obtained by FCC (PE/EtOAc 8:2) to afford compound 348 as a yellow oil.

To a solution of hydroxyketone 348 (13 mg, 0.035 mmol) in t-BuOH (2.0 mL) was added a solution of NaIO\textsubscript{4} (26 mg, 0.12 mmol, 2.0 equiv) in aqueous K\textsubscript{2}CO\textsubscript{3} (5 %, 1.0 mL), and the reaction mixture was stirred at 50 °C. The reaction mixture was cooled down to 0 °C, and saturated aqueous Na\textsubscript{2}SO\textsubscript{3} was added until the color disappeared. The aqueous solution was acidified...
to pH 2-3, and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by FCC (PE/EtOAc/AcOH 8:2:0.1) afforded the acid 340 as a yellow oil (13 mg, quantitative yield).

**One-pot preparation of 340**

To a solution of the olefin 347 (20 mg, 0.059 mmol) in t-BuOH/water/ (3:1, 1.5 mL) at 45 °C was added a solution of KMnO₄ (14 mg, 0.088 mmol, 1.5 equiv), NaIO₄ (64 mg, 0.30 mmol, 5.0 equiv) in 5% aqueous K₂CO₃ (1.0 mL). After 60 seconds of vigorous stirring, the reaction mixture was poured into an ice-cooled saturated Na₂SO₃ solution, and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by FCC (PE/EtOAc/AcOH 8:2:0.1) afforded the acid 340 as a yellow oil (15 mg, 72%, 83% BRSM).

**Hydroxyketone 348**

1H NMR (400 MHz, CDCl₃): δ 7.89 (dd, J = 7.7, 1.5 Hz, 1H, C¹²−H), 7.54 (td, J = 7.7, 1.5 Hz, 1H, C¹¹−H), 7.40 (td, J = 7.7, 1.4 Hz, 1H, C¹³−H), 7.32 (dd, J = 7.7, 1.4 Hz, 1H, C⁹−H), 4.76 (quint., J = 1.7 Hz, 1H, C²¹−H), 4.24 (s, 2H, C²²−H), 3.68 (s, 2H, C⁷−H), 3.22 (t, J = 6.7 Hz, 2H, C³−H), 2.31-2.22 (m, 4H, C₁₆,₁₈−H), 1.74-1.59 (m, 4H, C¹⁷,₁₉−H), 1.52-1.42 (m, 2H, C¹⁴−H), 1.39-1.31 (m, 2H, C¹₅−H). OH not observed.

13C NMR (101 MHz, CDCl₃): δ 210.3 (C⁶), 149.6 (C¹₃), 142.7 (C²), 134.4 (C⁸), 133.1 (C¹⁰), 132.5 (C⁹), 131.8 (C²¹), 127.7 (C¹¹), 125.0 (C¹²), 68.2 (C²²), 52.1 (C³), 51.5 (C²⁰), 37.5 (C¹⁵), 35.3 (C⁷), 35.1 (C¹₈), 34.1 (C¹⁷), 33.6 (C₁⁹), 33.1 (C¹⁶), 24.4 (C¹⁴).

IR: 3445 (br w), 2935 (w), 2852 (w), 2095 (s), 1718 (m), 1525 (s), 1353 (m), 1067 (w),


Rᶠ (PE/EtOAc/AcOH 6/3.5/0.5) = 0.4.

**Carboxylic acid 340**

1H NMR (400 MHz, CDCl₃): δ 7.93 (dd, J = 7.8, 1.4 Hz, 1H, C¹²−H), 7.53 (td, J = 7.8, 1.4 Hz, 1H, C¹¹−H), 7.38 (td, J = 7.8, 1.4 Hz, 1H, C¹³−H), 7.32 (d, J = 7.8 Hz, 1H, C⁹−H), 4.84 (s, 1H, C²¹−H), 3.68 (s, 2H, C⁷−H), 3.22 (t, J = 6.7 Hz, 2H, C³−H), 2.32-2.20 (m, 4H, C¹₆,₁₈−H), 1.73-1.64 (m, 4H, C¹⁷,₁₉−H), 1.53-1.44 (m, 2H, C¹⁴−H), 1.40-1.32 (m, 2H, C¹₅−H). OH not observed.
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\[^{13}C\text{ NMR} (101 \text{ MHz}, \text{CDCl}_3)\]: \( \delta \) 178.0 (C\(^6\)), 149.6 (C\(^{13}\)), 142.5 (C\(^2\)), 134.5 (C\(^8\)), 133.0 (C\(^{10}\)), 132.4 (C\(^9\)), 132.0 (C\(^{21}\)), 127.6 (C\(^{11}\)), 124.9 (C\(^{12}\)), 52.2 (C\(^3\)), 51.5 (C\(^{20}\)), 37.2 (C\(^{15}\)), 35.2 (C\(^{18}\)), 34.9 (C\(^7\)), 34.5 (C\(^{17}\)), 33.7 (C\(^{19}\)), 29.5 (C\(^{16}\)), 24.4 (C\(^{14}\)).

**IR**: 2923 (w), 2854 (w), 2095 (w), 1704 (s), 1526 (s), 1352 (m), 1298 (w).

**HRMS**: (ESI\(^+\)) m/z: \([M + Na]^+\) Calcd for C\(_{18}\)H\(_{22}\)N\(_4\)NaO\(_4\): 381.1533; Found: 381.1547.

**R\(_f\)** (PE/EtOAc/AcOH 6/3.5/0.5) = 0.56.

**pentafluorophenyl 3-(1-(3-azidopropyl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)-propanoate 355**

To a solution of the acid 340 (20 mg, 0.056 mmol) and pentafluorophenol (10 mg, 0.056 mmol, 1.0 equiv) in DCM (2.0 mL) was added EDCI (11 mg, 0.056 mmol, 1.0 equiv) and DIPEA (9.6 mL, 0.067 mmol, 1.2 equiv). The reaction mixture was stirred for 2 h. Saturated NaHCO\(_3\) solution was added and the mixture was extracted with EtOAc. The combined organic phases were washed with 1 M HCl, water, brine, dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded the ester 355 as a yellow oil (16 mg, 54%).

\[^1H\text{ NMR} (400 \text{ MHz}, \text{CDCl}_3)\]: \( \delta \) 7.90 (dd, \( J = 1.2, 8.1 \) Hz, 1H, C\(^{12}\)-H), 7.54 (td, \( J = 1.3, 7.5 \) Hz, 1H, C\(^{10}\)-H), 7.40 (td, \( J = 1.4, 8.1 \) Hz, 1H, C\(^{11}\)-H), 7.34 (dd, \( J = 1.2, 7.6 \) Hz, 1H, C\(^8\)-H), 4.88 (m, 1H, C\(^{21}\)-H), 3.70 (s, 2H, C\(^7\)-H), 3.27-3.22 (m, 2H, C\(^3\)-H), 2.57-2.51 (m, 2H, C\(^{16}\)-H), 2.35-2.28 (m, 2H, C\(^{18}\)-H), 1.82-1.72 (m, 4H, C\(^{17,19}\)-H), 1.56-1.44 (m, 4H, C\(^{14,16}\)-H), 1.43-1.33 (m, 2H, C\(^{15}\)-H).

\[^{13}C\text{ NMR} (101 \text{ MHz}, \text{CDCl}_3)\]: \( \delta \) 170.1 (C\(^6\)), 149.6 (C\(^{13}\)), 143.1 (C\(^2\)), 142.8-136.1 (m, C\(^{22-25}\)), 134.4 (C\(^8\)), 133.0 (C\(^{10}\)), 132.4 (C\(^9\)), 131.5 (C\(^{21}\)), 127.7 (C\(^{11}\)), 124.9 (C\(^{12}\)), 52.1 (C\(^3\)), 51.6 (C\(^{20}\)), 37.3 (C\(^{15}\)), 35.2 (C\(^{18}\)), 35.0 (C\(^7\)), 34.5 (C\(^{17}\)), 33.6 (C\(^{19}\)), 29.3 (C\(^{16}\)), 24.4 (C\(^{14}\)).

**IR**: 2926 (w), 2851 (w), 2095 (m), 1786 (w), 1518 (s), 1351 (m), 1088 (m), 993 (s), 733 (m).

**HRMS**: (ESI\(^+\)) m/z: \([M + Na]^+\) Calcd for C\(_{24}\)H\(_{21}\)F\(_5\)N\(_4\)NaO\(_4\): 547.1375; Found: 547.1375.

**R\(_f\)** (PE/EtOAc/AcOH 8:2) = 0.2.
methyl 3-(1-(3-azidopropyl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)propanoate

To a solution of the acid \(340\) (12 mg, 0.033 mmol) in MeOH (1.0 mL) was added TMS-diazomethane (1 M in THF) dropwise until the yellow color persisted and no more bubbling was observed (approximately 0.050 mL, 1.5 equiv). Excess of diazomethane was quenched by addition of acetic acid (2 drops). The reaction mixture was concentrated in vacuo, and the crude mixture was filtered through a plug of silica gel (PE/EtOAc 8:2) to afford the methyl ester \(349\) as a yellow oil (12 mg, quantitative yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.88 (dd, \(J = 7.6, 1.5\) Hz, 1H, C\(_{12}\)−H), 7.53 (td, \(J = 7.6, 1.5\) Hz, 1H, C\(_{10}\)−H), 7.37 (td, \(J = 7.6, 1.4\) Hz, 1H, C\(_{11}\)−H), 7.31 (dd, \(J = 7.6, 1.4\) Hz, 1H, C\(_9\)−H), 4.83 (m, 1H, C\(_{21}\)−H), 3.66 (s, 2H, C\(_7\)−H), 3.63 (s, 3H, C\(_{22}\)−H), 3.21 (t, \(J = 6.8\) Hz, 2H, C\(_3\)−H), 2.25 (t, \(J = 7.3\) Hz, 2H, C\(_{18}\)−H), 2.21-2.15 (m, 2H, C\(_{16}\)−H), 1.70-1.62 (m, 4H, C\(_{17,19}\)−H), 1.51-1.42 (m, 2H, C\(_{14}\)−H), 1.37-1.28 (m, 2H, C\(_{15}\)−H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 174.6 (C\(_6\)), 149.5 (C\(_{13}\)), 142.2 (C\(_2\)), 134.4 (C\(_8\)), 132.9 (C\(_{10}\)), 132.3 (C\(_9\)), 132.1 (C\(_{21}\)), 127.5 (C\(_{11}\)), 124.8 (C\(_{12}\)), 52.1 (C\(_3\)), 51.6 (C\(_{20}\)), 51.4 (C\(_{22}\)), 37.0 (C\(_{15}\)), 35.0 (C\(_{18}\)), 34.8 (C\(_7\)), 34.6 (C\(_{17}\)), 33.7 (C\(_{19}\)), 29.9 (C\(_{16}\)), 24.3 (C\(_{14}\)).

IR: 2933 (w), 2846 (w), 2095 (s), 1736 (s), 1526 (s), 1436 (w), 1352 (m), 1260 (w).

HRMS: (ESI\(^{+}\)) m/z: [M + Na]\(^{+}\) Calcd for C\(_{19}\)H\(_{24}\)N\(_4\)NaO\(_4\): 395.1690; Found: 395.1688.

\(R_f\) (PE/EtOAc/ 8:2) = 0.50.
To a solution of methyl ester 349 (20 mg, 0.054 mmol) at -78°C in DCM (0.50 mL) was added NaHCO₃ (9.0 mg, 0.11 mmol, 2.0 equiv). Ozone was bubbled through the solution until the blue color persisted. Argon was then bubbled through the solution for 15 minutes. Me₂S (excess) was added and the reaction mixture was stirred at RT overnight. Methanol (0.20 mL) was added, followed by HCl (0.5 M aqueous solution, 0.11 mL, 1.0 equiv) and zinc powder (0.18 g, 2.7 mmol, 50 equiv). The reaction was stirred for 30 min. Aqueous NaHCO₃ was added, and the reaction mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc/Et₃N 3:5:0.2) afforded the pure product (±)-353 as colourless oils (6.7 mg, 40% yield).

**¹H NMR (400 MHz, CDCl₃):** δ 7.84 (br s, 1H, N₁⁻H), 7.56 (d, $J = 7.1$ Hz, 1H, C₉⁻H), 7.26 (d, $J = 7.1$ Hz, 1H, C₁₂⁻H), 7.10 (td, $J = 7.1$, 1.5 Hz, 1H, C₁¹⁻H), 7.07 (td, $J = 7.1$, 1.2 Hz, 1H, C₁₀⁻H), 3.73 (s, 1H, C₂¹⁻H), 3.60 (s, 3H, C₂₂⁻H), 3.03 (br d, $J = 12.9$ Hz, 1H, C₃⁻H), 2.82-2.69 (m, 3H, C₃,₁₈⁻H), 2.47-2.23 (m, 3H, N⁴⁻H, C₁₆⁻H), 1.87-1.72 (m, 2H, C₁⁷,₁₄⁻H), 1.67-1.36 (m, 6H, C₁₄,₁₅,₁₇,₁₉⁻H).

**¹³C NMR (101 MHz, CDCl₃):** δ 174.8 (C₆), 136.3 (C₁₃), 133.8 (C₂), 127.5 (C₈), 121.3 (C¹₁), 119.6 (C¹₀), 117.8 (C⁹), 112.3 (C⁷), 110.6 (C¹₂), 56.7 (C₂¹), 51.8 (C₂²), 46.2 (C₃), 34.5 (C₂₀), 34.4 (C₁₅), 32.4 (C₁⁷), 28.9 (C₁₆), 24.6 (C₁⁹), 22.9 (C₁₄), 20.2 (C₁₈).

**IR:** 3342 (w), 2929 (m), 2850 (w), 1731 (s), 1436 (m), 1315 (w), 1254 (w), 741 (w),

**HRMS:** (ESI⁺) m/z: [M + H]⁺ Calcd for C₁₉H₂₅N₂O₂⁺: 313.1911; Found: 313.1899.

**$R_f$ (PE/EtOAc/Et₃N 3:5:0.5) = 0.17.**
8.5. Experimental Procedures of Chapter 5

Diphenylphosphine borane complex 444

Following a reported procedure,\textsuperscript{229} diphenylphosphine (10 g, 54 mmol) in THF (0.10 mL) was added dropwise to a solution of BH\(_3\)-THF in THF (1 M, 54 mL, 54 mmol, 1.0 equiv) at 0 °C. The mixture was stirred for 30 minutes at RT, and then concentrated \textit{in vacuo}. The oily residue was dissolved in DCM, filtered and concentrated \textit{in vacuo}. The crude complex 444 thus obtained was used for the next step without further purification (colorless wax, 11 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature.\textsuperscript{229}

\textbf{1H NMR (400 MHz, CDCl\(_3\))}: \(\delta 7.72-7.65\) (m, 4H, C\(_3\)-H), 7.55-7.50 (m, 2H, C\(_5\)-H), 7.50-7.43 (m, 4H, C\(_4\)-H), 6.31 (dq, \(J = 379.0, 7.0\) Hz, 1H, P\(_1\)-H), 1.07 (br q, \(J = 91.7\) Hz, 3H, B\(_6\)-H).

\textbf{13C NMR (101 MHz, CDCl\(_3\))}: \(\delta 133.0\) (d, \(J = 9.2\) Hz, C\(_3\)), 131.7 (d, \(J = 1.7\) Hz, C\(_5\)), 129.11 (d, \(J = 10.4\) Hz, C\(_4\)), 126.3 (d, \(J = 56.3\) Hz, C\(_2\)).

Bromomethyl thioacetate 445

Following a reported procedure,\textsuperscript{155c} a mixture of thioacetic acid (8.0 g, 0.12 mol) and paraformaldehyde (3.6 g) was stirred at 80 °C for 18 h. The reaction mixture was cooled down to 0 °C. Then, PBr\(_3\) (21 g, 80 mmol, 0.70 equiv) was added at 0 °C, and the reaction mixture was stirred at RT for 15 minutes. The reaction mixture was quenched with ice, and extracted with Et\(_2\)O. The combined organic phases were washed with water, brine, dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. Purification by FCC (PE/Et\(_2\)O/Et\(_3\)N 3:7) afforded product 445 as a yellow oil (16 g, 80% yield). The spectroscopic data of this compound were in accord with those reported in the literature.\textsuperscript{155c}

\textbf{1H NMR (400 MHz, CDCl\(_3\))}: \(\delta 4.69\) (s, 2H, C\(_3\)-H), 2.38 (s, 3H, C\(_1\)-H).

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$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 191.9 (C$_2$), 30.5 (C$_3$), 26.4 (C$_1$).

$R_f$ (Ether) = 0.8.

**S-((diphenylphosphino)methyl) ethanethioate borane complex 446**

Following a reported procedure,$^{155b}$ to a solution of the phosphine borane complex 444 (11 g, 54 mmol) in DMF (100 mL) at 0°C was added NaH (60% in mineral oil, 2.2 g, 54 mmol, 1.0 equiv). When the gas evolution stopped, the thioester 445 (9.1 g, 54 mmol, 1.0 equiv) was added. The reaction was stirred at RT overnight. Saturated aqueous NaHCO$_3$ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 8:2) afforded the pure product 446 as a colorless oils (8.7 g, 56% yield). The spectroscopic data of this compound were in accord with those reported in the literature.$^{155b}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.74-7.66 (m, 4H, C$_5$–H), 7.55-7.42 (m, 6H, C$_6$,7–H), 3.71 (d, $J$ = 6.8 Hz, 2H, C$_3$–H), 2.25 (s, 3H, C$_1$–H), 1.40-0.40 (m, 3H, B$_8$–H),

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 193.4 (C$_2$), 132.6 (d, $J$ = 8.3 Hz, C$_5$), 131.9 (C$_7$), 129.0 (d, $J$ = 9.8 Hz, C$_6$), 127.7 (d, $J$ = 55.6 Hz, C$_4$), 30.2 (C$_1$), 23.9 (d, $J$ = 35.5 Hz, C$_3$),

$R_f$ (PE/EtOAc 8:2) = 0.36.

**(diphenylphosphino)methanethiol borane complex 356**

Following a reported procedure,$^{155a}$ compound 446 (8.7 g, 30 mmol) was dissolved in MeOH (60 mL). NaOH (2.4 g, 60 mmol, 2.0 equiv) in MeOH (10 mL) was added dropwise. The reaction mixture was stirred for 2 h, and then concentrated *in vacuo*. Saturated aqueous NH$_4$Cl was added. The mixture was extracted with EtOAc. The combined organic phases were
washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded product 356 as a colorless oil (7.4 g, quantitative yield). The spectroscopic data of this compound were in accord with those reported in the literature. 155a

**¹H NMR (400 MHz, CDCl₃)**: δ 7.75-7.67 (m, 4H, C⁴-H), 7.57-7.44 (m, 6H, C⁵,6-H), 3.19 (dd, J = 8.2, 6.1 Hz, 2H, C²-H), 1.88 (ddd, J = 15.5, 8.2, 6.6 Hz, 1H, S¹-H), 1.03 (q, J = 95.6 Hz, 3H, B⁷-H),

**¹³C NMR (101 MHz, CDCl₃)**: δ 132.7 (d, J = 7.5 Hz, C⁴), 131.8 (C₆), 129.1 (d, J = 10.5 Hz, C⁵), 127.9 (d, J = 55.9 Hz, C³), 19.8 (d, J = 32.5 Hz, C²),

Rf (PE/EtOAc 8:2) = 0.43.

**S-((diphenylphosphino)methyl) 3-(1-(3-azidopropyl)-3-(2-nitrobenzyl)cyclopent-2-en-1-yl)propanethioate borane complex 357**

![Structural diagram](image)

To a solution of the acid 340 (0.20 g, 0.56 mmol) in DCM (10 mL) was added compound 356 (0.14 g, 0.56 mmol, 1.0 equiv). The solution was cooled down to 0°C. HATU (0.26 g, 0.67 mmol, 1.2 equiv) and DIPEA (0.12 mL, 0.67 mmol, 1.2 equiv) were added, and the solution was stirred at RT for 1 h. Saturated aqueous NH₄Cl was added. The mixture was extracted with EtOAc. The combined organic phases were washed with NaHCO₃, brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded product 357 as a yellow oil (0.31 g, 91% yield).

**¹H NMR (400 MHz, CDCl₃)**: δ 7.88 (d, J = 7.8 Hz, 1H, C₁₁-H), 7.73-7.65 (m, 4H, C₂₄-H), 7.53-7.48 (m, 3H, C₁₀,2₆-H), 7.48-7.41 (m, 4H, C²⁵-H), 7.38 (t, J = 7.8 Hz, 1H, C¹₁-H), 7.30 (d, J = 7.8 Hz, 1H, C⁹-H), 4.76 (s, 1H, C²¹-H), 3.69 (d, J = 6.8 Hz, 2H, C²₂-H), 3.64 (s, 2H, C⁷-H), 3.20 (t, J = 6.4 Hz, 2H, C³-H), 2.36-2.29 (m, 2H, C¹₆-H), 2.26-2.17 (m, 2H, C¹₈-H), 1.68-1.54 (m, 2H, C¹₉-H), 1.51-1.45 (m, 2H, C¹₇-H), 1.45-1.37 (m, 2H, C¹₄-H), 1.32-1.23 (m, 2H, C¹₅-H),

**¹³C NMR (101 MHz, CDCl₃)**: δ 197.3 (C₆), 149.6 (C₁₃), 142.7 (C²), 132.7 (C³), 133.1 (C¹₀), 132.7 (d, J = 9.4 Hz, C²₄), 132.4 (C²₅), 131.9 (d, J = 1.6 Hz, C²₆), 131.8 (C²¹), 129.0 (d, J = 10.2 Hz, C²₅), 127.8 (d, J = 53.5 Hz, C²₃), 127.6 (C¹₁), 124.9 (C¹₂), 52.1 (C³), 51.3 (C²₀), 39.7 (C¹₆), 37.2 (C¹₅),
35.2 (C$^{17}$), 35.1 (C$^{18}$), 34.9 (C$^{7}$), 33.6 (C$^{19}$), 24.3 (C$^{14}$), 23.6 (d, $J = 35.6$ Hz, C$^{22}$).

IR: 2924 (w), 2852 (w), 2385 (m), 2093 (s), 1697 (m), 1525 (s), 1436 (m), 1351 (m), 1261 (w), 1108 (w), 1058 (m), 741 (s), 703 (s),

HRMS: (ESI$^+$) m/z: [M + Na]$^+$ Calcd for C$_{31}$H$_{36}$BN$_4$NaO$_3$PS$: 609.2231; Found: 609.2231.

$R_f$ (PE/EtOAc 6:3) = 0.60.


To a refluxing solution of thioester 357 (0.80 g, 1.4 mmol) in THF/H$_2$O (99:1, 150 mL) was added DABCO (0.30 g, 2.7 mmol, 2.0 equiv). The reaction mixture was stirred at reflux for 24 h. The reaction mixture was cooled down to RT, and water was added. The mixture was extracted with EtOAc. The combined organic phases were washed with NaHCO$_3$, brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by FCC (EtOAc/MeOH 98:2) afforded the product 339 as a yellow wax (0.43 g, quantitative yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.88 (dd, $J = 7.8, 1.4$ Hz, 1H, C$_{12}$−H), 7.53 (td, $J = 7.8, 1.4$ Hz, 1H, C$_{10}$−H), 7.38 (td, $J = 7.8, 1.2$ Hz, 1H, C$_{11}$−H), 7.32 (dd, $J = 7.8, 1.2$ Hz, 1H, C$_{8}$−H), 5.70 (m, 1H, C$_4$−H), 5.21 (s, 1H, C$_{21}$−H), 3.70 (s, 2H, C$_7$−H), 3.29-3.21 (m, 2H, C$_3$−H), 2.40 (t, $J = 6.7$ Hz, 2H, C$_{16}$−H), 2.25-2.17 (m, 2H, C$_{18}$−H), 1.78-1.68 (m, 4H, C$_{17,19}$−H), 1.65-1.55 (m, 4H, C$_{14,15}$−H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 178.4 (C$^6$), 149.7 (C$^{13}$), 140.9 (C$^2$), 134.5 (C$^8$), 133.8 (C$^{10}$), 133.0 (C$^9$), 132.3 (C$^{21}$), 127.6 (C$^{11}$), 124.9 (C$^{12}$), 51.1 (C$^3$), 41.9 (C$^{17}$), 39.5 (C$^{19}$), 34.9 (C$^7$), 33.5 (C$^{15or18}$), 33.4 (C$^{15or18}$), 30.8 (C$^{16}$), 28.5 (C$^{14}$).

IR: 3236 (br w), 2928 (m), 2852 (w), 1659 (s), 1525 (s), 1438 (w), 1355 (m), 1193 (w).

HRMS: (ESI$^+$) m/z: [M + H]$^+$ Calcd for C$_{19}$H$_{23}$N$_2$O$_3^+$: 315.1703; Found: 315.1695.

$R_f$ (EtOAc/MeOH 98:2) = 0.21.
8.5. Experimental Procedures of Chapter 5

(±)-16-dehydroxykopsihainanine A 336

To a solution of the lactam 339 (10 mg, 0.031 mmol) in DCM (0.30 mL) was added 0.10 mg of Sudan III. The solution was cooled down to -78 °C and ozone was bubbled through the reaction mixture until the red color disappeared. Argon was then bubbled through the solution for 5 minutes, and PPh₃ (16 mg, 0.062 mmol, 2.0 equiv) was added. After 5 minutes, the reaction was allowed to warm to RT, and stirred for 30 minutes. PtO₂ (7.0 mg, 0.031 mmol, 1.0 equiv) and MeOH (0.30 mL) were added, and the flask was flushed with hydrogen. The mixture was stirred vigorously under H₂ atmosphere for 1.5 h. The hydrogen was replaced by argon, and HCl (1 M aqueous solution, 60 µL, 2.0 equiv) was added. The reaction mixture was stirred for 1 h at 50 °C. Aqueous NaHCO₃ was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 3:7) afforded product (±)-336 as a white amorphous solid (5.5 mg, 63% yield).

If Zinc/HCl or TiCl₃/NH₄OAc were used as reducing agents instead of H₂/PtO₂, the unstable side product 361 was observed as main product.

Compound 336

¹H NMR (400 MHz, CDCl₃): δ 7.79 (br s, 1H, C¹−H), 7.69 (d, J = 7.6 Hz, 1H, C⁹−H), 7.26 (m, 1H, C¹²−H), 7.12 (td, J = 7.6,0.9 Hz, 1H, C¹¹−H), 7.03 (td, J = 7.6,0.9 Hz, 1H, C¹⁰−H), 4.41 (dd, J = 12.9,5.4 Hz, 1H, C³−H), 4.34 (s, 1H, C²¹−H), 3.15 (td, J = 12.9,3.2 Hz, 1H, C³−H), 3.03 (m, 1H, C¹⁸−H), 2.77 (m, 1H, C¹⁸−H), 2.10-2.04 (m, 2H, C¹⁷−H), 2.00-1.85 (m, 4H, C¹⁶,19−H), 1.73-1.67 (m, 2H, C¹⁵−H), 1.58-1.47 (m, 2H, C¹⁴−H).

¹³C NMR (101 MHz, CDCl₃): δ 186.0 (C⁶), 136.3 (C¹³), 133.2 (C²), 125.1 (C⁸), 121.9 (C¹¹), 120.4 (C⁹), 119.8 (C¹⁰), 111.3 (C⁷), 110.4 (C¹²), 64.4 (C²¹), 53.8 (C³), 40.0 (C¹⁵), 37.1 (C²⁰), 35.0 (C¹⁷), 34.6 (C¹⁹), 27.8 (C¹⁶), 22.5 (C¹⁴), 19.8 (C¹⁸).

IR: 3274 (br w), 2923 (m), 2853 (w), 1655 (s), 1464 (m), 1331 (w), 1244 (w), 1168 (w), 741 (m).
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HRMS: (ESI+) m/z: [M + Na]+ Calcd for C_{18}H_{20}N_{2}NaO+: 303.1468; Found: 303.1456.

R_f (EtOAc/MeOH 2:8) = 0.45.

Compound 361

¹H NMR (400 MHz, CDCl₃): δ 7.08 (br, s, 1H), 7.48 (d, J = 7.0 Hz, 1H), 7.31 (d, J = 7.0 Hz, 1H), 7.15 (td, J = 7.0, 1.4 Hz, 1H), 7.11 (td, J = 7.0, 1.4 Hz, 1H), 6.36 (br, s, 1H), 3.60-3.40 (m, 2H), 2.82-2.75 (m, 2H), 2.71 (d, J = 15.3 Hz, 1H), 2.58 (m, 1H), 2.59 (d, J = 15.3 Hz, 1H), 2.48 (m, 1H), 1.98 (m, 1H), 1.92-1.72 (m, 5H), 1.68-1.62 (m, 2H).

Compound 361 proved unstable at RT and fully degraded before ¹³C NMR analysis and 2D spectra could be done.

IR: 3380 (br w), 2955 (s), 2924 (s), 2853 (w), 1733 (w), 1647 (m), 1463 (m), 1397 (w), 1016 (w), 749 (m).

HRMS: (ESI+) m/z: [M + Na]+ Calcd for C_{18}H_{22}N_{2}NaO+: 305.1624; Found: 305.1629.

R_f (EtOAc/MeOH/Et₃N 95:5:0.2) = 0.28

(±)-1-tributyldimethylsilyl-16-dehydroxykopsihainamine A 362

To a solution of (±)-336 (10 mg, 0.036 mmol) in THF (0.50 mL) at 0 °C was added NaH (60% in mineral oil, 2.9 mg, 0.072 mmol, 2.0 equiv), followed by TBSCI (11 mg, 0.072 mmol, 2.0 equiv). The reaction mixture was stirred at RT for 2h. Aqueous NH₄Cl was added. The mixture was extracted with EtOAc. The combined organic phases were washed with saturated NaHCO₃, water, brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by FCC (PE/EtOAc 1:1) afforded product (±)-362 as a white amorphous solid (14 mg, quantitative yield).

¹H NMR (400 MHz, CDCl₃): δ 7.72 (d, J = 7.8 Hz, 1H, C⁹−H), 7.48 (d, J = 7.8 Hz, 1H, C¹²−H), 7.07 (td, J = 7.8, 1.4 Hz, 1H, C¹¹−H), 7.02 (t, J = 7.8 Hz, 1H, C¹⁰−H), 4.41 (dd, J = 12.8, 5.1 Hz, 1H, C³−H), 4.32 (s, 1H, C²¹−H), 3.15 (td, J = 12.8, 3.3 Hz, 1H, C³−H), 2.99 (m, 1H, C¹⁸−H),
8.5. Experimental Procedures of Chapter 5

2.86 (m, 1H, C\(^{18}\)−H), 2.10-2.04 (m, 2H, C\(^{17}\)−H), 2.00-1.88 (m, 3H, C\(^{16},19\)−H), 1.79 (ddd, \(J = 12.9,11.1,6.0\) Hz, 1H, C\(^{15}\)−H), 1.71-1.64 (m, 2H, C\(^{14},15\)−H), 1.60-1.45 (m, 2H, C\(^{14},16\)−H), 0.91 (s, 9H, C\(^{24}\)−H), 0.68 (s, 6H, C\(^{22}\)−H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)):  δ 185.9 (C\(^6\)), 142.4 (C\(^{13}\)), 139.4 (C\(^2\)), 128.1 (C\(^8\)), 121.4 (C\(^{11}\)), 120.3 (C\(^9\)), 119.8 (C\(^{10}\)), 114.5 (C\(^7\)), 114.0 (C\(^{12}\)), 64.7 (C\(^{21}\)), 53.7 (C\(^3\)), 39.9 (C\(^{15}\)), 36.2 (C\(^{20}\)), 35.3 (C\(^{17}\)), 35.0 (C\(^{19}\)), 27.7 (C\(^{16}\)), 26.9 (C\(^{24}\)), 23.2 (C\(^{18}\)), 22.5 (C\(^{14}\)), 20.7 (C\(^{23}\)), -0.3 (C\(^{22}\)).

IR: 2929 (w), 2856 (w), 1677 (m), 1452 (m), 1256 (m), 1131 (w), 988 (w), 898 (w), 823 (s), 730 (s).

HRMS: (ESI\(^+\)) m/z: [M + H]\(^+\) Calcd for C\(_{24}\)H\(_{35}\)N\(_2\)O\(_2\)Si+: 395.2513; Found: 395.2519.

\(R_f\) (EtOAc/MeOH 3:7) = 0.57.

(±)-Kopsihainanine A 6

To a solution of dimethylamine (2 M in THF, 0.20 mL, 0.40 mmol, 14 equiv) and HMPA (0.14 mL, 0.84 mmol, 30 equiv) in THF (1.2 mL) at -78 °C was added \(n\)-BuLi (1.42 M in hexane, 0.24 mL, 0.34 mmol, 12 equiv). The mixture was stirred at RT for 15 min. This mixture was added dropwise to a solution of (±)-336 (8.0 mg, 0.028 mmol) in THF (1.2 mL) at 0 °C. The reaction mixture was stirred at RT for 15 min. The reaction mixture was cooled down to -78 °C, and bis(trimethylsilyl) peroxide (0.18 mL, 0.88 mmol, 30 equiv) was added. The reaction mixture was warmed to RT over 1 h. Aqueous NaHCO\(_3\) was added. The mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na\(_2\)SO\(_4\) and concentrated \(\text{in vacuo}\). Purification by preparative TLC (PE/EtOAc 3:7) afforded the pure (±)-kopsihainanine A 6 as a white amorphous solid (7.5 mg, 91% yield). The spectroscopic data of this compound were in accord with those reported in the literature.\(^{144}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.84 (br s, 1H, C\(^1\)−H), 7.62 (d, \(J = 7.8\) Hz, 1H, C\(^9\)−H), 7.27 (m, 1H, C\(^{12}\)−H), 7.13 (t, \(J = 7.8\) Hz, 1H, C\(^{11}\)−H), 7.04 (t, \(J = 7.8\) Hz, 1H, C\(^{10}\)−H), 4.43 (dd, \(J = 13.4,5.6\) Hz, 1H, C\(^3\)−H), 4.36 (s, 1H, C\(^{21}\)−H), 4.02 (dd, \(J = 10.6,8.4\) Hz, 1H, C\(^{16}\)−H), 3.55 (br s, 1H, C\(^{16}\)−OH), 3.26 (td, \(J = 12.9,3.1\) Hz, 1H, C\(^3\)−H), 3.09 (m, 1H, C\(^{18}\)−H), 2.78 (dd, \(J = 17.5,6.5\) Hz, 1H, C\(^{18}\)−H), 2.38 (dd, \(J = 14.1,8.8\) Hz, 1H, C\(^{17}\)−H), 1.99-1.92 (m, 2H, C\(^{14},19\)−H), 1.88-1.81 (m, 1H, C\(^{14}\)−H), 1.73-1.67 (m, 1H, C\(^{19}\)−H), 1.51-1.45 (m, 1H, C\(^{19}\)−H), 1.37-1.31 (m, 1H, C\(^{19}\)−H), 1.25-1.19 (m, 1H, C\(^{19}\)−H), 0.85-0.79 (m, 2H, C\(^{14}\)−H), 0.71-0.65 (m, 2H, C\(^{14}\)−H), 0.62-0.56 (m, 2H, C\(^{14}\)−H), 0.49-0.43 (m, 2H, C\(^{14}\)−H), 0.39-0.33 (m, 2H, C\(^{14}\)−H), 0.29-0.23 (m, 2H, C\(^{14}\)−H), 0.19-0.13 (m, 2H, C\(^{14}\)−H), 0.09-0.03 (m, 2H, C\(^{14}\)−H).
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1.82 (ddd, $J = 13.7, 12.2, 6.5$ Hz, 1H, C$_{19}$–H), 1.75–1.68 (m, 2H, C$_{15}$–H), 1.60 (m, 1H, C$_{14}$–H), 1.27 (m, 1H, C$_{17}$–H),

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 186.0 (C$_6$), 136.4 (C$_{13}$), 133.2 (C$_2$), 124.8 (C$_8$), 122.2 (C$_{11}$), 120.0 (C$_9$), 119.9 (C$_{10}$), 110.6 (C$_{12}$), 110.0 (C$_7$), 68.9 (C$_{16}$), 63.9 (C$_{21}$), 54.0 (C$_3$), 39.6 (C$_{15}$), 37.8 (C$_{20}$), 37.5 (C$_{17}$), 34.7 (C$_{19}$), 22.0 (C$_{14}$), 19.8 (C$_{18}$).

IR: 3394 (br w), 3314 (br w), 2925 (m), 2853 (w), 1660 (s), 1465 (m), 1329 (w), 1223 (w), 1134 (m), 1091 (m), 1037 (w), 736 (s).

HRMS: (ESI$^+$) m/z: [M + Na]$^+$ Calcd for C$_{18}$H$_{20}$N$_2$NaO$_2$: 319.1417; Found: 319.1418.

$R_f$ (PE/EtOAc 3:7) = 0.30.
8.6 Experimental Procedures of Chapter 6

methyl (E)-3-(3-oxocyclopent-1-en-1-yl)acrylate 384

Following a reported procedure\(^\text{173}\) to a solution of 3-iodopentenone \(^\text{172}\) (1.0 g, 4.8 mmol, 1.0 equiv) in DMF (20 mL) was added methyl acrylate (1.1 mL, 12 mmol, 2.5 equiv), Pd(OAc)\(_2\) (54 mg, 0.24 mmol, 5.0 mol%), dppp (50 mg, 0.12 mmol, 2.5 mol%) and Et\(_3\)N (1.3 mL, 9.6 mmol, 2.0 equiv). The mixture was heated at 85 °C for 16 h. The reaction mixture was allowed to cool down to RT, and quenched with 0.5 M HCl. The mixture was extracted with EtOAc. The combined organic phases were washed with NaHCO\(_3\), brine, dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 1:1) afforded compound 384 as a white solid (0.22 g, 31% yield). The spectroscopic data of this compound were in accord with those reported in the literature.\(^\text{173}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.67 (d, \(J = 15.9\) Hz, 1H, C\(^6\)−H), 6.37-6.30 (m, 2H, C\(^2,7\)−H), 3.82 (s, 3H, C\(^9\)−H), 2.81-2.76 (m, 2H, C\(^5\)−H), 2.56-2.50 (m, 2H, C\(^4\)−H).

\(^13\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 208.8 (C\(^1\)), 168.3 (C\(^8\)), 166.2 (C\(^3\)), 138.6 (C\(^2\)), 136.1 (C\(^6\)), 125.0 (C\(^7\)), 52.3 (C\(^9\)), 35.1 (C\(^5\)), 27.0 (C\(^4\)).

\(R_f\) (PE/EtOAc 1:1) = 0.44

dimethyl meso tartrate 386

Following a reported procedure\(^\text{230}\) to a solution of NaClO\(_3\) (1.2 g, 11 mmol, 1.3 equiv) and OsO\(_4\) (90 mg, 0.21 mmol, 2.5 mol%) in H\(_2\)O (14 mL) was added dropwise dimethyl maleate

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(1.1 mL, 8.6 mmol). The reaction mixture was stirred at 50 °C overnight. The reaction mixture was then allowed to cool down. Saturated aqueous Na$_2$S$_2$O$_3$ was added, followed by magnesium silicate (1 g). The slurry mixture was filtered. The filtrate was brought to pH 2, and the solution was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification by recrystallisation (Et$_2$O/PE) afforded pure compound 386 as a white solid (1.2 g, 77% yield). The spectroscopic data of this compound were in accord with those reported in the literature.$^{231}$

$\text{mp} = 113.5$-$114.8 \degree \text{C (Et}_2\text{O/PE)}$

$^1\text{H NMR (}400\text{ MHz, CDCl}_3\text{): } \delta 4.58 \text{ (s, 2H, C}^3\text{H}), 3.82 \text{ (s, 6H, C}^1\text{H}), 3.12 \text{ (br s, 2H, O}^3\text{H)},$

$^{13}\text{C NMR (}101\text{ MHz, CDCl}_3\text{): } \delta 171.53 \text{ (C}^2\text{), 73.1 \text{ (C}^3\text{), 53.1 \text{ (C}^1\text{)}}.$

$R_f \text{ (EtOAc) } = 0.17$

**dimethyl dioxolane meso tartrate 387**

To a solution of dimethyl tartrate 386 (1.0 g, 5.6 mmol) in toluene (20 mL) was added 2,2-dimethoxypropane (1.0 mL, 8.4 mmol, 1.5 equiv) and $p$-TsOH (96 mg, 0.56 mmol, 0.10 equiv). The reaction mixture was then heated to reflux with a Dean-Stark apparatus for 16 h. The reaction mixture was then allowed to cool down, and saturated aqueous NaHCO$_3$ was added. The mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude compound 387 thus obtained (1.2 g, quantitative yield) was used for the next step without further purification. The spectroscopic data of this compound were in accord with those reported in the literature.$^{232}$

$^1\text{H NMR (}400\text{ MHz, CDCl}_3\text{): } \delta 4.82 \text{ (s, 2H, C}^3\text{H}), 3.72 \text{ (s, 6H, C}^1\text{H}), 1.62 \text{ (s, 3H, C}^5\text{or6H), 1.39 \text{ (s, 3H, C}^5\text{or6H)}}.$

$^{13}\text{C NMR (}101\text{ MHz, CDCl}_3\text{): } \delta 168.7 \text{ (C}^2\text{), 113.1 \text{ (C}^3\text{), 76.4 \text{ (C}^3\text{), 52.6 \text{ (C}^1\text{), 26.7 \text{ (C}^5\text{or6), 25.8 \text{ (C}^5\text{or6)}.$

$R_f \text{ (EtOAc) } = 0.83$


210
tert-butyl 2-(2-nitrophenyl)acetate 400

\[
\begin{align*}
\text{NO}_2 & \quad \text{CO}_2\text{H} \\
\text{DCC, DMAP} & \quad \text{t-BuOH} \\
\text{DCM, RT,} & \quad 73\% \\
\end{align*}
\]

To a solution of 2-(2-nitrophenyl)acetic acid (1.0 g, 5.5 mmol) in DCM (20 mL) was added DCC (1.7 g, 8.3 mmol, 1.5 equiv), DMAP (0.30 g, 0.25 mmol, 0.50 equiv) and dry t-BuOH (1.2 g, 17 mmol, 3.0 equiv). The reaction mixture was stirred overnight. DCM was added and the organic phase was washed with saturated aqueous NH\textsubscript{4}Cl, NaHCO\textsubscript{3}, brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 3:1) afforded pure ester 400 as a yellow oil (0.95 g, 73% yield). The spectroscopic data of this compound were in accord with those reported in the literature.\textsuperscript{233}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}):
\[\delta 8.09 \text{ (dd, } J = 7.5, 1.3 \text{ Hz, } 1\text{H, } C^5 - \text{H}), 7.58 \text{ (td, } J = 7.5, 1.3 \text{ Hz, } 1\text{H, } C^3 - \text{H}), 7.45 \text{ (td, } J = 7.5, 1.3 \text{ Hz, } 1\text{H, } C^4 - \text{H}), 7.34 \text{ (dd, } J = 7.5, 1.3 \text{ Hz, } 1\text{H, } C^2 - \text{H}), 3.94 \text{ (s, } 2\text{H, } C^7 - \text{H}), 1.44 \text{ (s, } 9\text{H, } C^{10} - \text{H}).\]

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}):
\[\delta 169.3 \text{ (C}^8\text{), 149.0 \text{ (C}^6\text{), 133.5 \text{ (C}^1\text{), 133.4 \text{ (C}^3\text{), 130.5 \text{ (C}^2\text{), 128.5 \text{ (C}^4\text{), 125.3 \text{ (C}^5\text{), 81.9 \text{ (C}^9\text{), 41.1 \text{ (C}^7\text{), 28.1 \text{ (C}^{10}\text{).}}\]

\[R_f \text{ (PE/EtOAc 1:1) = 0.77}\]

tert-butyl 2-bromo 2-(2-nitrophenyl)acetate 402

\[
\begin{align*}
\text{NO}_2 & \quad \text{O} \\
\text{NBS, (BnO)}_2 & \quad \text{CCl}_4 \\
\text{45\%} & \quad 402
\end{align*}
\]

Following a reported procedure,\textsuperscript{192} dibenzoyl peroxide (97 mg, 0.40 mmol, 0.10 equiv) was added to a solution of ester 400 (0.95 g, 4.0 mmol) and NBS (0.78 g, 4.4 mmol, 1.1 equiv) in CCl\textsubscript{4} (20 mL). The reaction mixture was heated to refluxing temperature for 72 h. The reaction mixture was filtered on a plug of Celite. Additional NBS (0.78 g, 4.4 mmol, 1.1 equiv) and dibenzoyl peroxide (97 mg, 0.40 mmol, 0.10 equiv) were added, and the mixture was stirred for an additional 48 h. The mixture was filtered again, and poured into water. The mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over

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Na₂SO₄, and concentrated in vacuo. Purification by FCC (PE/EtOAc 95:5) afforded pure ester 402 as a yellow oil (0.57 g, 45% yield). The spectroscopic data of this compound were in accord with those reported in the literature.¹⁹²

¹H NMR (400 MHz, CDCl₃): δ 8.03-7.98 (m, 2H, C²,⁵−H), 7.69 (td, J = 7.7, 1.7 Hz, 1H, C⁴−H), 7.52 (td, J = 7.7, 1.7 Hz, 1H, C³−H), 5.96 (s, 1H, C⁷−H), 1.48 (s, 9H, C¹⁰−H).

¹³C NMR (101 MHz, CDCl₃): δ 166.7 (C⁸), 147.9 (C¹), 133.8 (C⁴), 133.3 (C⁵), 131.7 (C⁶), 129.7 (C³), 124.9 (C²), 83.9 (C⁹), 44.5 (C⁷), 27.8 (C¹⁰).

Rf (PE/EtOAc 9:1) = 0.48

2,3-O-Isopropylidene-D-Erythrolactone 392

Following a reported procedure,¹⁸⁶ to a solution of erythorbic acid (35 g, 0.20 mol) in H₂O (500 mL) at 0 °C was slowly added K₂CO₃ (42 g, 0.40 mol, 2.0 equiv). H₂O₂ (30 % in H₂O, 45 mL, 0.45 mol, 2.3 equiv) was then added dropwise over 10 min. The reaction mixture was stirred for 5 minutes before removing the ice bath and heating the mixture to 42 °C. The reaction mixture was stirred for 30 min, and then activated charcoal (8.0 g) was added. The mixture was stirred at 80 °C for 30 min. The hot mixture was filtered through a plug of Celite and acidified to pH 1 with 6 M HCl. Concentration in vacuo afforded a pale yellow solid (84 g). Acetone (180 mL) was added followed by MgSO₄ (50 g), 2,2-dimethoxypropane (350 mL, 2.8 mol, 14 equiv) and p-TsOH (0.42 g, 2.0 mmol, 1.0 mol%). The suspension was stirred at RT for 16 h. The reaction mixture was cooled down to 0 °C. Et₂O (500 mL) and triethylamine (62 mL, 0.44 mol, 2.2 equiv) were added, and the reaction mixture was filtered and concentrated in vacuo. Purification by FCC (PE/EtOAc 1:1) afforded pure compound 392 as a white solid (22 g, 70% yield). The spectroscopic data of this compound were in accord with those reported in the literature.¹⁸⁶

mp = 66.0-66.5 °C (Et₂O/PE)

[α]D²³ = -113.5 (c = 1.11, H₂O)

¹H NMR (400 MHz, CDCl₃): δ 4.88 (m, 1H, C²−H), 4.74 (d, J = 5.2 Hz, 1H, C³−H), 4.48-4.38 (m, 2H, C¹−H), 1.48 (s, 3H, C⁶or⁷−H), 1.39 (s, 3H, C⁶or⁷−H).
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$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 174.3 (C$^4$), 114.1 (C$^5$), 75.6 (C$^2$), 74.7 (C$^3$), 70.3 (C$^1$), 26.9 (C$^{6,7}$), 25.8 (C$^{6,7}$).

$R_f$ (DCM) = 0.39

1,5-bis(dimethyltertbutylsilyl)glycerol 447

Following a reported procedure,$^{234}$ to a solution of glycerol (5.0 g, 54 mmol) in THF (100 mL) were added TBSCl (17 g, 0.11 mol, 2.1 equiv) and imidazole (8.0 g, 0.12 mol, 2.2 equiv). The reaction mixture was stirred overnight at RT. Saturated aqueous NH$_4$Cl was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification by FCC (PE/EtOAc 95:5) afforded pure compound 447 as a colorless oil (16 g, 93% yield). The spectroscopic data of this compound were in accord with those reported in the literature.$^{234}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.69-3.58 (m, 5H, C$_{1,2}$–H), 0.89 (s, 18H, C$_5$–H), 0.06 (s, 12H, C$_3$–H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 72.0 (C$^1$), 63.6 (C$^2$), 26.0 (C$^5$), 18.4 (C$^4$), -5.3 (C$^3$).

$R_f$ (PE/EtOAc 9:1) = 0.26

1,3-bis(dimethyltertbutylsilyloxy)-2-iodopropane 403

To a solution of protected alcohol 447 (8.0 g, 25 mmol), PPh$_3$ (9.2 g, 35 mmol, 1.4 equiv) and imidazole (2.7 g, 40 mmol, 1.6 equiv) in THF (400 mL) at 0 °C was added slowly iodine (7.6 g, 30 mmol, 1.2 equiv). The reaction mixture was stirred at RT for 3 h, and saturated aqueous Na$_2$S$_2$O$_3$ was added. The reaction mixture was diluted with H$_2$O, and extracted with EtOAc.

The organic phases were combined, washed with brine, dried over Na$_2$SO$_4$, and concentrated *in vacuo*. Purification by FCC (PE/EtOAc 95:5) afforded pure iodide 403 as a colorless oil (8.2 g, 76% yield).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.09 (quint, $J = 5.7$ Hz, 1H, C$_1^-$H), 3.85 (d, $J = 5.7$ Hz, 4H, C$_2^-H$), 0.90 (s, 18H, C$_5^-H$), 0.08 (s, 6H, C$_3^-H$), 0.07 (s, 6H, C$_3^-H$).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 64.7 (C$_2$), 36.7 (C$_1$), 26.0 (C$_5$), 18.5 (C$_4$), -5.1 (C$_3$), -5.2 (C$_3$).

IR: 2955 (w), 2929 (w), 2864 (w), 2857 (w), 1472 (w), 1253 (m), 1136 (w), 1074 (m), 833 (s), 775 (s).

HRMS: (ESI$^+$) m/z: [M + H]$^+$ Calcd for C$_{15}$H$_{36}$IO$_2$Si$_2$: 431.1293; Found: 431.1285.

$R_f$ (PE/EtOAc 9:1) = 0.74

cyclopent-1-en-1-yl trifluoromethanesulfonate 419

Following a reported procedure,$^{235}$ to a solution of cyclopentanone (2.0 mL, 23 mmol) in THF (35 mL) at -78 °C was added dropwise LiHMDS (0.8 M solution in THF, 28 mL, 23 mmol, 1.0 equiv). The reaction mixture was stirred for 30 min. A solution of phenyl triflimide (8.0 g, 23 mmol, 1.0 equiv) in THF (35 mL) was added and the reaction mixture was stirred for 30 min before being allowed to warm up to RT. The reaction mixture was then stirred at RT for 18 h. Saturated aqueous NH$_4$Cl was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na$_2$SO$_4$, and concentrated *in vacuo*. Purification by FCC (PE) afforded pure vinyl triflate 419 as a colorless oil (3.4 g, 70% yield). The spectroscopic data of this compound were in accord with those reported in the literature.$^{235}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.63 (m, 1H, C$_3^-H$), 2.64-2.52 (m, 2H, C$_6^-H$), 2.46-2.35 (m, 2H, C$_4^-H$), 2.09-1.97 (m, 2H, C$_5^-H$).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 149.7 (C$_2$), 118.7 (q, $J = 320.7$ Hz (C$_1$), 117.9 (C$_3$), 30.9 (C$_6$), 28.1 (C$_4$), 21.0 (C$_5$).

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$^{235}$Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett.* 2006, 8, 2143–2146
8.6. Experimental Procedures of Chapter 6

$R_f$ (PE) = 0.45

2,3-bis(tertbutyldimethyl)-1,4-dimethyl-D-tartrate 389

Following a reported procedure,\textsuperscript{178} to a solution of dimetyl D-tartrate (5.0 g, 28 mmol) in DMF (26 mL) were added TBSCI (13 g, 84 mmol, 3.0 equiv) and Imidazole (5.8 g, 84 mmol, 3.0 equiv). The reaction mixture was stirred overnight at 60 °C. Saturated aqueous NH$_4$Cl was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na$_2$SO$_4$, and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 95:5) afforded pure compound \textbf{389} as a colourless oil (11 g, 96% yield). The spectroscopic data of this compound were in accord with those reported in the literature.\textsuperscript{178}

$[\alpha]^{22}_D$ -48.99 (c = 2.03, CHCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.64 (s, 2H, C$_3^\cdot$H), 3.72 (s, 6H, C$_1^\cdot$H), 0.87 (s, 18H, C$_6^\cdot$H), 0.08 (s, 6H, C$_4^\cdot$H), -0.01 (s, 6H, C$_4'^\cdot$H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 171.4 (C$_2$), 74.9 (C$_3$), 52.0 (C$_1$), 25.7 (C$_6$), 18.4 (C$_5$), -4.6 (C$_4$), -5.2 (C$_4'^\cdot$H).

$R_f$ (PE/EtOAc 9:1) = 0.60

methyl (4S,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate 394

To a solution of lactone \textbf{392} (1.0 g, 6.3 mmol) in MeOH (60 mL) was added MeONa (5.4 M in MeOH, 1.2 mL, 6.3 mmol, 1.0 equiv). The reaction mixture was stirred at RT for 24 h. 4 M HCl was added until pH 7, and the solution was concentrated \textit{in vacuo}. Purification by FCC
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(PE/EtOAc 4:6) afforded pure compound 394 as a colorless oil (0.75 g, 63% yield). The spectroscopic data of this compound were in accord with those reported in the literature.\textsuperscript{236} The expected (4R,5R) diastereoisomer was not observed.\textsuperscript{237}

\begin{align*}
\text{H NMR (400 MHz, CDCl}_3\text{):} & \ \delta 4.48 (d, J = 7.8 Hz, 1H, C^4\text{–H}), 4.25 (dt, J = 7.8, 2.9 Hz, 1H, C^3\text{–H}), 3.96 (dd, J = 12.7, 2.9 Hz, 1H, C^2\text{–H}), 3.80 (s, 3H, C^6\text{–H}), 3.76 (dd, J = 12.7, 2.9 Hz, 1H, C^2\text{–H}), 1.90 (brs, 1H, O^1\text{–H}), 1.49 (s, 3H, C^8or9\text{–H}), 1.45 (s, 3H, C^8or9\text{–H}). \\
\text{C NMR (101 MHz, CDCl}_3\text{):} & \ \delta 171.4 (C^5), 111.5 (C^7), 79.2 (C^3), 75.0 (C^4), 61.9 (C^2), 52.7 (C^6), 26.9 (C^8or9), 25.8 (C^8or9).
\end{align*}

\(R_f\) (PE/EtOAc 2:8) = 0.60

4-(tert-butoxycarbonyl)quinoline 1-oxide 405 and 4-(tert-butoxycarbonyl)-2-(2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)quinoline 1-oxide 406

To a solution of ester 400 (50 mg, 0.21 mmol) and iodide 403 (0.10 g, 0.23 mmol, 1.1 equiv) in DMF (1.0 mL) was added Cs\textsubscript{2}CO\textsubscript{3} (0.21 g, 0.63 mmol, 3.0 equiv). The reaction mixture was stirred at 60 °C overnight. H\textsubscript{2}O was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 9:1) afforded pure compounds 405 as a colorless oil (18 mg, 35% yield) and pure compound 406 as a yellow oil (7.0 mg, 6% yield). The spectroscopic data of compound 405 were in accord with those reported in the literature.\textsuperscript{238}

**Compound 405**

\begin{align*}
\text{H NMR (400 MHz, CDCl}_3\text{):} & \ \delta 9.02 (d, J = 7.8 Hz, 1H, C^5\text{–H}), 8.75 (d, J = 7.8 Hz, 1H, C^8\text{–H}), 8.49 (d, J = 7.2 Hz, 1H, C^2\text{–H}), 7.89 (d, J = 7.2 Hz, 1H, C^1\text{–H}), 7.76 (t, J = 7.8 Hz, 1H, C^7\text{–H}),
\end{align*}


\textsuperscript{238}Pagar, V. V.; Jadhav, A. M.; Liu, R. S. \textit{J. Am. Chem. Soc.} 2011, 133, 20728–20731

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7.71 (t, J = 7.8 Hz, 1H, C₆−H), 1.65 (s, 9H, C₁₃−H).

**13C NMR (101 MHz, CDCl₃):** δ 164.1 (C¹¹), 142.2 (C⁴), 134.5 (C²), 130.4 (C⁷), 130.0 (C⁶), 128.5 (C¹⁰), 126.9 (C⁵), 125.4 (C⁸), 124.2 (C¹), 119.9 (C⁹), 83.0 (C¹²), 28.3 (C¹³).

**Rᶠ** (PE/EtOAc 9:1) = 0.10

**Compound 406**

**1H NMR (400 MHz, CDCl₃):** δ 8.98 (d, J = 7.8 Hz, 1H, C₆−H), 8.80 (d, J = 7.8 Hz, 1H, C₈−H), 7.97 (s, 1H, C¹−H), 7.75 (t, J = 7.8 Hz, 1H, C⁷−H), 7.68 (t, J = 7.8 Hz, 1H, C⁶−H), 4.16-4.06 (m, 5H, C₁₄,₁₅−H), 1.65 (s, 9H, C₁₃−H), 0.82 (s, 18H, C₁₈−H), 0.01 (s, 6H, C₁₆−H), -0.07 (s, 6H, C₁₆′−H).

**13C NMR (101 MHz, CDCl₃):** δ 164.7 (C¹¹), 147.1 (C²), 142.3 (C⁴), 130.1 (C⁶), 129.0 (C⁷), 127.0 (C¹⁰), 126.7 (C⁵), 125.4 (C⁸), 123.6 (C⁹), 120.0 (C¹), 82.7 (C¹²), 60.1 (C¹⁵), 44.6 (C¹⁴), 28.4 (C¹₃), 26.0 (C¹₈), 18.3 (C¹⁷), -5.4 (C¹₆).

**IR:** 2934 (w), 2857 (w), 1714 (w), 1251 (m), 1156 (s), 837 (s).

**HRMS:** (ESI⁺) m/z: [M + H]⁺ Calcd for C₂₉H₅₀NO₅Si₂⁺: 548.3222; Found: 548.3224.

**Rᶠ** (PE/EtOAc 9:1) = 0.41

**tert-butyl 2-(2-nitrophenyl)-2-oxoacetate 415**

Following a procedure developed in our laboratory, to a solution of ester 400 (1.0 g, 4.2 mmol) in DMF (80 mL) were added 1,2-diiodoethane (1.3 g, 4.6 mmol, 1.1 equiv) and Cs₂CO₃ (3.0 g, 11 mmol, 2.5 equiv). The reaction mixture was stirred at RT for 4 h. H₂O was added and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by FCC (PE/EtOAc 8:2) afforded pure compound 415 as a yellow wax (0.70 g, 66% yield).

**1H NMR (400 MHz, CDCl₃):** δ 8.17 (d, J = 7.4 Hz, 1H, C²−H), 7.80 (td, J = 7.4, 1.4 Hz, 1H, C⁴−H), 7.71 (td, J = 7.4, 1.4 Hz, 1H, C³−H), 7.63 (dd, J = 7.4, 1.4 Hz, 1H, C⁵−H), 1.50 (s, 9H,
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C\textsuperscript{10}−H).

\textbf{13C NMR (101 MHz, CDCl\textsubscript{3})}: δ 185.0 (C\textsuperscript{7}), 158.6 (C\textsuperscript{8}), 147.9 (C\textsuperscript{1}), 134.8 (C\textsuperscript{3}), 133.5 (C\textsuperscript{6}), 132.3 (C\textsuperscript{4}), 130.4 (C\textsuperscript{5}), 123.9 (C\textsuperscript{2}), 85.3 (C\textsuperscript{9}), 27.7 (C\textsuperscript{10}).

\textbf{IR}: 2983 (w), 2933 (w), 1755 (m), 1717 (s), 1526 (s), 1372 (m), 1346 (s), 1254 (m), 1210 (s), 1153 (s), 984 (m), 845 (m), 830 (m), 789 (m), 740 (s), 705 (s).

\textbf{HRMS}: (ESI\textsuperscript{+}) m/z: [M + Na]\textsuperscript{+} Calcd for C\textsubscript{12}H\textsubscript{13}NNaO\textsubscript{5}: 274.0686; Found: 274.0688.

\textbf{Rf} (PE/EtOAc 8:2) = 0.43

\textbf{2,2-dimethyl-5-(2-nitrobenzylidene)-1,3-dioxane-4,6-dione 418}

To a solution of 2-nitrobenzaldehyde (6.0 g, 40 mmol) and Meldrum's acid (5.8 g, 40 mmol, 1.0 equiv) in toluene (100 mL) was added L-tyrosine (1.5 g, 8.0 mmol, 0.20 equiv). The reaction mixture was heated to reflux with a Dean-Stark apparatus for 16 h. H\textsubscript{2}O was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 8:2) afforded pure compound \textbf{418} as a yellow solid (7.5 g, 68% yield). The spectroscopic data of this compound were in accord with those reported in the literature.\textsuperscript{239}

\textbf{mp} = 117.0-118.5 °C (EtOH).

\textbf{1H NMR (400 MHz, CDCl\textsubscript{3})}: δ 8.78 (s, 1H, C\textsuperscript{7}−H), 8.29 (d, J = 8.4 Hz, 1H, C\textsuperscript{2}−H), 7.74 (t, J = 8.4 Hz, 1H, C\textsuperscript{4}−H), 7.64 (t, J = 8.4 Hz, 1H, C\textsuperscript{3}−H), 7.49 (d, J = 8.4 Hz, 1H, C\textsuperscript{5}−H), 1.82 (s, 6H, C\textsuperscript{11,12}−H).

\textbf{13C NMR (101 MHz, CDCl\textsubscript{3})}: δ 161.7 (C\textsuperscript{9or13}), 159.1 (C\textsuperscript{9or13}), 155.9 (C\textsuperscript{7}), 146.4 (C\textsuperscript{1}), 133.9 (C\textsuperscript{4}), 131.0 (C\textsuperscript{3}), 130.4 (C\textsuperscript{5}), 130.0 (C\textsuperscript{6}), 125.0 (C\textsuperscript{2}), 117.9 (C\textsuperscript{8}), 105.6 (C\textsuperscript{10}), 27.9 (C\textsuperscript{11}), 27.9 (C\textsuperscript{12}).

\textbf{IR}: 2999 (w), 2365 (w), 2338 (w), 1766 (w), 1733 (s), 1522 (s), 1344 (s), 1283 (s), 1198 (s), 1033 (w), 933 (m), 799 (w), 727 (m).


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Following a reported procedure,\textsuperscript{200} to a solution of 2-nitrobenzaldehyde (4.0 g, 27 mmol) in dimethyl malonate (3.0 mL, 27 mmol, 1.0 equiv) was added catalyst \textsuperscript{416}\textsuperscript{240} (2.7 g, 14 mmol, 0.50 equiv). The reaction mixture was stirred at RT for 16 h. H\textsubscript{2}O was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 7:3) afforded pure compound \textsuperscript{417} as a yellow solid (6.0 g, 85% yield). The spectroscopic data of this compound were in accord with those reported in the literature.\textsuperscript{200}

\textbf{mp} = 67.0-68.2 °C (Toluene / PE).

\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}):} δ 8.23-8.18 (m, 2H, C\textsubscript{2,7}−H), 7.65 (t, J = 7.1 Hz, 1H, C\textsubscript{4}−H), 7.57 (t, J = 7.1 Hz, 1H, C\textsubscript{3}−H), 7.40 (d, J = 7.1 Hz, 1H, C\textsubscript{5}−H), 3.87 (s, 3H, C\textsubscript{10or12}−H), 3.60 (s, 3H, C\textsubscript{10or12}−H).

\textbf{\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}):} δ 165.4 (C\textsubscript{9or11}), 163.8 (C\textsubscript{9or11}), 147.1 (C\textsubscript{1}), 141.9 (C\textsubscript{7}), 134.0 (C\textsubscript{4}), 130.4 (C\textsubscript{3}), 130.4 (C\textsubscript{6}), 128.5 (C\textsubscript{8}), 125.2 (C\textsubscript{2}), 53.0 (C\textsubscript{10or12}), 52.6 (C\textsubscript{10or12}).

\textbf{IR:} 3122 (w), 3005 (w), 2954 (w), 2851 (w), 1718 (s), 1520 (s), 1437 (m), 1341 (s), 1266 (s), 1223 (s), 1070 (s), 977 (m), 939 (m), 843 (m), 793 (m), 744 (s), 697 (m).

\textbf{HRMS:} (ESI\textsuperscript{+}) m/z: [M + Na]\textsuperscript{+} Calcd for C\textsubscript{13}H\textsubscript{11}NNaO\textsubscript{6}: 300.0479; Found: 300.0475.

\textbf{R\textsubscript{f} (PE/EtOAc 7:3)} = 0.50

\textbf{dimethyl 2-(2-nitrobenzylidene)malonate 417}

\textsuperscript{240}Catalyst \textsuperscript{416} was prepared by adding dry ice into a solution of piperidine (5.0 mL) in Et\textsubscript{2}O (10 mL). The catalyst precipitated and was filtered off, washed with Et\textsubscript{2}O and dried.
To a solution of 4-heptanone (60 mL, 0.43 mol) in MeOH (400 mL) was added trimethyl ortho-
formate (56 mL, 0.52 mol, 1.2 equiv) and p-TsOH (0.80 g, 4.0 mmol, 1.0 mol%). A distillation
head was connected to the flask, and the mixture was stirred at 70 °C for 2 h, distilling the
methyl formate formed. The reaction mixture was then heated to 100 °C, to distill the MeOH
and the unreacted trimethyl orthoformate. The crude 4,4-dimethoxyheptane thus obtained
was used in the reaction without further purification.

To a solution of erythorbic acid (35 g, 0.20 mol) in H₂O (500 mL) at 0 °C was slowly added
K₂CO₃ (42 g, 0.40 mol, 2.0 equiv). H₂O₂ (30 % in H₂O, 45 mL, 0.45 mol, 2.3 equiv) was then
added dropwise over 10 min. The reaction mixture was stirred for 5 minutes at 0 °C and then
30 min at 42 °C. Activated charcoal (8.0 g) was then added. The mixture was stirred at 80 °C
for 30 min. The hot mixture was filtered through a plug of Celite and acidified to pH 1 with
6M HCl. Concentration in vacuo afforded a pale yellow solid (84 g). AcOEt (180 mL) was
added followed by MgSO₄ (50 g), the freshly prepared 4,4-dimethoxyheptane and p-TsOH
(0.42 g, 2.0 mmol, 1.0 mol%). The suspension was stirred at RT for 16 h. The reaction mixture
was cooled down to 0 °C. Et₂O (500 mL) and triethylamine (62 mL, 0.44 mol, 2.2 equiv) were
added, and the reaction mixture was filtered and concentrated in vacuo. Purification by FCC
(PE/EtOAc 7:3) afforded pure compound 397 as a colourless oil (27 g, 62% yield).

[α]₂₂^D -113.9 (c = 0.49, CHCl₃)

¹H NMR (400 MHz, CDCl₃): δ 4.87 (m, 1H, C³−H), 4.74 (m, 1H, C⁴−H), 4.49-4.35 (m, 2H,
C²−H), 1.68-1.55 (m, 4H, C⁷,₁₀−H), 1.43-1.30 (m, 4H, C⁸,₁₁−H), 0.97-0.84 (m, 6H, C⁹,₁₂−H).

¹³C NMR (101 MHz, CDCl₃): δ 174.0 (C⁵), 117.8 (C⁶), 75.8 (C³), 75.0 (C⁴), 70.5 (C²), 39.7
(C⁷or₁₀), 39.3 (C⁷or₁₀), 17.4 (C⁸or₁₁), 16.6 (C⁸or₁₁), 14.4 (C⁹or₁₂), 14.2 (C⁹or₁₂).

IR: 2961 (m), 2875 (w), 1783 (s), 1466 (w), 1379 (w), 1180 (m), 1111 (w), 1063 (m), 989 (w), 946
(w).


Rf (DCM) = 0.38
To a solution of lactone \(397\) (0.86 g, 4.0 mmol) in MeOH (40 mL) was added MeONa (5.4 M in MeOH, 0.74 mL, 4.0 mmol, 1.0 equiv). The reaction mixture was stirred at RT for 24 h. Saturated aqueous \(\text{NH}_4\text{Cl}\) was added, and the mixture was extracted with EtOAc. The organic phases were combined, washed with brine, dried over \(\text{Na}_2\text{SO}_4\), and concentrated \textit{in vacuo}. Purification by FCC (PE/EtOAc 7:3) afforded pure compound \(398\) as a colorless oil (0.45 g, 46% yield, 90% BRSM).

\[\alpha\] \(_{22}^D\) -6.7 (c = 0.39, CHCl\(_3\))

\(\text{\(^1H\) NMR (400 MHz, CDCl}_3\)}: \(\delta\) 4.44 (d, \(J = 8.4\) Hz, 1H, \(C^{1-}\text{H}\)), 4.19 (dt, \(J = 8.4, 3.3\) Hz, 1H, \(C^{3-}\text{H}\)), 3.97 (dd, \(J = 12.1, 3.3\) Hz, 1H, \(C^{2-}\text{H}\)), 3.80 (s, 3H, \(C^{6-}\text{H}\)), 3.77 (m, 1H, \(C^{2-}\text{H}\)), 1.90 (br s, 1H, \(C^{1-}\text{H}\)), 1.70-1.62 (m, 4H, \(C^{8,11-}\text{H}\)), 1.47-1.36 (m, 4H, \(C^{9,12-}\text{H}\)), 0.92 (t, \(J = 7.4\) Hz, 6H, \(C^{10,13-}\text{H}\)).

\(\text{\(^{13}C\) NMR (101 MHz, CDCl}_3\)}: \(\delta\) 171.2 (C\(^5\)), 114.7 (C\(^7\)), 79.3 (C\(^3\)), 75.2 (C\(^4\)), 62.0 (C\(^2\)), 52.6 (C\(^6\)), 39.7 (C\(^{8,11}\)), 39.7 (C\(^{8,11}\)), 17.4 (C\(^9\)), 16.8 (C\(^{12}\)), 14.5 (C\(^{10}\)), 14.4 (C\(^{13}\)).

\(\text{IR}\): 3482 (w), 2960 (m), 2935 (w), 2875 (w), 1758 (m), 1741 (m), 1457 (w), 1438 (w), 1379 (w), 1294 (m), 1197 (m), 1169 (m), 1109 (s), 1050 (m), 957 (m), 907 (m), 840 (m).

\(\text{HRMS: (ESI\(^+\) m/z: [M + Na]\(^+\) Calcd for C}_{12}H_{22}NaO_{5\^+}: 269.1359; Found: 269.1358.}\)

\(R_f\) (PE/EtOAc 6:4) = 0.50
Notes and Bibliography


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[226] The chiral ligand used for enantioselective 1,4 additions on cyclopentenone was kindly provided by Professor Alexakis (Geneva University).


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[240] Catalyst 416 was prepared by adding dry ice into a solution of piperidine (5.0 mL) in Et₂O (10 mL). The catalyst precipitated and was filtered off, washed with Et₂O and dried.
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EDUCATION

PhD Candidate in Organic synthesis 2011! 2015
Swiss Federal Institute of Technology in Lausanne (EPFL), Switzerland
Laboratory of Synthesis and Natural Products (LSPN)
PhD Advisor: Prof. Jieping ZHU

M.S. in Molecular and Biological Chemistry 2009! 2011
Swiss Federal Institute of Technology in Lausanne (EPFL), Switzerland
Grade average: 5.63/6 (Ranking: 2nd over 33 students)
Thesis topic: Exploiting new organometallic chemistry and reactivity for N-Heterocycles (achieved 6/6)
Thesis Advisor: Professor Timothy C. Gallagher (University of Bristol)

B.S. in Chemistry 2005! 2009
Swiss Federal Institute of Technology in Lausanne (EPFL), Switzerland
Grade average: 5.53/6

PUBLICATIONS


AWARDS

Runner up for the Best Oral Presentation (Organic Chemistry Session) at the Fall Meeting of the Swiss Chemical Society 2014

SYMPOSIUMS AND SUMMER SCHOOLS

Fall Meeting of the Swiss Chemical Society 2014, Lausanne, Switzerland Oral Presentation (Runner up Price) 09.2014
Belgian Organic Synthesis Symposium 2014, Louvain-La-Neuve, Belgium Poster Presentation 06.2014
Fall Meeting of the Swiss Chemical Society 2013, Lausanne, Switzerland Poster Presentation 09.2013
Swiss Summer School 2013 - Synthesis & Catalysis, Villars, Switzerland -Poster Presentation 08.2013
Fall Meeting of the Swiss Chemical Society 2011, Lausanne, Switzerland 09.2011
CUSO Summer School 2011 - Challenges in Organic Chemistry, Villars, Switzerland 08-09.2011

TEACHING, EMPLOYMENT & INTERNSHIP

Swiss Federal Institute of Technology in Lausanne (EPFL), Switzerland 2011-2014
Teaching duties
659 hours of teaching done during my PhD, Including:
- Supervision for Master Thesis
- Class exercises preparation and following corrections for students from bachelor to master level.
- Practical course for 1st and 2nd year Bachelor as well as 1st year Master.
- Preparation, supervision and correction of the exams for bachelor classes.
Internship in the Laboratory of Biomolecular Magnetic Resonance  
- Studies of molecules in Long-lived coherence state  
- Helped in the development of the NMR sequence  
- Development of Matlab program to analyze the results  
Skills: analysis skills, Problem-solving skills, Informatics skills

Software Tester  
- Debugging new fire-detection software

LANGUAGES

French  
Mother language

English  
Fluent (C1)

Chinese  
Beginner (A2)

German  
Basics

Italian  
Basics

OTHER SKILLS

IT  
Good experience in LATEX and Microsoft office. Basic skills in Matlab and Mathematica, C, C++ and Visual Basic

Technical  
I was responsible of HPLC and GC/MS during my PhD for four years, including maintenance and simple reparation. I’m familiar with Gloveboxes, SFC, UPLC/MS and NMR.

INTERESTS

Game of Go  
Good level (3 kyu); Ex-president of the Yverdon-les-Bains Go-club; Financial responsible of the EPFL Go-club.

Violin  
5 years of daily practicing.

Sport  
I practice hiking, swimming and occasionally jogging.