



**HAL**  
open science

# Total synthesis of biologically relevant natural products in the diketopiperazine and oxepine series: oxidative functionalizations and oxa-Cope rearrangement studies

Wei Zhang

► **To cite this version:**

Wei Zhang. Total synthesis of biologically relevant natural products in the diketopiperazine and oxepine series: oxidative functionalizations and oxa-Cope rearrangement studies. Organic chemistry. Sorbonne Université, 2018. English. NNT: 2018SORUS433 . tel-02957219

**HAL Id: tel-02957219**

**<https://theses.hal.science/tel-02957219>**

Submitted on 5 Oct 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Sorbonne Université

Ecole doctorale 406, Chimie Moléculaire

*Molécules de Communication et Adaptation des Micro-organismes (UMR 7245, CNRS-MNHN)*

## **TOTAL SYNTHESIS OF BIOLOGICALLY RELEVANT NATURAL PRODUCTS IN THE DIKETOPIPERAZINE AND OXEPINE SERIES**

*Oxidative functionalizations and oxa-Cope rearrangement studies*

Par **Wei ZHANG**

Thèse de doctorat de Chimie organique

Dirigée par **Bastien NAY et Didier BUISSON**

Présentée et soutenue publiquement le 3 OCTOBRE 2018

**Devant un jury composé de :**

Dr. GRIMAUD Laurence	Directrice de Recherche	Examinatrice
Dr. EVANNO Laurent	Maître de conférences	Rapporteur
Dr. DE PAOLIS Michaël	Chargé de Recherche	Rapporteur
Dr. ROUSSI Fanny	Directrice de Recherche	Examinatrice
Dr. NAY Bastien	Directeur de Recherche	Examineur
Dr. BUISSON Didier	Directeur de Recherche	Examineur







# ACKNOWLEDGEMENTS

First and foremost, I would like to express my deepest gratitude to my research supervisors Dr. **Bastien Nay** and Dr. **Didier Buisson**, for giving me this great opportunity to work with them. Thank you for your patient guidance, enthusiastic encouragement and useful advises already from my master internship. Thanks, Bastien, your broad knowledge and experience in organic chemistry brought me a lot and helped me understand the chemical research field. Thank Didier, for sharing your great knowledge in biotransformation and every interesting skill in lab with me. Your scientific rigor and passion taught me how to be a real chemist. The discussions with all of you has motivated me to keep moving forward in my project and as well in my future.

I want to express my very special thanks to Dr. **Gilles Frison**. Thank you for investing time for guiding me to finish all the calculation work. I enjoyed immensely the project I've worked on, even only several months. With your help, I have learned more than I could have imagined during my thesis project. Many thanks go equally to Dr. **Emmanuel Baudouin** for carrying out all biological testes for radulanins. Your amazing work brought more value to my project.

I would like to thank all the members of the jury committee, Dr. **Laurent Evanno**, Dr. **Michaël De Paolis**, Dr. **Laurance Grimaud** and Dr. **Fanny Roussi** for sparing your time to evaluate my Ph.D. research work and come to my defense.

Secondly, I would like also to thank all the group members from MCAM and LSO for their warm welcome and generous help during my stay.

Dr. **Sébastien Prevost** and Dr. **Alexis Archambeau**, thanks for giving thought-provoking chemical and technical suggestions every time when I need help, as well as for your patience to help me solve all problems. Your contributions to the lab of Muséum and LSO make the lab life much easier. I would like also to acknowledge Pr. **Bernard Bodo**, Dr. **Stéphane Mann**, Pr. **Soizic Prado**, Dr. **Caroline Kuntz** for rich conversations and useful advices during the seminars or coffee time.

Dr. **Benjamin Laroche** and Dr. **Mehdi Zaghouni**, thanks for all your chemical help from my very beginning work in the lab. Your guys have set up outstanding examples for me. Even for today, I'm still learn from you and regard you as models (Some of your advices, I began to understand in the end of my thesis, such a pity).

Dr. **Marine Vallet**, Dr. **Ambre Dezaire**, **Cécile Anne**, **Margot Barenstrauch**, **Anne Tourneroché**, **Laura Guedon** and **Andrea Diaz**, thank you for all your help in Myco and for every pleasant chat with you. I can still remember the birthday surprise you brought me in my first year of my Ph.D. It's always been much appreciated to go out with you girls. Lunch, drinking and of course our 10km running, such unforgettable moments. I promise that there will be for sure a big party organized in my home after my defense!

**Vincent Revil-Baudard** and **Oscar Gayraud**, thanks for helping me dealing with any small or big problems (NMR, computer...). I really enjoy having coffee time with you guys and appreciate all fruitful discussions about science and life. We should go back again to the best falafel with **Eloi Astier**!

**Gabriela Siemiaszko**, thank you for sharing your research experiences at lunch break and especially thanks for shifting your schedule to night-work mode at last period of our Ph.D., so that I could finish a lot of work even after **Pjotr Roest** left. My thanks also go to Dr. **Qi Huang** for taking time to read this manuscript and giving helpful and constructive criticism. PhD made all of us great friends. I really love to spend every joyful moment with you. We'll for sure play the card game together!

I would like to give a big hug for **Aimilia Meichanetzoglou**. Thank you for your constant companion from our M2 internships. I'll never forget your support whenever I feel joyful or upset. Best wishes for your Ph.D. journey (καλή τύχη). It should be as great as you!

I would like to thank cordially **Alain Blond**, **Alexandre Deville**, **Arul Marie**, **Lionel Dubost** and **Vincent Jactel**. Thank you for dealing with equipments and affording great NMR and HRMS analytic work.

Big thanks to **Séverine Amand**, **Christine Bailly**, **Brice Mollinelli**, **Zhilai Hong**, **Djéna Mokhtari**, **Cethaise Hyacinathe**, **Samir Zard**, **Yvan Six**, **Laurent El Kaïm**, **Béatrice Sire**, **Kieu Dung Ly**, **Xuan Chen**, **Julien Morain** and any other group members in MCAM and LSO that I haven't mentioned. You've all helped me in some way over these years, thank you for setting a great and funny work environment. I really enjoy working with you and will definitely miss all the moments that we spent together.

Last but not least, I would like to express especially my love and gratitude to my **Mum** and **Dad**, who worked so hard to help me get here, and who always let me do things my own way and in my own time. Thank you for your unconditional support, both financially and

emotionally for all my decision through these years abroad. Your love and encouragement keep me strong. I need also to give my grateful acknowledgment to **all my friends**, who have been always so encouraging and supportive during this journey, and so understanding of my hobbit-like social reclusiveness while I've been writing up this thesis. Thanks to you, I'm living a wonderful and colorful life.





# LIST OF ABBREVIATIONS

A:	adenylation domain
aa:	amino acids
Ac:	acetyl
Ac <sub>2</sub> O:	acetic anhydride
AIBN:	2,2'-azobis(2-methylpropionitrile)
Ar/ar:	aryl
Bn:	benzyl
Boc:	tert-butoxycarbonyl
BSTFA:	<i>N,O</i> -bis(trimethylsilyl)trifluoroacetamide
C:	condensation domain
CAN:	ceric ammonium nitrate
cat.:	catalytic quantity
CoA:	coenzyme-A
Cbz:	benzyloxycarbonyl
CDI:	1,1'-carbonyldiimidazole
CSA:	camphor sulfonic acid
CDPS:	cyclodipeptide synthase
COD:	1,5-cyclooctadiene
DKP:	diketopiperazine
DCM:	dichloromethane
DMAP:	4- <i>N,N</i> -dimethylaminopyridine
DMF:	dimethylformamide
DMSO:	dimethylsulfoxide
DIPEA:	<i>N,N</i> -diisopropylethylamine
d.r.:	diastereomeric ratio
DBU:	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE:	1,2-dichloroethane
DMDO:	dimethyldioxirane
DMBn:	dimethoxybenzoin
DDQ:	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT:	density functional theory
DEAD:	diethyl azodicarboxylate
DIAD:	diisopropyl azodicarboxylate
equiv.:	equivalent
E <sup>+</sup> :	electrophile
EWG:	electron withdrawing group
EDG:	electron donating group
Fmoc:	fluorenylmethyloxycarbonyl
HMDS:	hexamethyldisilazane
HTIB:	hydroxy(tosyloxy)iodobenzene (Koser's reagent)
IEFPCM:	integral equation formalism polarizable continuum model
IBX:	2-iodoxybenzoic acid
IC <sub>50</sub> :	half maximal inhibitory concentration
LA:	Lewis acid
L:	liter or neutral ligand

LDA:	lithium diisopropylamide
LAH:	lithium aluminium hydride
LSF:	late-stage functionalization
mCPBA:	m-chloroperoxybenzoic acid
Ms:	mesylate
MIC:	minimum inhibitory concentration
MoOPH:	oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide)
MPO:	4-methoxypyridine <i>N</i> -oxide
MS:	molecular seive
NRPS:	non-ribosomal peptide synthase
NBS:	<i>N</i> -Bromosuccinamide
NMO:	<i>N</i> -methylmorpholine- <i>N</i> -oxide
Nu:	nucleophile
NR:	no reaction
[O]:	oxidation
pH:	hydrogen ion concentration in aqueous solution
pKa:	acid dissociation constant
p-TSA:	p-toluenesulfonic acid
p-ABSA:	para-acetamidobenzenesulfonyl azide
PCC:	pyridinium chlorochromate
py:	pyridine
PG:	protecting group
PE:	petroleum ether
ph:	phenyl
piv:	pivalate
PCP (or T):	peptide carrier protein
PHBP:	pyridinium bromide perbromide
RCM:	ring-closing metathesis
Rf:	retention factor
rt:	room temperature (~25 °C)
sat.:	saturated
TBAF:	tetrabutyl ammonium fluoride
TBDPS:	tert-butyldiphenylsilyl
TBS:	tert-butyl silyl
TFA:	trifluoroacetic acid
Tf:	triflate (trifluoromethanesulfonyl)
TfO <sub>2</sub> :	triflic anhydride
TMS:	trimethylsilyl
THF:	tetrahydrofuran
TFDO:	methyl(trifluoromethyl)dioxirane
tRNA:	transfer RNA
TEMPO:	2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TBHP:	<i>tert</i> -Butyl hydroperoxide
Ts:	toluenesulfonyl (tosyl)
TBAI:	tetrabutylammonium iodide
TPP:	tetraphenylporphyrin

$^1\text{H}$ NMR:	proton nuclear magnetic resonance
$^{13}\text{C}$ NMR:	carbon nuclear magnetic resonance
HMBC:	heteronuclear multiple bond correlation
COSY:	correlation spectroscopy or homonuclear correlation
TLC:	thin layer chromatography
HPLC:	high pressure liquid chromatography
HRMS:	high resolution mass spectrometry
LC-MS:	liquid chromatography-mass spectrography
APCI:	atmospheric pressure chemical ionization
ESI:	electrospray ionization
ES:	electrospray
IR:	infrared spectrometer
Mp:	melting point
UV:	Ultraviolet
$^{\circ}\text{C}$ :	degree Celsius
Hz:	hertz
M:	mole per litre
ppm:	parts per million
h $\nu$ :	photochemical irradiation
$[\alpha]_{\text{D}}$ :	angle of optical rotation of plane-polarized light
Å:	angstrom(s)
kDa:	kilodalton
ua:	unified atomic mass unit
c:	concentration of sample for measurement of optical rotation
/C:	supported on activated carbon charcoal
Calcd.:	calculated
$\text{cm}^{-1}$ :	wavenumber(s)
e.g.:	for example (Latin: <i>exempli gratia</i> )
et al.:	and others (Latin: <i>et alii</i> )
g:	gram(s)
h:	hour(s)
J:	coupling constant
kcal:	kilocalorie(s)
mg:	milligram(s)
min:	minute(s)
mL:	milliliter(s)
mol:	mole(s)
m/z:	mass-to-charge ratio
w/v:	weight per volume
v/v:	volume per volume



# FOREWORD

Natural products are known for their enormous chemical diversity and biological functions, providing promising candidates for drug discovery. However, their low quantities isolated from the natural sources often restrict the development of natural product leads. Total synthesis, as an efficient alternative to prepare structurally complex natural products, has made undeniable contributions to the development of the pharma industry and also to research on new synthetic methodologies. Successful endeavors during the last century illuminated our understanding about obscure areas of chemical reactivities, which helped to achieve many natural product syntheses.

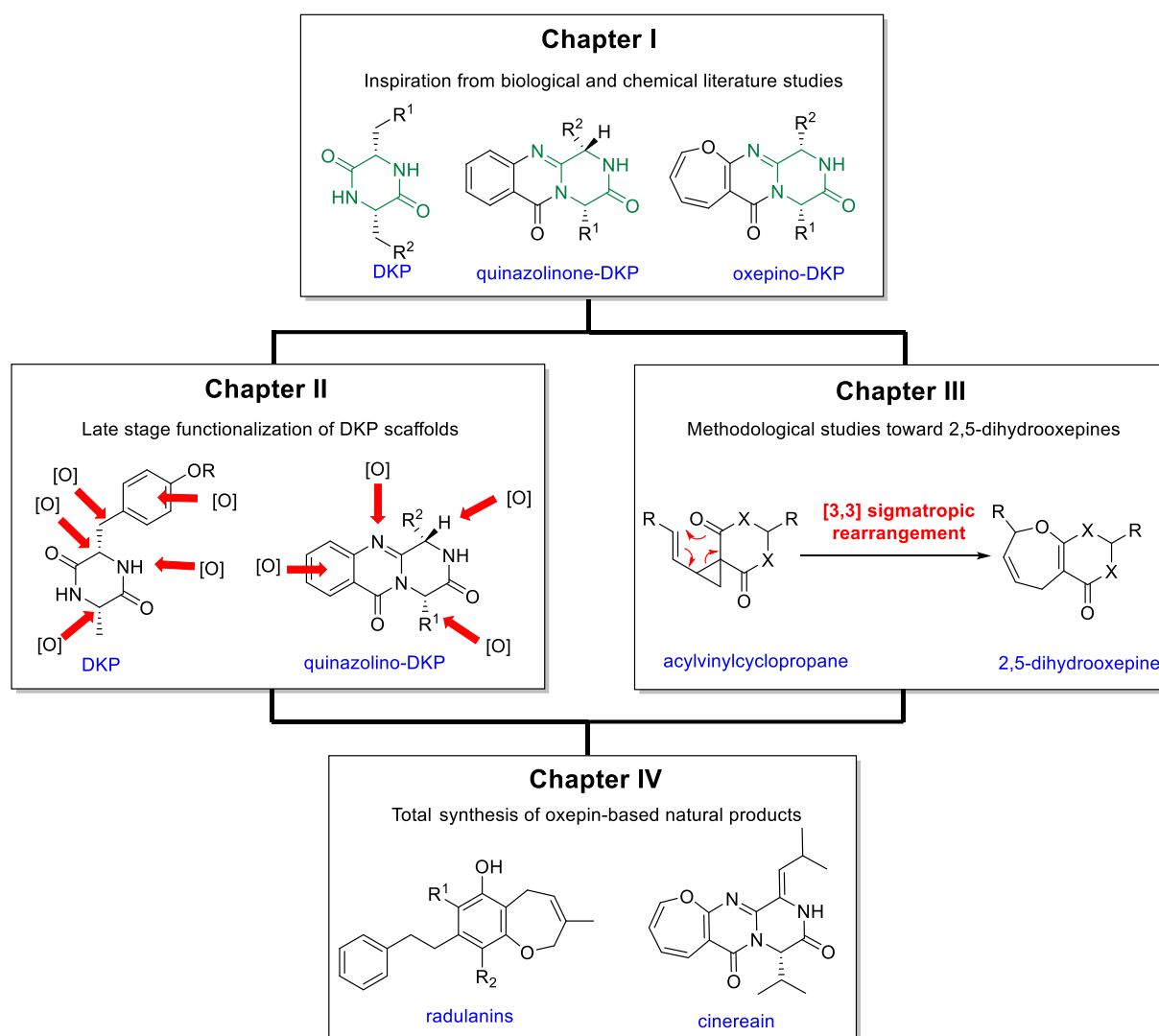
Nowadays, the total synthesis of complex natural products is moving toward efficiency, straightforwardness, scalability and simplicity. So were born collective synthetic approaches allowing multiple synthetic targets to be reached by the same strategy through a shared intermediate. Biomimetic synthesis is another efficient way to produce complex natural products, inspired by the direct and fast biosynthetic processes.

The core aim of this Ph.D. project was to develop biomimetic and collective synthetic routes to get a quick access to several families of natural products of interest and explore downstream their biological activities.

Diketopiperazines (DKP) are common cyclic dipeptide dimers (also called cyclodipeptides), dotted with a large structural diversity and a broad spectrum of pharmacological activities. However, their biosynthetic pathways are very simple and direct, which led us to think about whether we could design similar collective synthetic routes using late-stage oxidative functionalization. The following question thus arose from this reasoning: could we use a combination of chemical and biological functionalization strategies to perform biomimetic and collective total synthesis from highly functionalized intermediates like DKPs?

To answer this question, two biomimetic intermediates (DKPs and quinazolino-DKPs) and one more advanced biomimetic intermediate (oxepino-DKPs) were selected to be synthesized during this project. Their installations and functionalizations will be discussed in this manuscript, giving the first insights about the possibility of their collective total synthesis.

## General presentation of the research project



**Chapter I** will give a quick overview of challenges in synthetic strategies toward natural products, especially dealing with collective synthesis and biomimetic synthesis. Inspiration sources, from the biochemical origin of our natural product to related chemical and biochemical late-stage functionalization strategies, will be presented in the second part of the same chapter.

**Chapter II** will describe the installation of the DKP core, gliocladrin-type DKP and the quinazolino-DKP scaffolds, as well as our corresponding investigation on late-stage chemical oxidation reactions and microbial transformations.

Following repetitive failures of this first approach, especially to get the challenging oxepino-DKP scaffold, **Chapter III** will focus on the development of an alternative approach to

construct oxepine systems by oxa-Cope rearrangement, which stood as an inevitable journey toward the oxepino-DKP compounds.

**Chapter IV** will end up with the applications of our oxepine constructing methodology to the total synthesis of benzoxepine natural products and preliminary attempts on the total synthesis of cinereain and janoxepin, by taking advantages of the methods developed in the previous two chapters.





## Table of contents

<b>ACKNOWLEDGEMENTS</b> .....	i
<b>LIST OF ABBREVIATIONS</b> .....	v
<b>FOREWORD</b> .....	ix
<b>Chapter I. General Introduction</b> .....	1
1. New era of natural product total synthesis.....	3
1.1. From natural products to drug candidates .....	3
1.2. From target-oriented strategies to collective strategies in natural product synthesis ..	4
1.3. Biomimetic synthesis.....	7
1.4. Challenges and new perspectives for biomimetic collective natural product synthesis	10
2. Diversity and biosynthesis origins of 2,5-diketopiperazines (DKPs).....	10
2.1. Simple DKPs: structure and biosynthesis.....	10
2.2. Gliocladrone DKPs and their biosynthesis .....	13
2.3. Quinazolino-DKPs and their biosynthesis.....	15
2.4. Oxepino-DKP natural products and their biosynthesis.....	17
3. Late-stage functionalization strategies in organic and bio-organic chemistry.....	22
3.1. Late-stage C-C bond formation .....	24
3.2. Late-stage C-O bond formation.....	26
3.3. Biocatalytic functionalization.....	30
4. Objectives of the doctoral research.....	33
<b>Chapter II. Installation Biomimetic Gliocladrone and Quinazolino-DKP Scaffolds and their Functionalization</b> .....	35
1. Synthetic works on gliocladrone and quinazolino-DKP scaffolds .....	37
1.1. Gliocladrone DKPs.....	37
1.1.1. Short literature review on approaches to the DKP motif .....	37

1.1.2.	Short literature review on approaches to the total synthesis of gliocladrine-DKP alkaloids .....	39
1.1.3.	Synthesis of the gliocladrine DKP scaffold.....	40
1.2.	Synthesis of quinazolino-DKP intermediates .....	45
1.2.1.	Literature review on approaches to the 2,3-disubstituted quinazolinone motif and some examples of total syntheses of quinazolino-DKP alkaloids .....	45
1.2.2.	Biomimetic synthesis of the quinazolino-DKP scaffold .....	48
2.	Post-functionalization attempts of biomimetic DKP scaffolds .....	55
2.1.	Chemical oxidations .....	56
2.1.1.	Oxidation attempts of DKPs and gliocladrine-type DKP scaffolds .....	56
2.1.2.	Oxidation attempts of the quinazolino-DKP scaffold .....	59
2.2.	Biotransformation attempts .....	63
2.2.1.	A short state of the art on biotransformations .....	64
2.2.2.	Microbial oxidations for gliocladrine-type DKPs.....	66
2.2.3.	Microbial oxidation of quinazolino-DKP substrates.....	68
3.	Conclusion and perspectives.....	71
<b>Chapter III. From Tandem Cyclopropanation/ Oxa-Cope Rearrangement Studies to the Total Synthesis of Oxepin-Based Natural Products .....</b>		<b>74</b>
1.	Literature review.....	76
1.1.	Synthetic methods towards oxepins .....	76
1.2.	[3,3]-Sigmatropic rearrangements for the formation of carbocycles.....	78
1.2.1.	Definitions.....	78
1.2.2.	Cope rearrangements.....	79
1.2.3.	Rearrangements of vinylcyclopropanes and divinylcyclopropanes into cyclopentenes and cycloheptadienes .....	81
1.3.	Hetero-Cope-type rearrangements for the synthesis of heterocycles, especially 2,5-	

dihydro-1-heterocycloheptenes.....	84
1.3.1. Oxa-Cope rearrangements (= retro-Claisen rearrangements) .....	84
1.3.2. The Cloke-Wilson rearrangements to heterocyclopentenes.....	89
1.3.3. A few words on 1-aza-Cope rearrangements (aza-retro-Claisen rearrangements) .....	90
2. Experimental studies for the synthesis of 2,5-dihydrooxepines through one-pot tandem cyclopropanation/oxa-Cope rearrangement .....	91
2.1. Attempts of Knoevenagel condensation followed by cyclopropanation .....	92
2.2. Attempts of cyclopropanation followed by Wittig reaction .....	94
2.2.1. Cyclopropanation with $\alpha$ -bromodicarbonyl compounds .....	95
2.2.2. Cyclopropanation by using diazo-derived carbenoids .....	96
2.3. Tandem cyclopropanation/oxa-Cope rearrangement by using 1,4-dibromobut-2-ene substrate as a conjunctive reagent.....	98
2.3.1. First encouraging results .....	98
2.3.2. Optimization of reaction conditions by NMR studies .....	100
2.3.3. Reaction attempts with cyclic substrates .....	106
2.3.4. Reaction attempts with linear substrates.....	112
2.3.5. Comments on the associated Cloke-Wilson rearrangement during these experiments	113
2.4. Conclusions .....	115
3. DFT calculations on the transformations of acylvinylcyclopropanes to dihydroxepines and dihydroxyfurans.....	116
3.1. General background introduction .....	116
3.1.1. Computational chemistry and associated methods .....	116
3.1.2. Literature review on [1,3] and [3,3] rearrangement calculations for 2-vinylcyclopropyl aldehyde.....	119
3.2. Modelisation results of [1,3] and [3,3] rearrangements for cyclohexadione and acetylacetone vinylcyclopropane derivatives .....	121

3.2.1.	Calculations results for cyclohexadione derivative III-133c .....	122
3.2.2.	Calculation results for acetylacetone vinylcyclopropane II-164 .....	124
3.2.3.	Electronic and steric effects for acyclic substrate .....	126
3.3.	Conclusions .....	127
<b>Chapter IV. Total Synthesis of Benzoxepines and Oxepino-Diketopiperazines by using Oxa-Cope Rearrangements .....</b>		<b>130</b>
1.	Total synthesis of radulanin natural products .....	132
1.1.	Introduction: isolation and biological activities of radulanins .....	132
1.2.	Literature reviews on radulanin synthesis .....	133
1.3.	New synthetic strategy and results .....	135
1.4.	Bioactivity tests of radulanins .....	148
1.5.	Conclusion and perspectives .....	148
2.	Total synthesis of janoxepin and cinereain by using the oxa-Cope rearrangement .....	150
2.1.	Taylor's total synthesis of janoxepin .....	150
2.2.	Total synthesis of janoxepin and cinereain .....	151
2.3.	Conclusions and perspectives .....	158
<b>Chapter V. General Conclusion .....</b>		<b>160</b>
<b>Experimental Section .....</b>		<b>162</b>
1.	Chemical experimental procedures and spectroscopic data.....	165
2.	Microbial oxidations .....	278
3.	Computational methods and results .....	281
4.	X-Ray Crystallographic Data.....	285

# CHAPTER I.

## GENERAL INTRODUCTION

---

*“The great book, always open and which we should make an effort to read,  
is that of nature”*

*---Antoni Gaudi*

---



## Chapter I. General Introduction

### 1. New era of natural product total synthesis

#### 1.1. From natural products to drug candidates

Natural product chemistry focuses on the study of chemical compounds derived from plants, animals, microorganisms or marine-organisms, specifically those known to have biological activities for medicinal chemistry and drug discovery.<sup>1</sup> For example, in China, Traditional Chinese Medicine (TCM) has historically been well-known to make use of nature-based materials as medicines against various diseases.<sup>2</sup> Isolation and purification of active components from natural materials are often considered as a leading approaches to find new drug candidates. In 1971, artemisinin or qinghaosu **I-1** (Figure I-1), a sesquiterpene lactone bearing an endoperoxide, was isolated by Prof. Youyou Tu from the herb *Artemisia annua*, which has been used as a Chinese traditional medicine against fever and malaria dating from 168 B.C.<sup>3</sup> As most of other antimalarials contain an aza-heterocyclic ring (for example quinine **I-2** and febrifugine **I-3**), this discovery offered a promising direction toward a new class of antimalarials.<sup>4</sup>

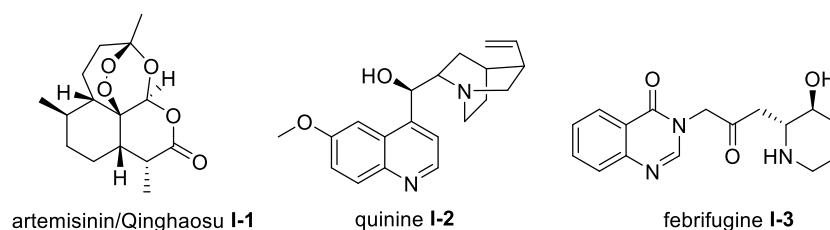


Figure I-1 Antimalarial natural products

Natural products contain a wide range of chemical structures, optimized by evolution for various interactions with macromolecular receptors, resulting in divergent biological activities. Even in current research, the exploration of natural products for medicinal purposes thrives. It has been estimated that about 50% of anticancer and 65% of antibacterial small

<sup>1</sup> a) S. J. Danishefsky, R. M. Wilson, *J. Org. Chem.* **2006**, *71*, 8329-8351; b) D. A. Dias, *Phytochem Rev.* **2015**, *14*, 299-315.

<sup>2</sup> Famous ancient books describe the use of traditional Chinese medicines like *Ben Cao Gang Mu* (1596) by Shizhen Li.

<sup>3</sup> Y. Tu, *Nature Medicine* **2011**, *17*, 1217-1220.

<sup>4</sup> a) D. L. Klayman, *Science* **1985**, *228*, 1049-1055.; b) J. Krungkrai, S. R. Krungkrai, *Asian Pac J Trop Biomed* **2016**, *6*, 371-375.



molecule drugs launched between the 1940s and 2014 are either based on, or inspired by natural products or semi-synthetic structures.<sup>5</sup> Antibiotics (*e.g.*, penicillin G, tetracycline, erythromycin A), antiparasitics (*e.g.*, avermectin), antimalarials (*e.g.*, quinine, artemisinin), lipid control agents (*e.g.*, lovastatin and analogs), immunosuppressants for organ transplants (*e.g.*, cyclosporine A, FK506, rapamycins) and anticancer drugs (*e.g.*, taxol, doxorubicin) have revolutionized medicine.

However, many compounds are only available in small quantities from natural sources, such as artemisinin.<sup>6</sup> The total synthesis of natural products provides a solution to supply adequate amounts of drug candidates for preclinical and clinical studies,<sup>7</sup> and enables the design of natural product analogs,<sup>8</sup> thus optimizing druglike properties (bioactivity, pharmacokinetics, solubility, etc.). Synthetic structural modifications, such as reducing unnecessary molecular complexities,<sup>9</sup> have also brought a breakthrough for in commercial scale up of drug synthesis.

## 1.2. From target-oriented strategies to collective strategies in natural product synthesis

In 1956, R.B. Woodward's famous Perspective was published.<sup>10</sup> As a pioneer in the natural product synthesis field, his vision about the way to construct complex structures in a beautifully organized campaign amazed all the fields of science. Soon after, Corey's retrosynthetic deconstruction theory<sup>11</sup> led to set up reasoned and logical strategies, and allowed achieving elegant syntheses of many complex natural products (*e.g.* vitamin B-12,<sup>12</sup> erythronolide,<sup>13</sup> ginkgolides<sup>14</sup>) in the following decades. As more and more synthetic Gordian knots have been remarkably overcome, the impressive synthesis of taxol<sup>15</sup>, palytoxin<sup>16</sup> and

---

<sup>5</sup> a) M. S. Butler, *Nat. Prod. Rep.* **2005**, *22*, 162–195; b) J. Newman, G. M. Cragg, *J. Nat. Prod.* **2012**, *75*, 311–335; c) J. C. Vederas, J. W. Li, *Science* **2009**, *325*, 161–165.

<sup>6</sup> E. A. Anderson, *Science* **2005**, *310*, 451–453.

<sup>7</sup> K. C. Nicolaou, S. A. Snyder, *PNAS* **2004**, *101*, 11929–11936.

<sup>8</sup> P. J. Hergenrothe, K. C. Morrison, *Nat. Prod. Rep.* **2014**, *31*, 6–14.

<sup>9</sup> a) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40–49; b) P. Burch, A. Chicca, J. Gertsch, K. Gademann, *ACS Med. Chem. Lett.* **2014**, *5*, 172–177.

<sup>10</sup> R. B. Woodward, In *Perspectives in Organic Chemistry*, Todd, A. R., Ed. Interscience Publishers: **1956**, p 155.

<sup>11</sup> E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, **1989**.

<sup>12</sup> R.B. Woodward, *Pure Appl. Chem.* **1973**, *33*, 145–178.

<sup>13</sup> a) D. A. Evan, A. S. Kim, R. Metternich, V. J. Novack, *J. Am. Chem. Soc.* **1998**, *120*, 5921–5942; b) E. M. Carreira, D. Muri, N. Lohse-Fraefel, *Angew. Chem. Int. Ed.* **2005**, *44*, 4036–4038.

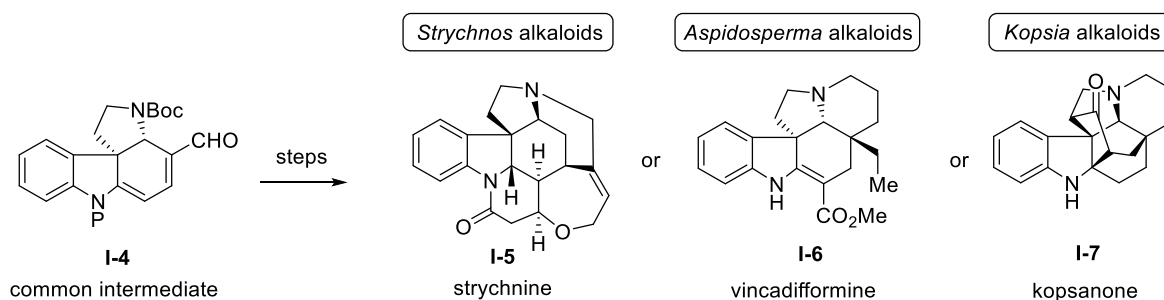
<sup>14</sup> a) E.J. Corey, M. C. Kang, M. C. Desai, A. K. Ghosh, I. N. Houpis, *J. Am. Chem. Soc.* **1988**, *110*, 649–651; b) M. T. Crimmins, J. M. Pace, P. G. Nantermet, A. S. Kim-Meade, J. B. Thomas, S. H. Watterson, A. S. Wagman, *J. Am. Chem. Soc.* **1999**, *121*, 10249–10250.

<sup>15</sup> K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P.G. Nantermet, R. K. Guy et al. *Nature* **1994**, *367*, 630–634.

maybe soon maitotoxin<sup>17</sup> became possible, bringing chemical synthesis to a new milestone.

With these achievements, the ‘next’ direction for natural product synthesis is no longer only to furnish the final target compounds (target-oriented synthesis (TOS)<sup>18</sup>), but also to design synthetic strategies in a tangible and meaningful manner.<sup>19</sup> Together with the conception of “economies”<sup>20</sup> of synthesis or “ideal synthesis”<sup>21</sup>, innovative strategies are needed to be developed. To this extent, alternative synthetic strategies have been propounded, including function-oriented synthesis (FOS),<sup>22</sup> biology-oriented synthesis (BiOS),<sup>23</sup> diversity-oriented synthesis (DOS),<sup>24</sup> and divergent total synthesis.

Among these new approaches, divergent or collective total synthesis, proposed by Boger in 1984,<sup>25</sup> is extremely attractive. The idea to construct a collection of complex compounds from a common intermediate has been meaningfully realized by MacMillan in 2011.<sup>26</sup> Six indolomonoterpene alkaloids were successfully synthesized in a collective manner from a common tetracyclic intermediate (Scheme I-1).



*Scheme I-1 MacMillan's divergent total syntheses of three families of indole alkaloids*

Compared with other approaches, this kind of total synthesis relies on efficient

<sup>16</sup> Y. Kishi, R. W. Armstrong, J. M. Beau, S. H. Cheon et al., *J. Am. Chem. Soc.* **1989**, *111*, 7530-7533.

<sup>17</sup> a) K. C. Nicolaou, K. P. Cole, M. O. Frederick, R. J. Aversa, R. M. Denton, *Angew. Chem. Int. Ed.* **2007**, *46*, 8875-8879; b) K.C. Nicolaou, P. Heretsch, T. Nakamura, A. Rudo, M. Murata, K. Konoki, *J. Am. Chem. Soc.* **2014**, *46*, 16444-16451; c) only protected fomed has been achieved.

<sup>18</sup> S. L. Schreiber, *Science* **2000**, *287*, 1964-1969.

<sup>19</sup> K. C. Nicolaou, *J. Org. Chem.* **2009**, *74*, 951-972.

<sup>20</sup> a) R. W. Hoffmann, N. Z. Burns, P. S. Baran, *Angew. Chem. Int. Ed.* **2009**, *48*, 2854 – 2867; b) P. S. Baran, T. Newhouse, R. W. Hoffman, *Chem. Soc. Rev.*, **2009**, *38*, 3010-3021.

<sup>21</sup> a) J. B. Hendrickson, *J. Am. Chem. Soc.* **1975**, 5784-5800; b) P. A. Wender, *Nat. Prod. Rep.* **2014**, *31*, 433-440; c) P. S. Baran, T. Gaich, *J. Org. Chem.* **2010**, *75*, 4657-4673.

<sup>22</sup> T. H. Pillow, P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40-49.

<sup>23</sup> H. Waldmann, S. Wetzler, R. S. Bon, K. Kumar, *Angew. Chem. Int. Ed.* **2011**, *50*, 10800- 10826.

<sup>24</sup> a) S. L. Schreiber, *Science* **2000**, *287*, 1964-1969; b) D. R. Spring, W. R. J. D. Galloway, A. Isidro-Lkobet, *Nat. Commun.* **2010**, *1*, 80.

<sup>25</sup> D. L. Boger, C. E. Brotherton, *J. Org. Chem.* **1984**, *49*, 4050-4055.

<sup>26</sup> D. W. C. MacMillan, S. B. Jones, B. Simmons, A. Mastracchio, *Nature* **2011**, *475*, 183-188.

transformations, which require a forward-synthetic design. Four different subclasses of strategies to establish the diversity have been resumed to understand how this efficiency works (Scheme I-2).<sup>27</sup>

**1) Redox-driven diversity.** Some natural products are accessible collectively by regioselective oxidations from a common structural core. The total synthesis of eudesmanes terpenes is an excellent example performed by Baran and co-workers. Four different natural products (compounds **I-9** to **I-12**) are generated rapidly by selective TFDO or Hofmann-Löffler-Freytag mediated oxidations from common core **I-8**.<sup>28</sup>

**2) Stereochemistry-driven diversity.** Natural product diversification can also be achieved by using highly stereospecific reactions on a common structural core. For example, Nagorny and co-workers synthesized two natural cardenolides, (+)-trewianin aglycone **I-14** and (+)-19-hydroxy-sarmentogenin **I-15** by using a tandem copper catalyzed asymmetric Michael addition/aldol cyclization sequence.<sup>29</sup>

**3) Reorganization-driven diversity.** The skeleton reorganization of a common precursor can directly lead to some families of natural products. For example, William and co-workers reorganized Heathcock's tricycle precursor **I-16** to fawcettimine-type lycopodium alkaloids (**I-17** to **I-19**).<sup>30</sup>

**4) Appendage-driven diversity.** The assemblage of different appendages on a common substructure could afford collectively related or different families of natural products. For example, Kerr and co-workers achieved the divergent synthesis of eustifolines (**I-21**, **I-23**) and glycomaurrol **I-22** by adding half, one, or two isoprene moieties.<sup>31</sup>

In order to collectively deliver complex products, two important factors must be considered: a suitable design of common intermediates and the correct use of powerful reagents and selective reactions which can override substrate bias.

Since advanced common intermediates improve synthetic efficiency but give less variability, the balance between simplicity and diversity can make this strategy design a real brainteaser.<sup>41</sup>

---

<sup>27</sup> a) J. Shimokawa, *Tetrahedron Letters* **2014**, *55*, 6156-6162; b) Y. Jia, L. Li, Z. Chen, X. Zhang, *Chem. Rev.* **2018**, *118*, 3752-3832.

<sup>28</sup> P. S. Baran, K. Chen., *Nature* **2009**, *459*, 824-828.

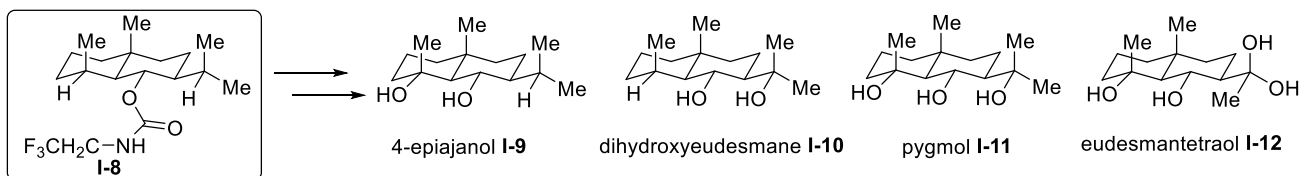
<sup>29</sup> P. Nagorny, W. Kaplan, H. R. Khatri, *J. Am. Chem. Soc.* **2016**, *138*, 7194-7198.

<sup>30</sup> R. M. Williams, G. Pan, *J. Org. Chem.* **2012**, *77*, 4801-4811.

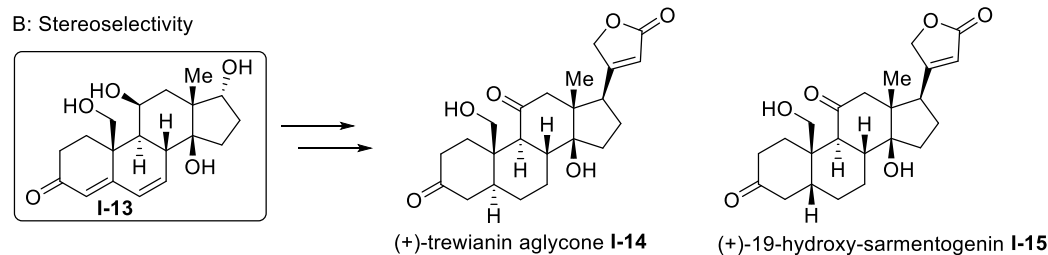
<sup>31</sup> M. A. Kerr, T. P. Lebold, *Org. Lett.* **2007**, *9*, 1883-1886.

With millions of years' evolution, nature has developed the most efficient working system. The successful design of pluripotent late-stage intermediates for versatile transformations could thus be inspired from the comprehension of biosynthetic pathways.<sup>32</sup>

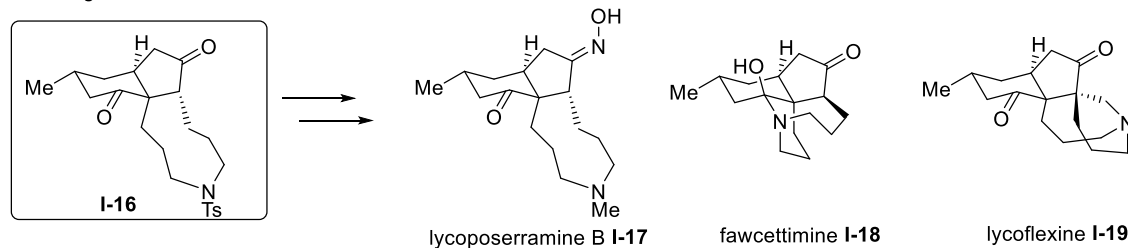
A: Redox process



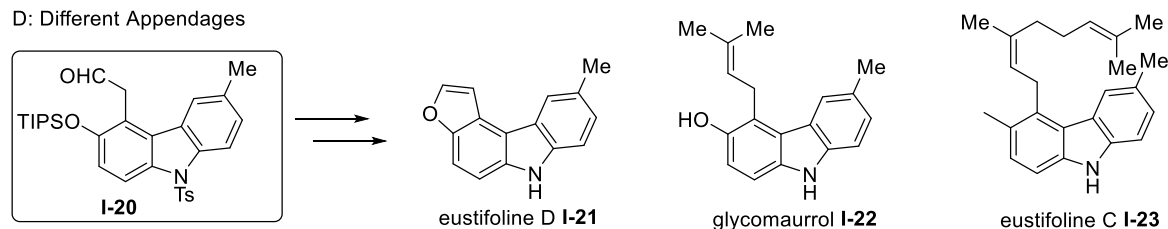
B: Stereoselectivity



C: Reorganization



D: Different Appendages



Scheme I-2 Four general categories of divergent strategy

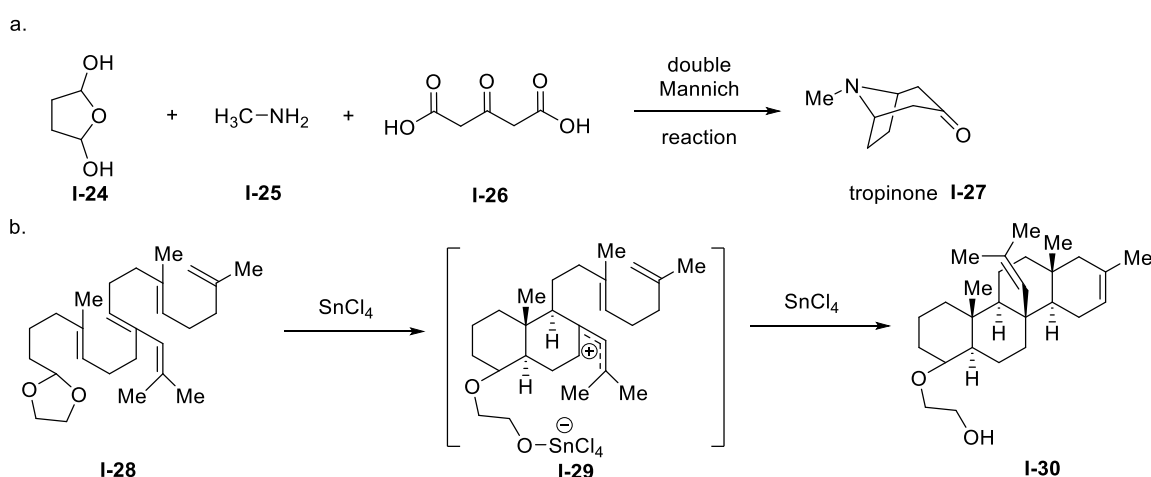
### 1.3. Biomimetic synthesis

The concept of biomimetic synthesis was first introduced by Robinson in 1917.<sup>33</sup> He used a straightforward strategy to synthesize tropinone from simple biomimetic building blocks: glutaraldehyde I-24, methylamine I-25, and acetonedicarboxylic acid I-26 (Scheme I-3a). In the 1970's, Van Tamelen and Johnson achieved brilliant polyene cyclization studies,

<sup>32</sup> A. L. Zografos, E. E. Anagnostaki, *Chem. Soc. Rev.* **2012**, *41*, 5613–5625.

<sup>33</sup> a) R. Robinson, *J. Chem. Soc. Trans.* **1917**, *111*, 762-768; b) M. Movassaghi, J. W. Medley, *Chem. Commun.* **2013**, *49*, 10775-10777.

illustrating the power of biomimetic strategies to generate complex structures by imitating terpene cyclase (Scheme I-3b).<sup>34</sup> They summarized afterwards biomimetic synthesis as a specific reaction or a sequence of reactions that mimic a proposed biological pathway. From then on, more and more studies have been carried out to understand and stimulate the participation of specific enzymes in every step of the biosynthesis of numerous natural products.<sup>35</sup>



Scheme I-3 a) Robinson's one-step synthesis of tropinone; b) Van Tamelen's biomimetic polyene cyclization by a cation-stabilizing auxiliary

Nature assembles complex natural products by using mere building blocks and limited reaction types in the living systems. Most natural products are biosynthesized via iterative coupling of bifunctional building blocks.<sup>36</sup> For example, cyclic peptides are usually derived from the 20 common amino acids plus many unconventional ones; polyketides are constructed from malonyl coenzyme A (CoA) and acetyl-CoA and polyterpenes are assembled from isopentenyl diphosphate and dimethylallyl diphosphate (Figure I-2).

In addition, groups of natural products are usually biosynthesized from a key common intermediate in a collective manner (Scheme I-4).<sup>37</sup> For example, indolemonoterpene alkaloids such as tabersonine **I-35**, catharathine **I-36** and andranginine **I-37**, are synthesized from the same intermediate **I-31** through intramolecular Diels-Alder reactions catalyzed by

<sup>34</sup> a) E. E. Van Tamelen, *Acc. Chem. Res.* **1968**, *1*, 111-120; b) W.S. Johnson, *Angew. Chem. Int. Ed.* **1976**, *15*, 9-17; c) E. E. Van Tamelen, *Fortschr. Chem. Org. Naturst.* **1961**, *19*, 242-290.

<sup>35</sup> E. Poupon, B. Nay, *Biomimetic Organic Synthesis*, Wiley-VCH, **2011**.

<sup>36</sup> J. K. De. Brabander, *Nature Chemical Biology* **2011**, *7*, 865-875.

<sup>37</sup> H. Oguri, H. Mizoguchi, H. Oikawa, *Nat. Chem.* **2014**, *6*, 57-64.

different enzymes. Applying such biogenetic strategy, Oguri has achieved these skeletally distinct scaffolds in a beautiful collective and biomimetic way. In this manner, bio-inspired strategies revolutionized natural product total syntheses, especially in collective syntheses.

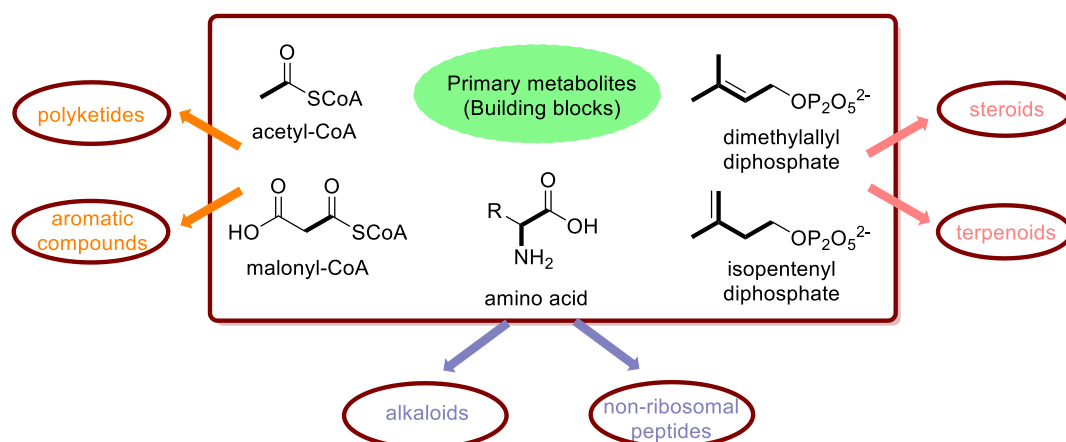
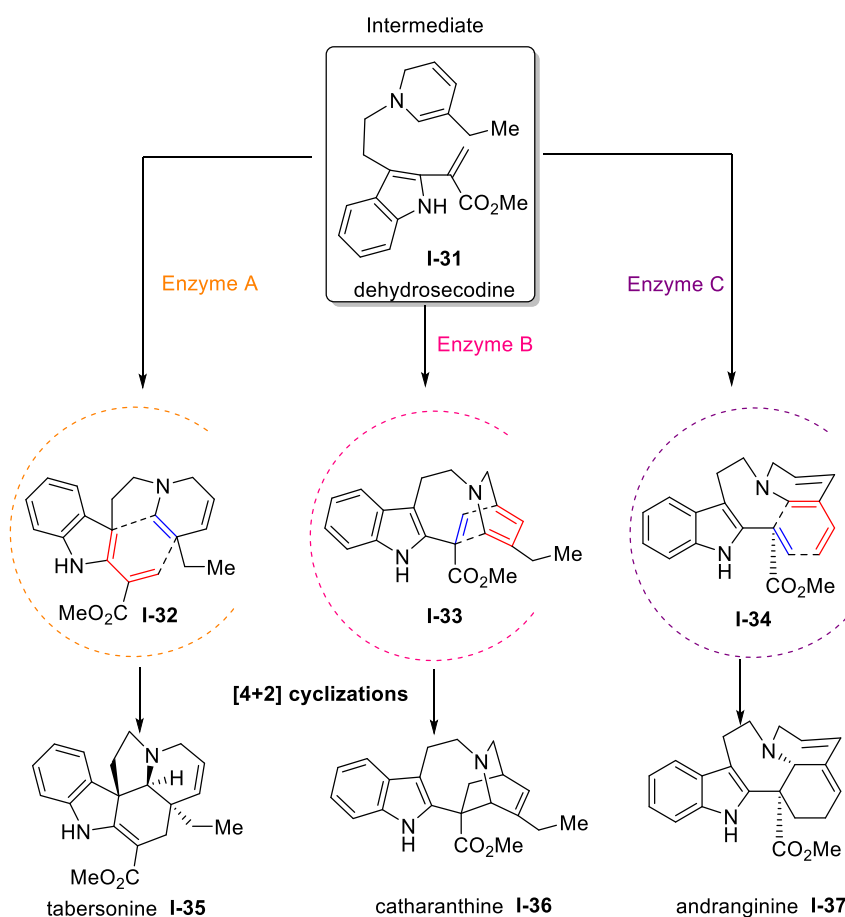


Figure I-2 Origins of some natural products



Scheme I-4 Proposed biogenesis of indole alkaloids from a common intermediate I-31

## 1.4. Challenges and new perspectives for biomimetic collective natural product synthesis

Challenges have emerged along with biomimetic approaches for the development of unparalleled reactions which nature itself utilizes. It is often difficult to reproduce nature's enzymatically driven selectivity in the laboratory. Nowadays however, successful biomimetic syntheses often imitate biogenetic processes in which minimal enzymes are involved. Concerning complex biochemical transformations, the exact role of enzymes is moreover not always well understood. A striking exception is found with polyterpene cyclizations for which biomimetic processes have been well designed (Scheme I-3b),<sup>38</sup> while the enzymatic mechanism of this cyclization is now well understood.<sup>39</sup>

In addition, biochemical pathways of functionalization are now well decrypted, bio-inspiration may also drive new discoveries in the development of synthetic methodologies for specific transformations. Innovative methods and catalysis procedures, such as C–H bond activation, stereoselective late-stage functionalization or heterocyclic ring substitution, are thus necessary for efficient collective syntheses of natural products. Moreover, the direct use of micro-organisms, as done in fermentation or biocatalysis, could allow the functionalization and diversification in natural product synthetic design.

## 2. Diversity and biosynthesis origins of 2,5-diketopiperazines (DKPs)

### 2.1. Simple DKPs: structure and biosynthesis

2,5-Diketopiperazines constitute a class of cyclic dipeptides made by two  $\alpha$ -amino acids or their derivatives (Figure I-3).<sup>40</sup> DKPs are natural compounds produced by bacteria, fungi, plants, and mammals. They also occur in food and beverages, particularly as polypeptide degradation products, sometimes contributing to their taste.<sup>41</sup> This constrained pattern is also found embedded in larger and more complex natural products, especially those isolated from marine organisms,<sup>42</sup> playing important roles in regulatory mechanism of quorum sensing or

---

<sup>38</sup> R. A. Yoder, J. N. Johnston, *Chem Rev.* **2005**, *105*, 4730–4756.

<sup>39</sup> a) D. W. Christianson, *Chem Rev.* **2017**, *117*, 11570–11648; b) D. J. Tantillo, *Nat. Prod. Rep.* **2011**, *28*, 1035

<sup>40</sup> A. D. Borthwick, *Chem. Rev.* **2012**, *112*, 3641–3716.

<sup>41</sup> a) C. Prasad, *Peptides* **1995**, *16*, 151; b) G. Kilian, *Comprehensive Natural Products II: Chemistry and Biology*; Mander, L., Liu, H.-W., Eds.; Elsevier: Amsterdam, **2010**, *5*, 657–698.

<sup>42</sup> a) Y. Liu, R. Huang, X. Zhou, T. Xu, X. Yang, *Chem. Biodiv.* **2010**, *7*, 2809–2827; b) C. H. Gao, R. Huang, X. Yi, Y. Zhou, X. Su, Y. Peng, *Mar. Drugs* **2014**, *12*, 6213–6235.

show anti-bacterial and cytotoxic activity.<sup>43</sup>

Structurally similar to peptides, the diversity of these simplest representatives depends on the asymmetric origin of amino acids and their various side chains. However, they are more resistant to proteolysis thanks to their rigid conformation.<sup>44</sup> NMR and calculation studies have shown that 2,5-DKP **I-38** could adopt either a slightly puckered boat form **I-39** or a flat conformation **I-40** (Figure I-3).<sup>45</sup> The difference in energy is small (1.3-1.7 kcal/mol), and it was demonstrated that the di- or tri-substituted compounds are more stable in flattened-boat or twist-boat forms in the solid state;<sup>46</sup> whereas, they could change to the flat form in solution environment.

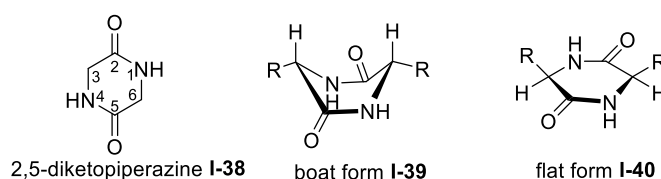


Figure I-3 Conformations of 2,5-diketopiperazines

This stable framework and the existing two hydrogen bond donors and two hydrogen bond acceptors give DKPs important chemical pharmacophore potentials, and make them relevant to the development of new lead compounds and drug candidates.<sup>47</sup>

The biosynthesis of DKP metabolites could be catalyzed by two kinds of enzymes: non-ribosomal peptide synthetases (NRPSs) and tRNA-dependent cyclodipeptide synthases (CDPSs). The NRPSs machinery for peptide synthesis is a common biological process to catalyze stepwise peptide condensation by using large multimodular enzymes as an assembly line.<sup>48</sup> Each module is responsible for the incorporation of one amino acid and three essential domains are mainly present in each module: the adenylation (**A**) domain, the peptidyl carrier protein (**PCP** or **T**) domain and the condensation (**C**) domain (Scheme I-5). DKPs result from an intramolecular cyclization of a linear peptidyl thioester intermediate bound to the PCP domain, and could also be sometimes produced as a byproduct released during a longer peptide synthesis (for example, cyclo(D-Phe-L-Pro) is produced during tyrocidine

<sup>43</sup> G. Degrossi, C. Aguilar, M. Bosco, S. Zahariev, S. Pongor, V. Venturi, *Curr. Microbiol.* **2002**, *45*, 250–254.

<sup>44</sup> P. M. Fischer, *J. Peptide Sci.* **2003**, *9*, 9-35.

<sup>45</sup> B. J. Persson, J. D. Hirst, *J. Phys. Chem.A.* **1998**, *102*, 7519-7524.

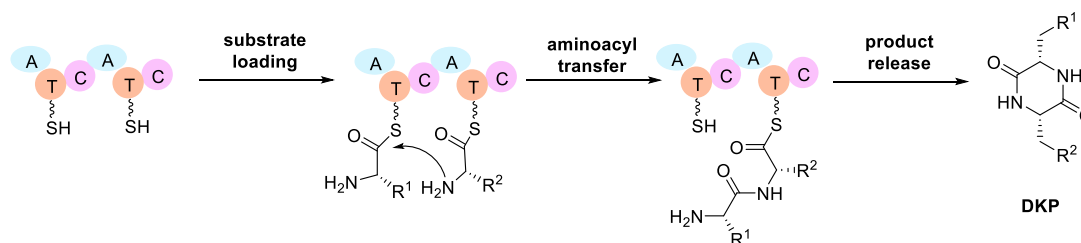
<sup>46</sup> G. M. Whitesides, J. C. MacDonald, *Chem. Rev.* **1994**, *94*, 2383-2420.

<sup>47</sup> I. Carvalho, M. B. Martins, *Tetrahedron* **2007**, *63*, 9923–9932.

<sup>48</sup> C. T. Walsh, *Nat. Prod. Rep.* **2016**, *33*, 127-135.

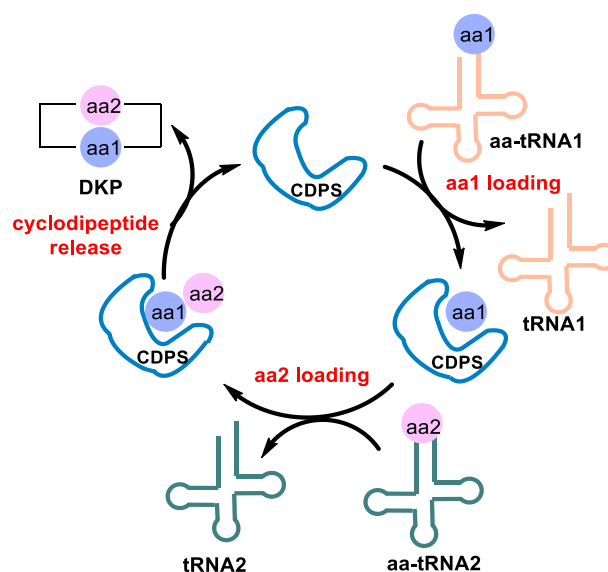


biosynthesis).<sup>49</sup> The cyclopeptides formed by NRPSs can be further modified by tailoring enzymes, for example by prenylation, oxidation, dehydrogenation, acetylation, hydroxylation or methylation, to generate a higher functional diversity, resulting in more diverse biological activities of the resulting natural products.<sup>50</sup>



*Scheme I-5: Biosynthesis of DKPs catalyzed by NRPSs (A is responsible for substrate recognition and activation; T is bound to the activated substrate in the form of a thioester via a phosphopantetheinyl arm; C catalyze the peptide bond formation)<sup>51</sup>*

Compared to NRPSs, the biosynthesis of DKPs catalyzed by the enzyme CDPS has been recognized recently. Few examples are known, and many remain hypothetical.<sup>52</sup> CDPSs are small enzymes (about 26 kDa) and the amino acid activation process needs to be finished by “hijacking” aminoacyl-tRNAs (Scheme I-6).<sup>53</sup>



*Scheme I-6 Biosynthesis of DKPs catalyzed by CDPSs (tRNA recognize the amino acid and then delivers it to CDPS. The cyclodipeptide is released by CDPS after twice substrate (aa) loadings)*

<sup>49</sup> T. W. Giessen, M. A. Marahiel, *Front. Microbiol.* **2015**, *6*, 785.

<sup>50</sup> B. Gu, S. He, X. Yan, L. Zhang, *Appl. Microbiol. Biotechnol.* **2013**, *97*, 8439–8453.

<sup>51</sup> M. G. Thomas, *Mol Pharm.* **2008**, *5*, 191–211.

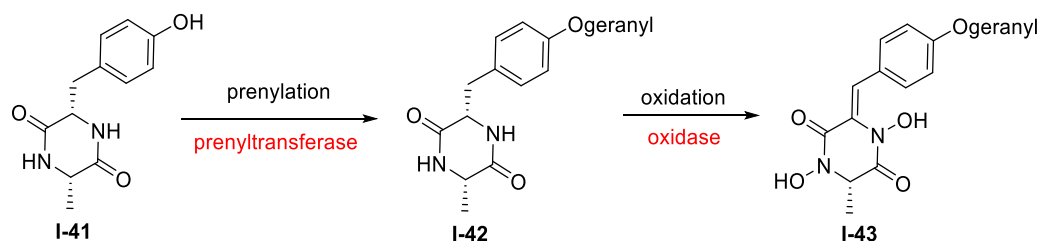
<sup>52</sup> S. Lautru, M. Gondry, R. Genet, J. L. Pernodet, *Chem. Biol.* **2002**, *9*, 1355–1364.

<sup>53</sup> M. A. Marahiel, T. W. Giessen, *Int. J. Mol. Sci.* **2014**, *15*, 14610–14631.

Therefore, the substrates of CDPSs are restricted to the 20 L-amino acids, which could be charged on tRNAs; whereas the range of NRPS incorporated amino acids is much wider, including for example anthranilic acid for quinazolino-DKPs. Until now only three cyclodipeptide-tailoring activities linked to CDPS have been characterized: cyclic dipeptide oxidase (CDO) for dehydrogenation; cytochrome P450 CYP134A1 for ring oxidation and cytochrome P450 CYP121A1 for C-C aryl coupling.<sup>54</sup> Thus, a wider structural complexity of DKPs can result from NRPS pathways than that generated from CDPS pathways.

## 2.2. Gliocladrine DKPs and their biosynthesis

Mycelianamide (**I-43**) was first isolated from the mycelium of *Penicillium griseofulvum* by Anslow and Raistrick in 1931.<sup>55</sup> Then its chemical structure was demonstrated as a geranylated DKP with a high oxidation states in 1948 by Oxford and Raistrick.<sup>56</sup> Birch proved that the lactone of mevalonic acid could be a precursor in the biosynthesis of a part of the molecule.<sup>57</sup> In 1973 and 1974, Narayanaswami and MacDonald studied the incorporation of L-[<sup>14</sup>C]tyrosine in the formation of the cyclic dipeptide part, which permitted to propose a biosynthetic pathway (Scheme I-7).<sup>58</sup>



Scheme I-7 Postulated biosynthesis of mycelianamide

Two isomeric deoxymycelianamides PJ147 (**I-44**) and PJ157 (**I-45**) were isolated from marine fungi *Gliocladium* sp. in 2007 by Shenyang Pharmaceutical of the University of China.<sup>59</sup> From the same fungus species, Yao isolated three other DKP derivatives, also

<sup>54</sup> M. Gondry, P. Belin, M. Moutiez, S. Lautru, J. Seguin, J. L. Pernodet, *Nat. Prod. Rep.* **2012**, 29, 961-979.

<sup>55</sup> W. R. Anslow, H. Raistrick, *Biochem. J.* **1931**, 25, 39-44.

<sup>56</sup> A. E. Oxford, H. Raistrick, *Biochem. J.* **1948**, 42, 323-329.

<sup>57</sup> a) A. J. Birch, R. J. English, R. A. Massy-Westropp, H. Smith, *J. Chem. Soc.* **1958**, 369-375.; b) A. J. Birch, M. Kocor, N. Sheppard, J. Winter, *J. Chem. Soc.* **1962**, 1502-1505; c) A. J. Birch, R. A. Massy-Westropp, R. W. Rickard, *J. Chem. Soc.* **1956**, 3717-3721.

<sup>58</sup> a) S. Narayanaswami, G. W. Kirby, *J. Chem. Soc., Chem. Commun.* **1973**, 322-323; b) J. C. MacDonald, G. P. Slater, *Can. J. Biochem.* **1975**, 53, 475-478.

<sup>59</sup> Shenyang Pharmaceutical University. Antineoplastic active substance of diketopiperazine PJ147 and PJ157. CN101041640; **2007**.

containing a geranyloxy group side chain: gliocladrin (**I-47**), gliocladrin A (**I-48**) and gliocladrin B (**I-49**) (Figure I-4).<sup>60</sup> The phomamide (**I-46**) was isolated from blackleg fungus *Phoma lingam* in Canada and in France.<sup>61</sup>

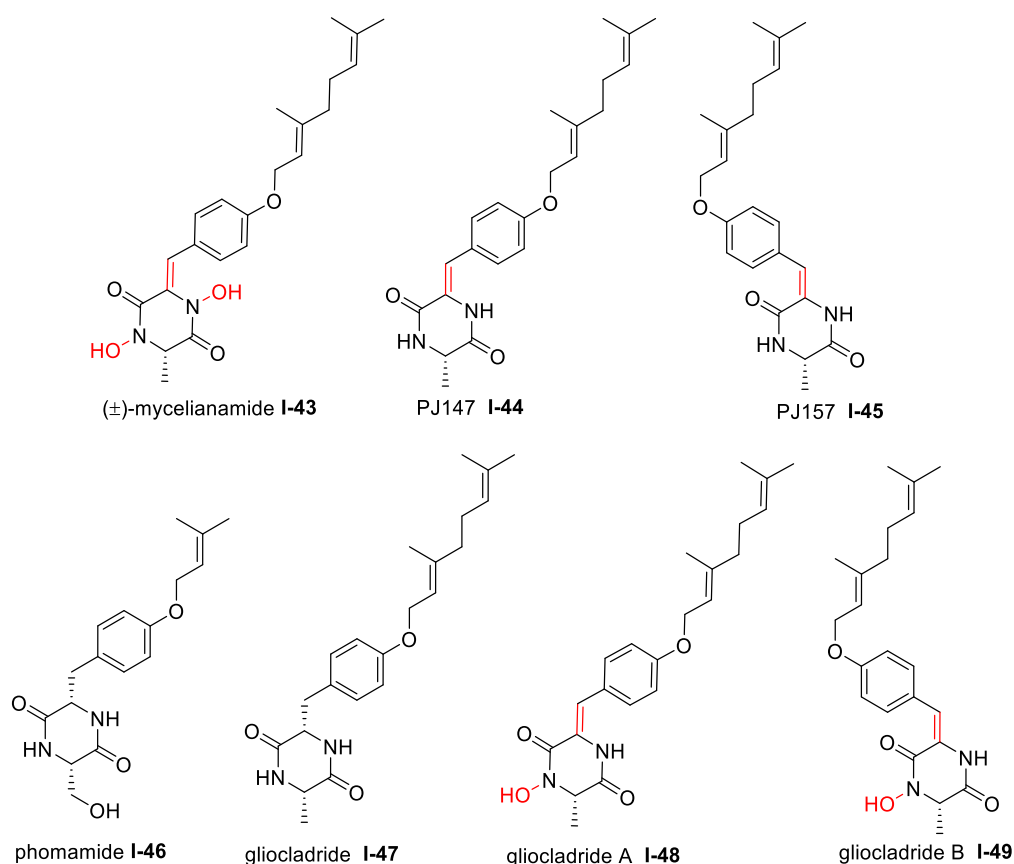


Figure I-4 Gliocladrin-DKP natural products

Figure I-4 shows that all the compounds have a similar structure with only differences of oxidation states, which might prove the proposed biosynthetic pathway. Besides, all of them exhibit a good cytotoxicity against gram-positive microorganisms or cancer cells (Table I-1). Interestingly, it appears that the presence of the N-OH moiety in gliocladrin-DKPs is likely to decrease the cytotoxicity. In addition, the unsaturation at the benzyl position affects the efficiency of bioactivity. Compared with phomamide and gliocladrin, the lipophilicity may also influence its anti-cancer activity.

<sup>60</sup> a) Y. Yao, L. Tian, J. Li, J. Cao, Y. Pei, *Pharmazie* **2009**, *64*, 616-618; b) Y. Yao, L. Tian, J. Li, J. Cao, Y. Pei, *Pharmazie* **2007**, *62*, 478-479.

<sup>61</sup> a) J. P. Ferezou, A. Quesneau-Thierry, M. Barbier, A. Kollmann, J. F. Bousquet, *J. Chem. Soc. Perkin Trans. 1* **1980**, *0*, 113-115.; b) S.C. Pedras, G. Slguin-Swaetz, S. R. Abrams, *Phytochemistry* **1990**, *29*, 777-782.

Table I-1 Cytotoxicity for glioclarid-DKPs

Compound I-43 to I-39	Cytotoxic activities	IC <sub>50</sub> (µg/mL)
phomamide <sup>62</sup> (I-46)	against cancer cells (Hs683, A549, SKMEL-28, U373)	33-100
mycelianamide (I-43)	against gram-positive microorganisms (Micrococcus pyogenes var.aureus and var.albus, Streptococcus pyogenes, Streptococcus and Bacillus anthracis)	20-50
gliocladride A & B (I-48 and I-49)	against cancer cells (U937, T47D, HL-60)	11.6-52.83
PJ 147 & PJ 157 (I-44 and I-45)	against cancer cells (HeLa, A549, A375-S2, HL-60)	0.785
Gliocladrid (I-47)	against human A375-S2 melanoma cell line	3.86

### 2.3. Quinazolino-DKPs and their biosynthesis

Nitrogen-containing heterocycles often exhibit diverse biological and pharmacological activities. Quinazoline and quinazolinone scaffolds with potential bioactive properties have drawn the significant attention in the areas of natural product synthesis.<sup>63</sup> 4-Quinazolinone **I-51** is an oxo-derivative of quinazoline **I-50**, also known as 1,3-diazanaphthalene or benzopyrimidine (Figure I-5).

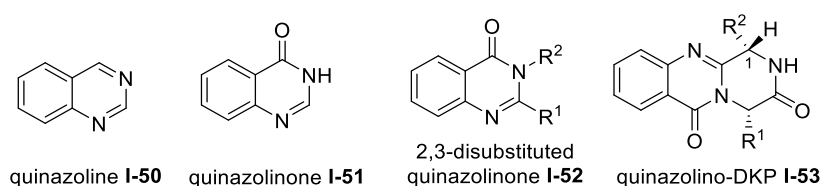


Figure I-5 Quinazolines and quinazolinones

Quinazolinone and their derivatives are also building blocks for approximately 200 naturally occurring alkaloids isolated from plants, animals and microorganisms, known for their wide range of biological properties, such as anti-malaria, hypnotic, anti-diabetic, anti-inflammatory,

<sup>62</sup> A. Mollica, R. Costante, S. Fiorito, S. Genovese, A. Stefanucci, V. Mathieu, R. Kiss, F. Epifano, *Fitoterapia* **2014**, *98*, 91-97.

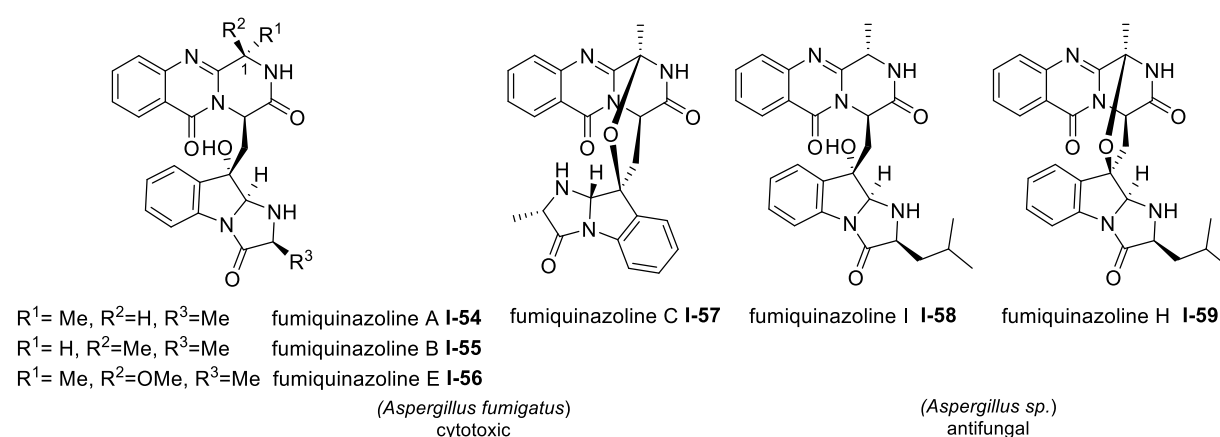
<sup>63</sup> A. D. Brown, *J. Heterocycl. Chem.* **1997**, *34*, 145-151.

anti-bacterial, anti-tumor, and several others.<sup>64</sup> As an important pharmacophore, quinazolinone natural products are well documented and their synthesis was largely developed.<sup>65</sup> Here, we are mainly interested in 2,3-quinazolinones fused to a piperazine ring system, also called quinazolino-DKPs (**I-53**) in this manuscript (Figure I-5).

Quinazolino-DKPs are biologically synthesized by NRPS machineries, as mentioned previously. Their structural diversity is produced by various tailoring enzymes. Three major subclasses of compounds can be found in this family:

- 1) quinazolinones fused to a simple piperazine ring (such as fumiquinazoline A, B, E, I, S and aurantiomide A-C) (Figure I-6);
- 2) quinazolinones fused to a piperazine ring, along with a spirocyclic-ring functionality (such as fumiquinazoline C, H, sartorymiensin and cottoquinazoline D) (Figure I-6);
- 3) quinazolinones fused with a piperazine ring, along with a prenyl-substituted indole moiety, *i.e.* the alkaloids, ardeemins.<sup>66</sup>

In the first two series of natural products, functionalizations of the tricyclic-peptide main core **I-53** at position C1 (Figure I-5), affording either spirocyclic-ring forms or oxidized derivatives, are usually the main biosynthetic processes to diversify structures and biological activities.



<sup>64</sup> a) X. F. Wu, L. He, H. Li, J. Chen, *RSC Adv.* 2014, 4, 12065-12077; b) J. P. Michael, *Nat. Prod. Rep.* **2003**, 20, 476-493.

<sup>65</sup> a) U. A. Kshirsagar, R. S. Rohokale, *Synthesis* **2016**, 48, 1253-1268; b) U. A. Kshirsagar, *Org. Biomol. Chem.* **2015**, 13, 9336-9352; c) A. Saeed, I. Khan, A. Ibrar, N. Abbas, A. Saeed, *Eur. J. Med. Chem.* **2014**, 76, 193-244.

<sup>66</sup> N. P. Argade, S. B. Mhaske, *Tetrahedron* **2006**, 62, 9787-9826.

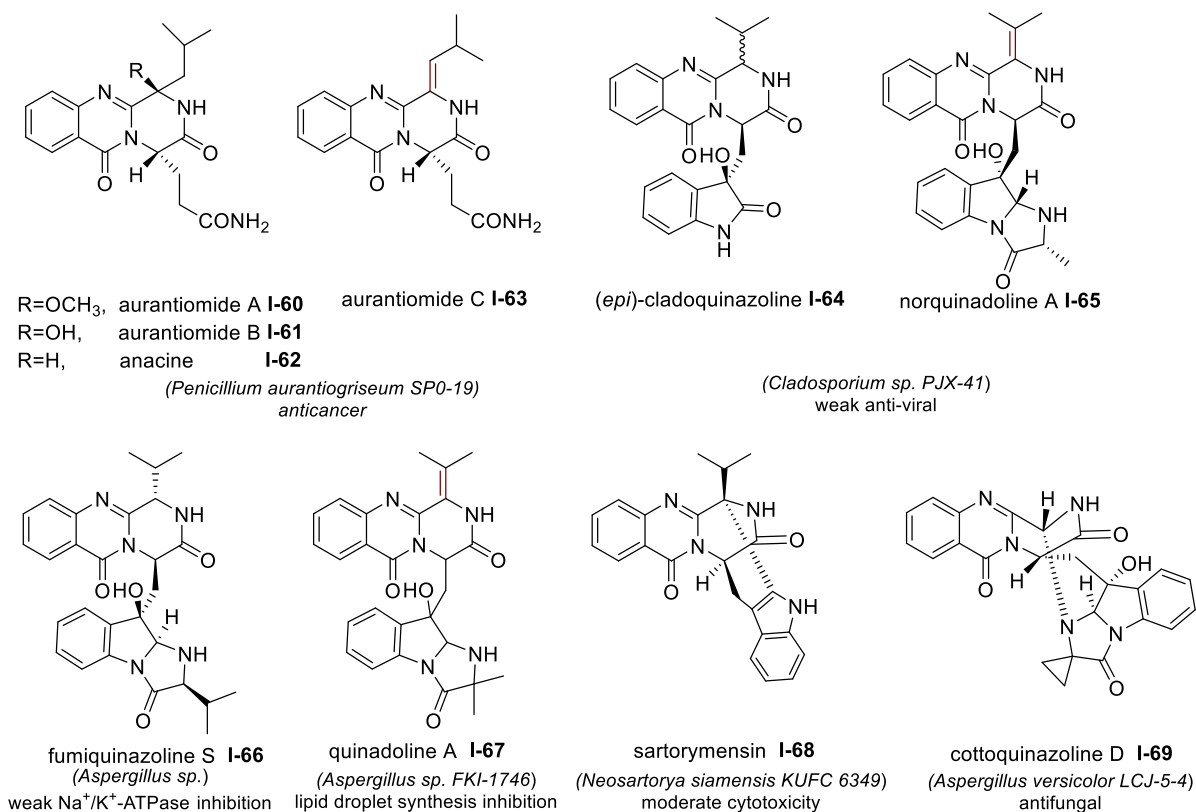


Figure I-6 Quinazolino-DKP natural products

## 2.4. Oxepino-DKP natural products and their biosynthesis

The intricacy of complex natural product structures containing unsaturated seven-membered oxacycles attract increased attention of synthetic chemists as well. For example, the fascinating marine-derived toxin brevetoxin A, most complex of its congeners,<sup>67</sup> and far simpler natural benzoxepines<sup>68</sup> contain such an oxacycle. These seven-membered rings containing a single oxygen atom are classified as ‘oxepines’. Depending on different the levels of saturation, this family of heterocycle have been categorized in four different types (Figure I-7):

- An oxepine or oxepin **I-70** is termed when the heterocyclic ring contains ‘the maximum number of double bonds’, three carbon-carbon double bonds. It is present in the structure of varioxepine **I-104** and cinereain **I-98** (Figure I-9).
- A dihydrooxepine **I-71** is defined for an oxacycle bearing two double bonds in the ring.

<sup>67</sup> K. C. Nicolaou, Z. Yang, G. Shi, J. L. Gunzner, K. A. Agrios, P. Gärtner, *Nature* **1998**, 392, 264-269.

<sup>68</sup> E. Dominguez, R. Olivera, R. Sanmartin, F. Churrua, *organic preparations and procedures I*. **2004**, 6, 297-330.

This structural pattern can be largely found in the family of benzo[b]oxepines.

- A tetrahydrooxepine **I-72** is named when only one double bond is present in the heterocycle.
- An oxepane **I-73** is a fully saturated seven-membered oxacyclic ring.

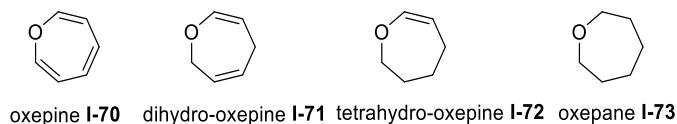
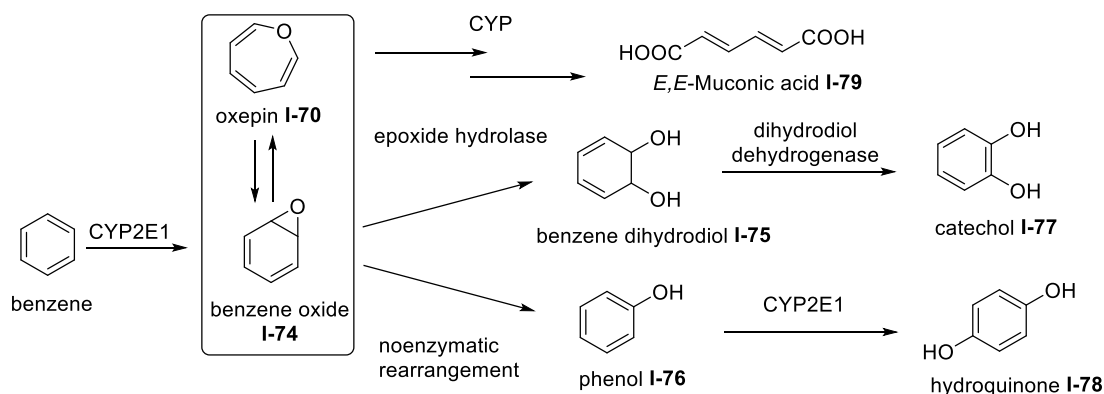


Figure I-7 'Oxepines' defined according to the level of saturation

In this study, we will investigate the oxepine pattern **I-70** and **I-71**, as a part of a DKP-based heterotricyclic system or a dihydrobenzoxepine system. The simplest structure, oxepine **I-70**, exists in a state of spontaneous equilibrium with the valence bond isomer benzene oxide **I-74** (Scheme I-8) at ambient temperature, which can make it difficult to be isolated experimentally.<sup>69</sup> Biologically, oxepines are produced during the benzene metabolic pathway. The enzymatic epoxidation of benzene and aromatic compounds involves the formation of an epoxide **I-74**, followed by epoxide opening or electronic isomerization to give a phenol **I-76** or an oxepine **I-70**, respectively. Because of this equilibrium, the final excreted metabolites are primarily *E,E*-muconic acid **I-79**, catechol **I-77** and hydroquinone **I-78**.<sup>70</sup> Despite the potential instability of the oxepine moiety, more and more bioactive oxepine-containing products are isolated from natural sources. They may result from similar metabolic pathways. Their synthesis is thus of interest to challenge the complexity and the instability of these compounds, and also to study their biological properties.



Scheme I-8 Simplified human benzene metabolic pathway

<sup>69</sup> D. R. Boyd, *Comprehensive Heterocyclic Chemistry* **1984**, 7, 547-592.

<sup>70</sup> S. M. Rappaport, S. Kim, Q. Lan, G. Li, V. Roel, S. Waidyanatha, L. Zhang, S. Yin, M. T. Smith, N. Rothman, *Chemico-Biological Interactions*, **2010**, 184, 189-195.

Benzannulation may stabilize arene oxides or oxepines. Dibenzoxepine compounds **I-79** are the first isolated class of oxepine-containing natural products, exhibiting excellent biological and pharmacological activities (Figure I-8).<sup>71</sup> For example, compounds bauhinoxepin A **I-81** and bauhiniastatin 1 **I-82**, isolated from plants of the *Bauhinia* genus, bear a dibenz[*b,f*]oxepin skeleton<sup>72</sup>. Doxepin **I-83** is a widely used antidepressant synthetic drug,<sup>73</sup> of which the synthesis was accomplished forty years ago. Natural sources of benzoxepins **I-80** are rare but also show good biological activities (Figure I-8). Pterulone **I-84**, isolated from coral fungus *Pterula sp.*, is an effective inhibitor of eukaryotic respiration. Its furan-annulated benzoxepin derivative pterulinic acid **I-85** also exhibits significant antifungal activity.<sup>74</sup> Finally, the benzoxepin drug **I-86** is a strong inhibitor of the enzyme steroid sulfatase, useful for treating breast cancer.<sup>75</sup>

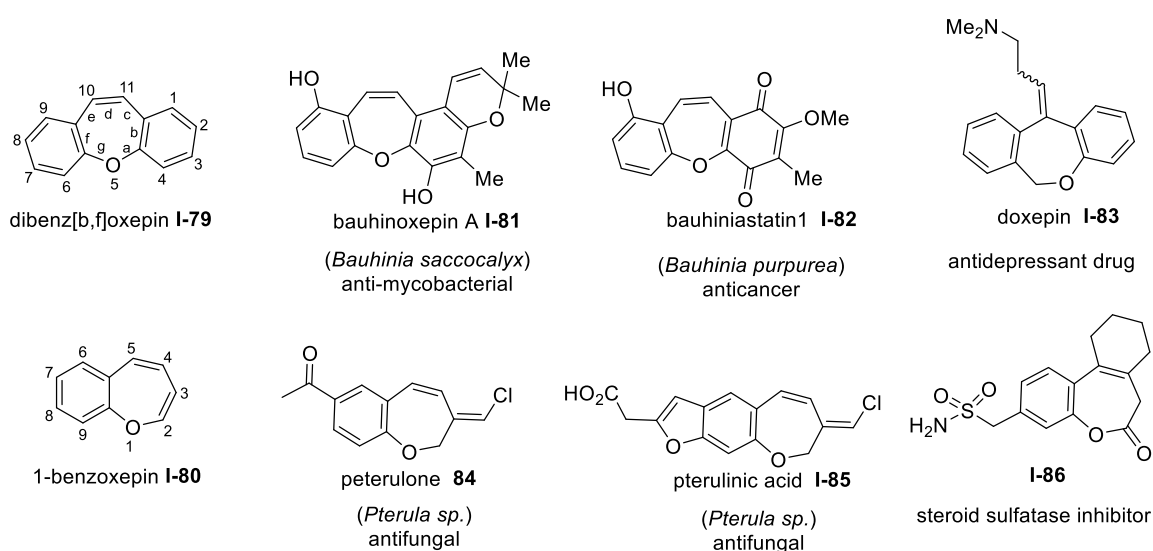


Figure I-8 Some bioactive products containing dibenz[*b,f*]oxepins and 1-benzoxepins

Since the 1980s, a small number of oxepino-pyrimido-DKP compounds have been isolated. They are structurally similar to quinazolino-DKPs, which are biosynthetic precursors through a biosynthetic epoxidation step of the aromatic ring (as previously described for benzene metabolism, Scheme I-10 and next discussion below). As a part of secondary metabolites produced by NRPSs, the large choice of amino acid precursors (especially alanine, valine,

<sup>71</sup> L.A. Summers, J. D. Loudon, *J. Chem. Soc.* **1957**, 3809-3813.

<sup>72</sup> R. A. Tapia, D. R. R. Moreno, G. Giorgi, C. O. Salas, *Molecules* **2013**, *18*, 14797-14806.

<sup>73</sup> K. F. Chung, W. F. Yeung, K. P. Yung, T. H. Ng, *Sleepmedicine reviews* **2015**, *19*, 75-83.

<sup>74</sup> J. B. P. A. Wijnberg, B. W. t. Gruijters, A. van Veldhuizen, C. A. G. M. Weijers, *J. Nat. Prod.* **2002**, *65*, 558-561.

<sup>75</sup> S. von Angerer, *Science of synthesis* **2004**, *7*, 627-653.



leucine, phenylalanine or tryptophan) and additional enzymatic functionalization steps lead to a large structural diversity (Figure I-9).

Cinereain **I-98** was the first discovered member of the series, isolated by Culter and co-workers from the phytopathogenic fungus *Botrytis cinerea* in 1988. It behaved as a plant growth regulator of wheat coleoptiles.<sup>76</sup> In 2013, its analog dihydrocinereain (**I-99**) was isolated from *Aspergillus carneus*, but showed no comparable activity.<sup>77</sup>

Oxepinamides A-C (**I-87** to **I-89**) were isolated in 2000 from the culture broth and mycelia of an *Acremonium sp.*<sup>78</sup> Oxepinamide A (**I-87**) showed a good topical anti-inflammatory activity in a resiniferatoxin-induced mouse ear edema assay. Oxepinamides D-G (**I-90** to **I-93**) were isolated from the fungus *Aspergillus puniceus* F02Z-1744 obtained from a Chinese soil sample in 2011.<sup>79</sup> All of them were shown to be novel liver X receptor agonists with potential use in the treatment of atherosclerosis, diabetes and Alzheimer's disease. Brevianamides L-P (**I-94** to **I-96**) were isolated from the harmful fungus *Aspergillus versicolor* in 2000.<sup>80</sup> Brevianamide L **I-94** bears a 13-oxygenated dihydrooxepine ring, as that of oxepinamide E-G. Janoxepin **I-97** was isolated from the fungus *Asperillus janus* in 2005 by Sprogøe and co-workers.<sup>81</sup> It has demonstrated the antiplasmodial activity against the malaria parasite *Plasmodium falciparum* 3D7, with a poor IC<sub>50</sub> value of 28 µg/mL. Protuboxepins A **I-100** and B **I-101** are close relatives of brevianamide P and were isolated from *Aspergillus species* SF-5044 from a Korean sediment sample in 2011. Only protuboxepin A displayed weak cell growth inhibition properties against a panel of cell lines.<sup>82</sup> Versicoloids A **I-102** and B **I-103** were isolated from deep-sea-derived fungi *Aspergillus versicolor* SCSIO 05879 in 2016, showing strong fungicidal effect (MIC of 1.6 µg/mL) against *Colletotrichum acutatum*.<sup>83</sup>

---

<sup>76</sup> a) R. G. Robert, H. G. Cutler, J. P. Springer, R. F. Arrendale, *Agric. Biol. Chem.* **1988**, *52*, 1725-1733; b) B. Asselbergh, K. Curvers, S. C. França, K. Audenaert, M. Vuylsteke, F. V. Breusegem, M. Höfte, *Plant Physiology* **2007**, *144*, 1863-1877.

<sup>77</sup> S. S. Afiyatullo, O. I. Zhuravleva, E. A. Yurchenko, V. A. Denisenko, N. N. Kirichuk, P.S. Dmitrenok, *Natural Product Communications* **2013**, *8*, 1071-1074.

<sup>78</sup> G. N. Belofsky, M. Anguera, P. R. Jensen, W. Fenical, M. Köck, *Chem. Eur. J.* **2000**, *6*, 1355-1360.

<sup>79</sup> H. Kiyota X. Lu, Q. Shi, Z. Zheng, A. Ke, H. Zhang, C. Huo et al., *Eur. J. Org. Chem.* **2011**, *2011*, 802-807.

<sup>80</sup> G. L. Zhang, G. Li, L. Li, T. Yang, X. Chen, D. Fang, *Helvetica Chimica Acta.* **2010**, *93*, 2075-2080.

<sup>81</sup> K. Sprogøe, S. Manniche, T. O. Larsen, C. Christophersen, *Tetrahedron* **2005**, *61*, 8718-8721.

<sup>82</sup> H. Oh, S. U. Lee, Y. Asami, D. Lee, J. Jang, J. Ann, *J. Nat. Prod.* **2011**, *74*, 1284-1287.

<sup>83</sup> Y. Liu, J. Wang, W. He, X. Huang, X. Tian, S. Liao, B. Yang, F. Wang, X. Zhou, *J. Agric. Food Chem.* **2016**, *64*, 2910-2916.

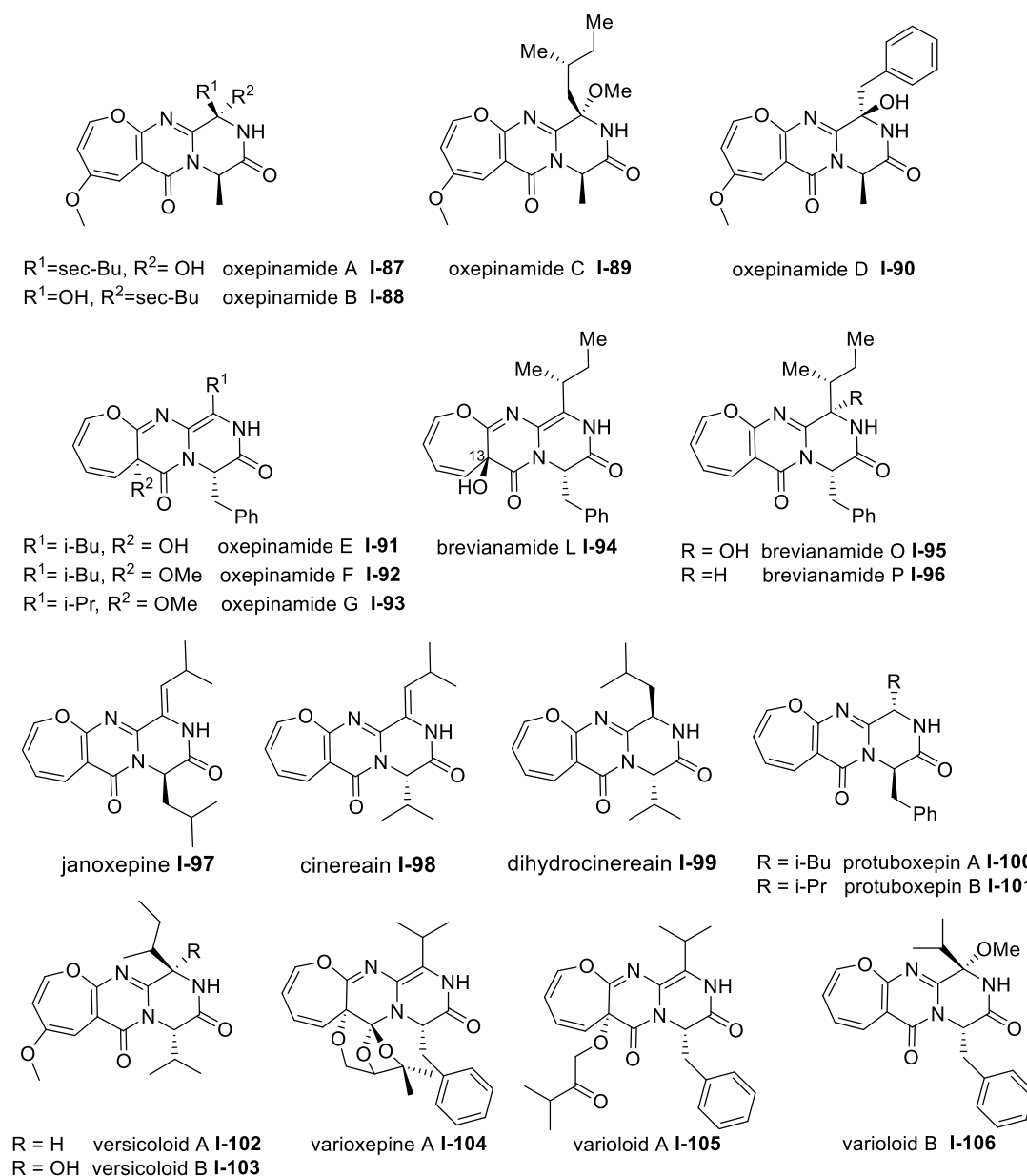


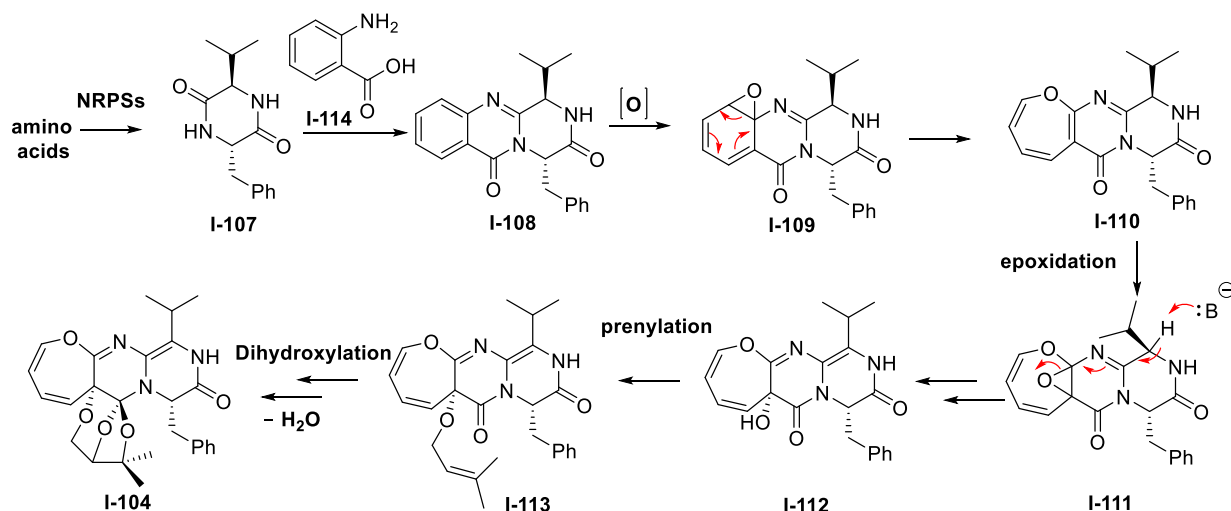
Figure I-9 Oxepin-containing natural products

Varioxepine A **I-104** was recently isolated from the marine-derived endophytic fungus *Paecilomyces variotii* EN-291 in 2014, possessing diverse antimicrobial activities.<sup>84</sup> From the same fungal strain, two alkaloids varioloid A **I-105** and varioloid B **I-106** were also described in 2015.<sup>85</sup> The isolation of these two latter compounds confirms their roles as biosynthetic intermediates in the biosynthesis of varioxepine A, consequently allowing a hypothetical biosynthetic pathway to be proposed (Scheme I-9). In the same article, the author proposed

<sup>84</sup> B. G. Wang, P. Zhang, A. Mándi, X. Li, F. Du, J. Wang, X. Li, T. Kurtán, *Org. Lett.* **2014**, *16*, 4834–4837.

<sup>85</sup> B. G. Wang, P. Zhang, X. Li, J. Wang, *Helvetica Chimica Acta.* **2015**, *98*, 800-804.

that varioxepine A was biosynthesized firstly by the condensation of anthranilic acid **I-114** with diketopiperazine **I-107** to yield **I-108**, followed by oxidation of the benzene ring to get oxepine derivative **I-110**. Subsequent epoxidation of the fusion bond in the oxepin ring, leading to **I-111**, is followed by a prototropic rearrangement with epoxide opening to yield tertiary alcohol **I-112**. Then selective enzymatic prenylation (into **I-113**) and oxidation of the prenyl double bond were followed by final acetal cyclization to yield varioxepin A **I-104**.



Scheme I-9 Plausible biosynthetic pathway for varioxepine A

### 3. Late-stage functionalization strategies in organic and bio-organic chemistry

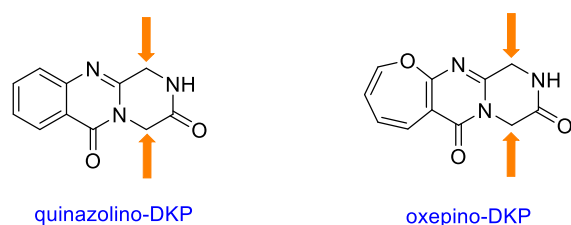
One of the most popular topics in organic synthesis today is the ability to carry out selective functionalization of inert C-H bonds at a late stage of the workflow. Especially, for complex molecule synthesis, reactive functionalities could be masked as relatively inert C-H bond, thus reducing side reactions during earlier multistep synthesis. The successful and appropriate application of site- (regio- or chemo-) and stereo-selective C-H functionalization methods, including arylation, alkylation, alkenylation, oxygenation, halogenation, amination, trifluoromethylthiolation and azidation<sup>86</sup>, would substantially shorten the synthetic route and bring the potential to generate chemical diversity without resorting to *de novo* synthesis. Furthermore, from a drug industry perspective, the late-stage functionalization strategy facilitates the addition of biological active functional groups (such as Me, OMe, CH<sub>2</sub>OH,

<sup>86</sup> J. Yamaguchi, K. Itami, A. D. Yamaguchi, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960 – 9009.

NH<sub>2</sub>, OH, F or CF<sub>3</sub>) on specific positions of an unprotected and complex lead molecule, which may not be tolerant to traditional synthetic strategies.<sup>87</sup>

As shown in the previous biological pathways, the diversity and complexity of secondary metabolite DKPs derive both from various chiral amino acids building blocks and selective post-assembly oxidations of the peptide scaffolds. If various C-H functionalizations could be regarded as powerful tailoring enzymes, we could streamline a bio-inspired “two-phase” synthetic process. At the first phase, some biomimetic cyclopeptide precursors are built by using simple amino acids. Then the selective C-H functionalizations of these common intermediates, by generating new C-C and C-O bonds, may lead a collective production of advanced synthetic intermediates or complex target molecules or analogs at the second phase. (Figure I-10).

#### C-C bond formation



#### C-O bond formation

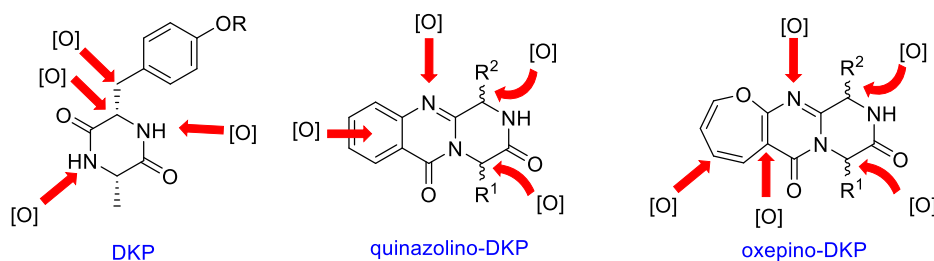


Figure I-10 Late-stage functionalizations of interest in this project

To achieve this goal, a summary of the most relevant accomplishments of late-stage C-H bond functionalizations for this project is provided below. Post-synthetic substitutions, polar elements introduction and biocatalytic functionalizations of C-H bonds, the most accessible at that time in our laboratories, provide great opportunities to achieve late-stage structural diversification of our target compounds.<sup>88</sup>

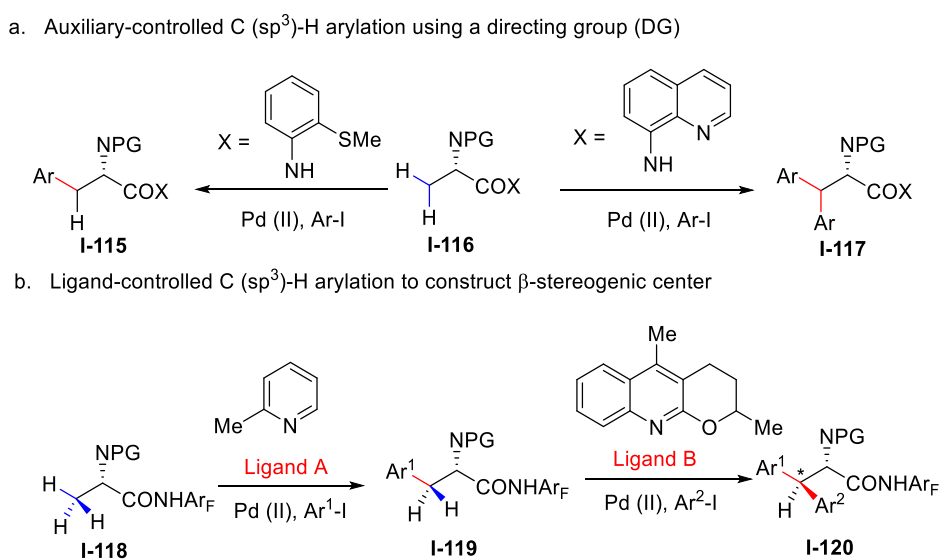
<sup>87</sup> David C. Blakemore, Luis Castro, Ian Churcher, David C. Rees, Andrew W. Thomas, David M. Wilson, Anthony Wood, *Nature Chemistry* **2018**, *10*, 383–394.

<sup>88</sup> G. Mehta, S. Sengupta, *Tetrahedron Letters* **2017**, *58*, 1357-1372.

### 3.1. Late-stage C-C bond formation

Significant advances have lately been completed to realize the post-synthetic modification of peptides. Studies of direct C(sp<sup>2</sup>)-H functionalizations of inherent phenylalanine and tryptophan moieties have been abundantly exploited;<sup>89</sup> whereas a few elegant achievements have been realized to selectively functionalize inert C(sp<sup>3</sup>)-H bonds in a peptide chain.<sup>90</sup> Since a seminal report by Corey,<sup>91</sup> the  $\beta$ -functionalization of amino acids or peptides has brought more and more attention.

The most successful examples are the site-selective functionalizations of alkyl side chains by installing an external auxiliary or appropriate ligand. Daugulis reported an efficient palladium-catalyzed directed C-H activation of protected amino acid **I-116** in 2012.<sup>92</sup> The use of a 2-thiomethylaniline derivative allows selective monoarylation of the methyl group of an alanine derivative, whereas a 8-aminoquinoline directing group can be used for diarylation to afford phenylalanine and diphenyl analogs, respectively (Scheme I-10a).



Scheme I-10 Directed  $\beta$ -functionalization of amino acids or peptides

Taking advantage of the coordinating properties of amide auxiliaries and the use of appropriate ligands on the catalyst, Yu's group reported a catalyst-controlled C(sp<sup>3</sup>)-H arylation using pyridine or quinoline derivatives to achieve the mono- or di-arylation of

<sup>89</sup> Y. Segawa, T. Maekawa, K. Itami, *Angew. Chem. Int. Ed.* **2015**, *54*, 66-81.

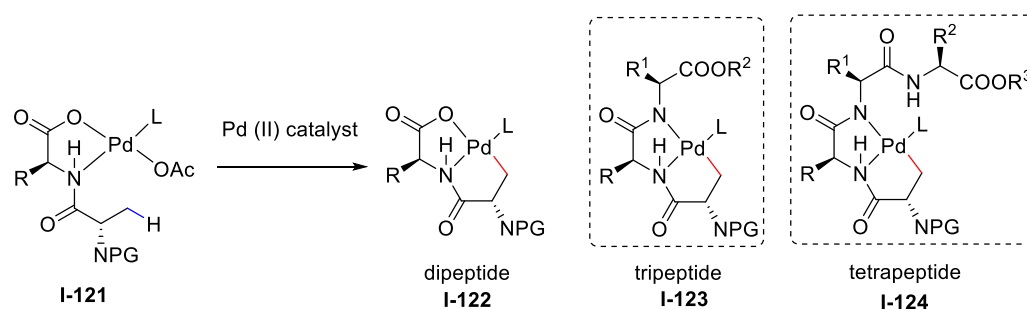
<sup>90</sup> M. A. Brimble, A. F. M. Noisier, *Chem. Rev.* **2014**, *114*, 8775-8806.

<sup>91</sup> B. V. Subba Reddy, Leleti Rajender Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391-3394.

<sup>92</sup> D. O. Daugulis, L. D. Tran, *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 5188-5191.

alanine with excellent diastereoselectivities (d.r. > 20:1) (Scheme I-10b).<sup>93</sup> Both possible configurations of the  $\beta$ -chiral center can be accessed by selecting the order in which the aryl groups are installed.

Progress in direct peptide arylation or alkylation via  $C(sp^3)$ -H activation of aliphatic amino acids is just beginning to surface. Yu has recently reported the site-selective C-H activation of *N*-terminal alanine for di-, tri- and tetrapeptides, where the peptide acts itself as the innate ligand, to yield unnatural phenylalanine peptides (Scheme I-11).<sup>94</sup> In general, the arylation reaction was highly selective for *N*-terminal alanine irrespective of the nature of other amino acids (Leu, Val, Ile, Phe, Tyr, Asp) present elsewhere in the peptide. From their scope, it is quite intriguing that only the *N*-terminal alanine could undergo C-H activation, even in the presence of *C*-terminal alanine residues, which could potentially compete for C-H activation.



Scheme I-11 C-H activation in peptides directed by the native C-terminus amino acid moiety

The  $\alpha$ -functionalization of peptides often requires an appropriate base or oxidant. O'Donnell<sup>95</sup> and Maruoka<sup>96</sup> reported elegant methods to introduce alkyl groups into activated *N*-terminal glycine unit of a short-chain peptide, by using asymmetric phase-transfer catalyzed enolate chemistry (Scheme I-12a). Li developed a free-(NH) glycine-specific copper-catalyzed oxidative cross-coupling reaction to introduce aryl, vinyl, alkynyl and indole groups (Scheme I-12a).<sup>97</sup> The only successful oxidant-free and base-free selective  $\alpha$ -functionalization was established to couple glycine arylamino esters **I-128** with  $\beta$ -ketoesters or indole derivatives by visible light catalysis (Scheme I-12b). As the complex molecules are often sensitive to base and oxidants at late-stage, the development of direct dehydrogenative cross-couplings to

<sup>93</sup> J. Q. Yu, J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, *Science* **2014**, *343*, 1216-1220.

<sup>94</sup> J. Q. Yu, W. Gong, G. Zhang, L. T. Liu, R. Giri, *J. Am. Chem. Soc.* **2014**, *136*, 16940-16946.

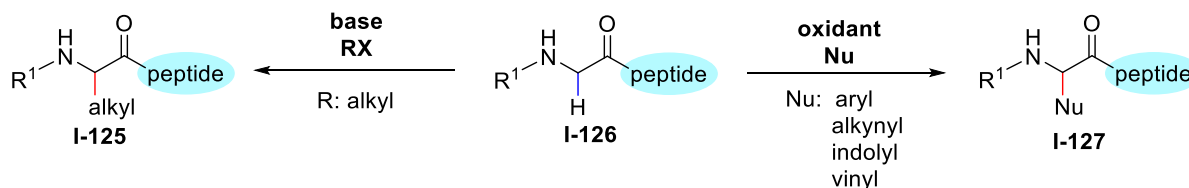
<sup>95</sup> M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506-517.

<sup>96</sup> a) K. Maruoka, T. Ooi, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222-4266; b) K. Maruoka, E. Tayama, T. Ooi, *PNAS* **2004**, *101*, 5824-5829.

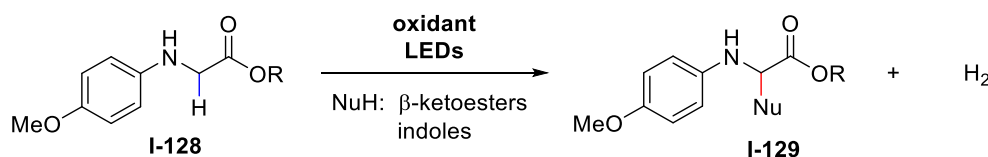
<sup>97</sup> C. J. Li, L. Zhao, O. Baslé, *PNAS* **2009**, *106*, 4106-4111.

construct C-C bond without using harsh conditions is still challenging.

a.  $\alpha$ -functionalization by enolate chemistry or oxidative catalysis



b.  $\alpha$ -functionalization by visible light catalysis without oxidant



Scheme I-12  $\alpha$ -functionalization of amino acids or peptides

### 3.2. Late-stage C-O bond formation

Protein oxidation is a common post-synthetic modification in nature. In the case of NRPSs, stereo- and regio-specific tailoring enzymes catalyze oxidation of pluripotent intermediates on its backbone or on the amino acid side chains to generate a structural and functional diversity. Compared to this efficient late-stage modification, traditional organic methods for installing oxidized functionality rely heavily on acid–base reactions that require extensive functional-group manipulations. Selective C-H oxidation methods to transform one common hydrocarbon skeleton to specifically oxidized compounds are still very inspiring and demanding challenges.

The most important factor of late-stage strategies relies on predictable selectivity for new reaction design over a broad range of substrates. Two major categories of reactions are being explored to achieve site-selectivity: innate reactions and guided reactions.<sup>98</sup> Innate reactions achieve selectivity by the intrinsic reactivity of the C–H bond to be functionalize. Guided reactions, meanwhile, achieve C–H selectivity by directing groups, steric or molecular recognition. Thus, the corresponding approaches are being developed.

The first approach for attaining site-selectivity in C–H oxidations is the development of special reaction conditions that use intrinsic reactivities of C–H bonds in complex molecular settings. Since a vast majority of metal-free C-H activation reagents are electrophilic, the most

<sup>98</sup> S. K. Krska et al., *Chem. Soc. Rev.* **2016**, 45, 546-576

electron rich site is usually the one that is first oxidized. For metal-free insertion pathways the reactivity trend is typically: tertiary > secondary > primary > other electron deficient sites (especially the ones closer to heteroatoms).<sup>99</sup> In the presence of electron-withdrawing groups (EWGs) on a substrate, the rate of C-H bond oxidation could be affected. The selectivity of an oxidation reaction can be modulated by both the extent of electron withdrawal and the distance from the EWGs. In addition, factors like steric hindrance, stereoelectronic effects (conjugation, hyperconjugation) and strain release delicately change the inherent preferences of C(sp<sup>2</sup>)-H and C(sp<sup>3</sup>)-H bonds in diverse settings.<sup>100</sup> In the case of certain metal-mediated C-H activations, the reactivity order of oxidation is sometimes reverse of what is seen in metal-free mediated oxidation reactions. In consequence, in this category of reactions, site-selectivity is usually difficult to predict.

Due to the electron deficiency of the amide group, direct oxidation of amide-containing molecules are generally a difficult issue, exhibiting rare selectivities. Proximal oxidation of hyperconjugative unfunctionalized  $\alpha$ -C-H bonds have been widely developed by electrochemical anodic oxidations since 1975, also known as the Shono oxidation.<sup>101</sup> Recently, Maulide and coworkers have successfully developed a transition-metal-free chemoselective method of amides to  $\alpha$ -keto amides and  $\alpha$ -hydroxy amides, using triflic anhydride along with 2,6-lutidine-*N*-oxide (LNO)<sup>102</sup> or TEMPO<sup>103</sup> (Scheme I-13a). This approach was further applied to synthesize a precursor of potent histone deacetylase inhibitor **I-133** by shortening the eight-step synthesis to two synthetic steps. For low reactivity intermediates, direct oxidation of nitrogen occurs instead of the C-H oxidation. Williard observed a *N*-hydroxylation of the terminal nitrogen occurred for Boc-protected peptide methyl esters **I-134**, when using methyl(trifluoromethyl)dioxirane (TFDO) under mild conditions (Scheme I-13b).<sup>104</sup> Besides, this chemoselectivity can be modulated by protecting groups. In the case of acetyl-protected peptides **I-136**, the side chain hydroxylation of tertiary

---

<sup>99</sup> a) M. C. White et al., *Science*, **2007**, 318, 783-787; b) M. C. White, *Science* 2012, 335, 807-809

<sup>100</sup> P. S. Baran et al., *Angew. Chem. Int. Ed.* **2011**, 50, 3362 – 3374

<sup>101</sup> a) A. M. Jones et al., *Beilstein J. Org. Chem.* **2014**, 10, 3056–3072; b) J. Grimshaw, *Electrochemical Reactions and Mechanisms in Organic Chemistry*, Elsevier Science, **2000**, 261-299; c) K. D. Moeller, *Electrochemistry of Nitrogen-containing Compounds*, Wiley-VCH, Verlag GmbH & Co., 2007

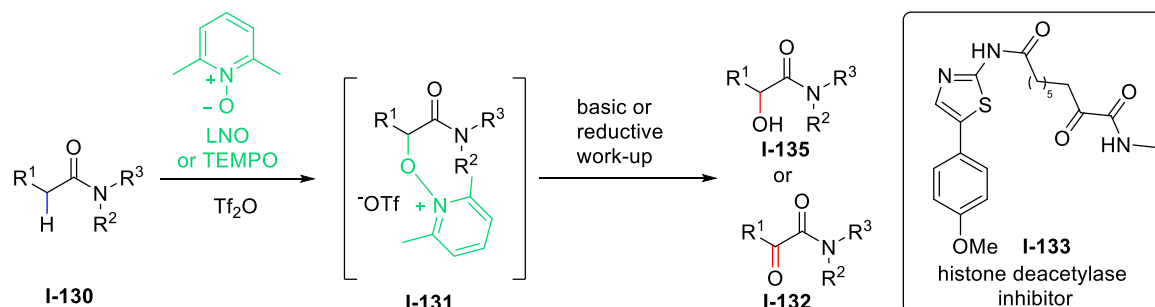
<sup>102</sup> N. Maulide et al., *J. Am. Chem. Soc.*, **2017**, 139 (19), 6578–6581

<sup>103</sup> a) N. Jiao et al., *Angew. Chem. Int. Ed. Engl.* **2017**, 56, 12307-12311; b) P. Somfai et al., *Synlett.* **2016**, 27, 2587–2590

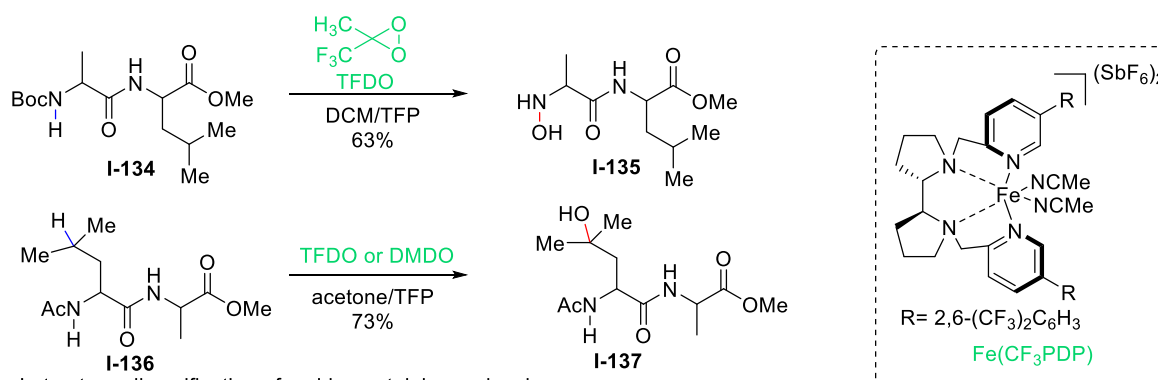
<sup>104</sup> P. G. Williard et al., *J. Org. Chem.* **2007**, 72, 525-531



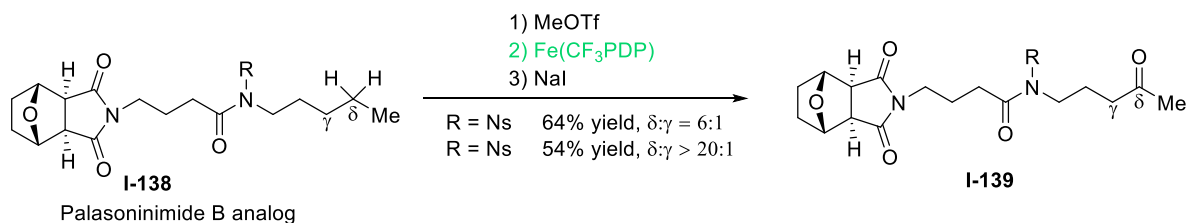
C-H bonds took place, which was also observed by Saladino<sup>105</sup> upon treatment with dimethyldioxirane (DMDO). The late-stage oxidation of bioactive molecules has been remarkably studied by White and co-workers (Scheme I-13c).<sup>106</sup> An elegant example is that they used an imidate salt strategy that promoted site-selectivity for remote  $\delta$ -oxidation in amide-containing molecules **I-138**, by employing electrophilic  $\text{Fe}(\text{CF}_3\text{PDP})$  catalysis.

a.  $\alpha$ -oxidation of amides

## b. Oxidation of peptides by methyl (trifluoromethyl)dioxirane (TFD)



## c. Late-stage diversification of amide-containing molecules



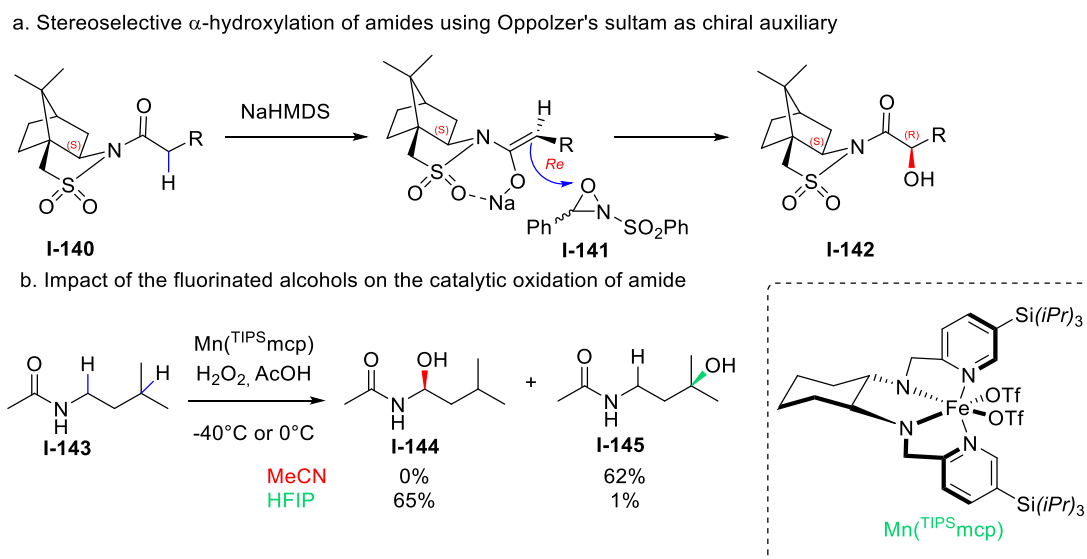
Scheme I-13 Innate C-H oxidations

The second site-selective C-H oxidative method is a directing-group approach where substrates must bear a specific functional group that guides the catalyst to achieve selectivity. Preparative catalysts associated to chiral auxiliaries in C-H hydroxylations have been reported

<sup>105</sup> R. Saladino et al., *J. Org. Chem.* **1999**, 64, 8468-8474

<sup>106</sup> a) M. C. White, T. Nanjo, E. C. de Lucca, *J. Am. Chem. Soc.* **2017**, 139, 14586-14591; b) M. C. White, T. J. Osberger, D. C. Rogness, J. T. Kohrt, A. F. Stepan, *Nature* **2016**, 537, 214-219.

to considerably control the enantioselectivity. For example, Hong developed an Oppolzer sultam-based  $\alpha$ -hydroxylation of amides by using Davis oxaziridine **I-141** to deliver the oxidated products **I-142** in good yield and excellent diastereoselectivity (d.r. > 20:1) (Scheme I-14a).<sup>107</sup>



Scheme I-14 Guided C-H oxidations

Nature uses C–H oxidation methods, frequently mediated by oxygen-activating heme- and non-heme iron enzymes (*e.g.* cytochrome P450), to directly install oxidized functionalities onto the hydrocarbon framework of complex molecules. Several biomimetic complexes with shape or functional group recognition elements that proceed via metalloporphyrin catalysts (Mn, Fe, Ru, Os and Rh porphyrins)<sup>108</sup> or non-heme metal-oxo complexes<sup>109</sup> have also shown impressive site-selectivity for C–H hydroxylations. The specific functionalizations of C–H bonds are achieved via oxygen insertion processes, and regio- and chemo-selectivity can also result from steric interactions. For example, Bietti developed a directed selective hydroxylation of methylenic or remote aliphatic C–H bonds of amide substrates **I-143**, by employing aqueous hydrogen peroxide as the oxidant in the presence of Mn (<sup>TIPSmcp</sup>) (Scheme I-14b). In addition, the selectivity is also tunable by solvents. Fluorinated alcohols like hexafluoro-*iso*-propanol (HFIP) could be engaged in a hydrogen bonding interaction with

<sup>107</sup> R. Hong, L. Zhang, L. Zhu, J. Yang, J. Luo, *J. Org. Chem.* **2016**, *81*, 3890–3900.

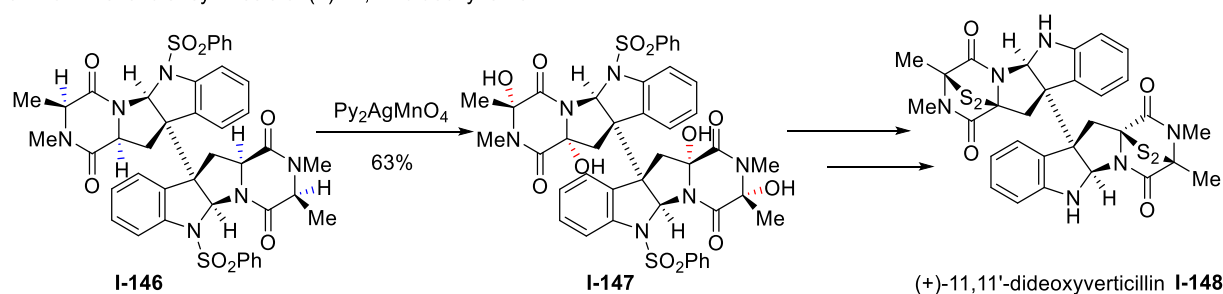
<sup>108</sup> a) J. S. Huang, C. Che, V. K. Lo, C. Y. Zhou, *Chem. Soc. Rev.* **2011**, *40*, 1950–1975; b) H. Liu, X. P. Zhang, *Chem. Soc. Rev.* **2011**, *40*, 1899–1909.

<sup>109</sup> a) K. Ray, X. Engelmann, I. Monte-Pérez, *Angew. Chem. Int. Ed.* **2016**, *55*, 7632–7649; b) R. H. Crabtree, M. Zhou, *Chem. Soc. Rev.* **2011**, *40*, 1875–1884.

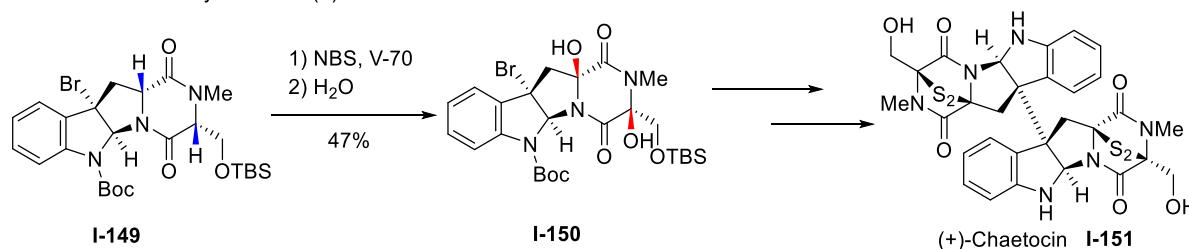
electron rich functional groups, directing iron- and manganese-catalyzed oxidations towards a priori stronger and unactivated C–H bonds.<sup>110</sup>

Having achieved these initial breakthroughs, some oxygen-containing natural products and pharmaceuticals have been synthesized by applying pioneering late-stage oxidations of C–H bonds.<sup>111</sup> The high chemo- and regioselectivities of C–H activation reactions have also inspired attempts to chemically mimic some of biosynthetic hydroxylation processes.<sup>112</sup> For example highly stereo- and chemoselective advanced-stage hydroxylations were achieved by using bis(pyridine)-silver(I) permanganate (Py<sub>2</sub>AgMnO<sub>4</sub>) and NBS initiated by V-70, to synthesize (+)-11,11'-dideoxyverticillin **I-148**<sup>113</sup> and (+)-chaetocin **I-151**<sup>114</sup> successfully (Scheme I-15).

a. Biomimetic total synthesis of (+)-11,11'-dideoxyverticillin



b. Biomimetic total synthesis of (+)-Chaetocin



*Scheme I-15 Total synthesis examples by using late-stage oxidation strategies on heterocyclic compounds*

### 3.3. Biocatalytic functionalization

Although nature is capable to achieve spectacular site selective C–H bond functionalizations,

<sup>110</sup> M. Bietti, V. Dantignana, M. Milan, O. Cussó, A. Company, M. Costas, *ACS Cent. Sci.* **2017**, *3*, 1350–1358.

<sup>111</sup> M. J. Gaunt, L. McMurray, F. O'Hara, *Chem. Soc. Rev.* **2011**, *40*, 1885–1898.

<sup>112</sup> J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009.

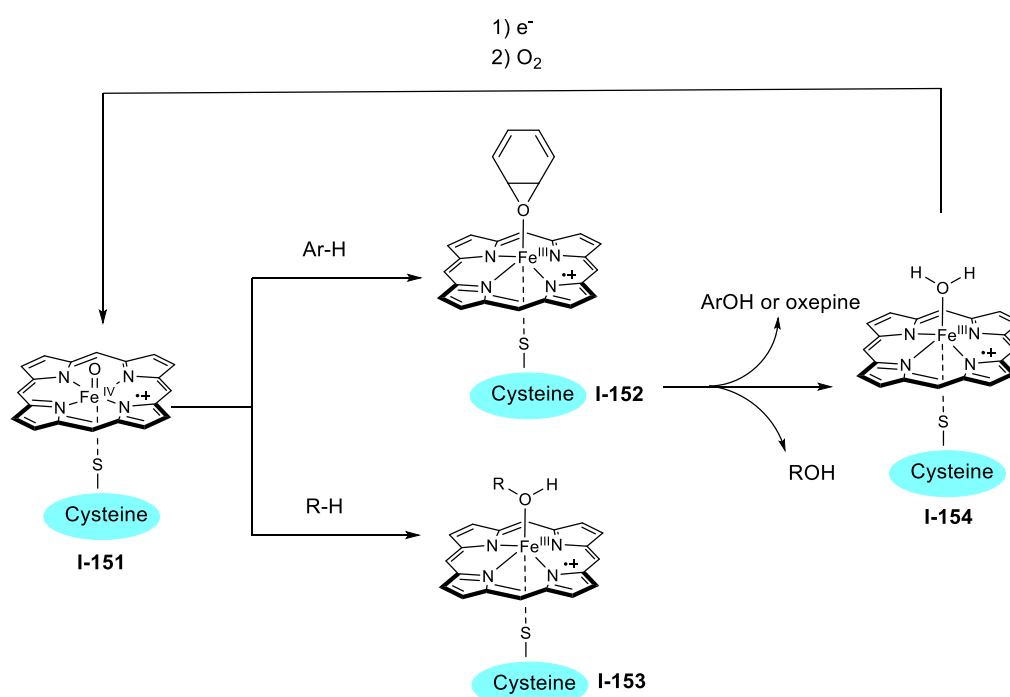
<sup>113</sup> M. Movassaghi, J. Kim, J. A. Ashenurst, *Science* **2009**, *324*, 238–241.

<sup>114</sup> M. Sodeoka, E. Iwasa, Y. Hamashima, S. Fujishiro, E. Higuchi, A. Ito, M. Yoshida, *J. Am. Chem. Soc.* **2010**, *132*, 4078–4079.

current synthetic reactions in the laboratory still hardly succeeds to match this efficiency. However, the direct use of biocatalyzed C–H functionalization as a synthetic tool shows sometimes an awesome potential.<sup>115</sup> Besides, it would be attractive if one could combine the advantages of chemical and microbial reactions in organic synthesis, to broaden the scope of late functionalization strategies.

The use of enzymes or microorganisms for the synthesis of chemical products is referred to as biocatalysis. Nowadays, the biochemical mechanisms of some frequent enzymes, such as oxidoreductases (*e.g.* cytochrome P450), transferases (*e.g.* methyl transferases), hydrolases, isomerases and ligases, have been well studied. The heme-containing enzymes cytochrome P450 are responsible for various aerobic oxidations in biological systems, including highly selective C–H bond functionalization and heteroatom hydroxylation.<sup>116</sup>

Direct hydrogen atom abstraction is usually the main mechanism for aliphatic oxidations, while the aromatic hydroxylation is still not fully understood. It is proposed to proceed via an intermediated arene oxide (Scheme I-16).



Scheme I-16 Proposed mechanism of P450 catalyzed oxidation of aliphatic or aromatic substrates

The formation of oxepin products, valence-tautomers of arene oxides, has been observed from

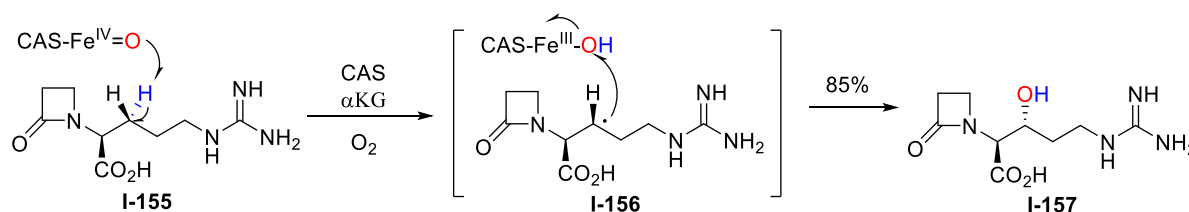
<sup>115</sup> F. H. Arnold, J. C. Lewis, P.S. Coelho, *Chem. Soc. Rev.* **2011**, 40, 2003–2021.

<sup>116</sup> B. Shen, J. D. Rudolf, C. Y. Chang, *Nat. Prod. Rep.* **2017**, 34, 1141–1172.

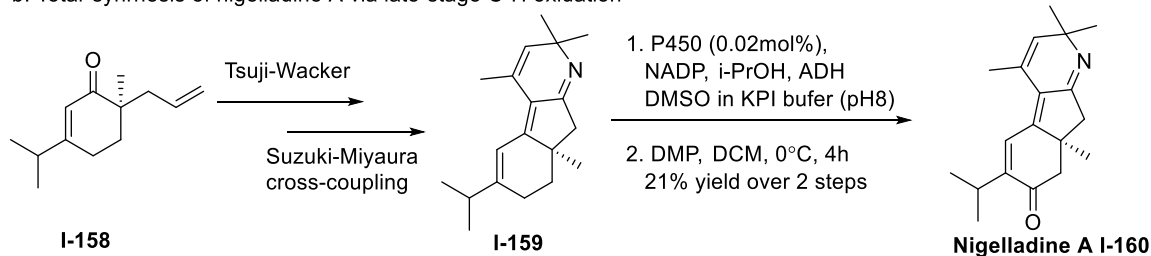
labeling biotransformation experiments of benzene to phenol in cultures of *Phellinus ribis* and *Phellinus pomaceus*.<sup>117</sup> In 2016, De Voss's group reported the detailed P450<sub>cin</sub>- and P450<sub>cam</sub>-mediated oxidations, explaining why oxepines and their derivatives can be more stable than aryl oxides in aqueous solutions.<sup>118</sup> But how biological organisms promote the formation of oxepins over hydroxylation is still worth to be investigated.

Besides, studies on the functionalization of small molecules, the selectivity of biocatalytic processes such as biotransformations, attributed to the high regio- and enantioselectivity of enzymes, could be useful to perform complex transformations under “green” condition (low temperature, low pressure and aqueous reaction).<sup>119</sup> For example, ferrous iron-dependent oxygenase CS2 could specifically mediate  $\beta$ -C–H bond hydroxylation of lactam **I-155**, which is usually inert under traditional synthetic methods (Scheme I-17a).<sup>120</sup> The selective removal of the *pro-R* hydrogen provides a new entry to asymmetric late-stage C–H oxidation.

a. Hydroxylation reaction catalyzed by clavamate synthase (CAS)



b. Total synthesis of nigelladine A via late-stage C–H oxidation



Scheme I-17 Biocatalysts mediated selective C–H oxidation

Some beautiful applications have been achieved in synthesis, demonstrating that the integration of biocatalytic steps in total synthesis can dramatically expand the elegance and efficiency of the strategy. For example, an engineered cytochrome P450 enzyme was

<sup>117</sup> D. B. Harper, D. R. Boyd, N. D. Sharma, J. S. Harrison, J. F. Malone, W. Colin MacRoberts, T. G. Hamilton, *Org. Biomol. Chem.* **2008**, *6*, 1251-1259.

<sup>118</sup> J. E. Stok, S. Chow, E. H. Krenske, C. F. Soto, C. Matyas, R. A. Poirier, C. M. Williams, J. J. De Voss et al., *Chem. Eur. J.* **2016**, *22*, 4408-4412.

<sup>119</sup> G. L. Tang, S. Meng, W. Han, J. Zhao, X. H. Jian, H. X. Pan, *Angew. Chem. Int. Ed. Engl.* **2018**, *57*, 719-723.

<sup>120</sup> C. J. Schnofield, K. H. Baggaley, A. G. Brown, *Nat. Prod. Rep.* **1997**, *14*, 309-333.

employed by Stoltz to regioselectively oxidize precursor **I-159** in a late-stage functionalization step, followed by subjecting the crude product mixture to Dess-Martin periodinane oxidation to achieve the total synthesis of nigelladine A **I-160** (Scheme I-17b).<sup>121</sup>

#### 4. Objectives of the doctoral research

Collective natural product synthetic strategies aim at facilitating the preparation of decent quantities of natural products from a common scaffold. The huge structural diversity of DKP natural products provides perfect opportunities to apply such strategies. The main objective of this doctoral research was to apply the biomimetic and collective approach to design several bio-inspired common intermediates (DKP (**A**), quinazolino-DKP (**B**) and oxepino-DKP (**C**)) at first and subsequently access a wide range of natural products (Figure I-11).

The DKP core **A** is the simplest motif in these families. Direct *O*-alkylation and selective oxidation would allow the total synthesis of all gliocladrin families. The quinazolino-DKP **B** is a tripeptide derivative of DKP core **A**. The post-appendage modification or late-stage oxidation on the DKP pattern could directly diversify scaffold **B**, leading to new collective total syntheses (*e.g.* aurantiomide A, B and C). The advanced scaffold oxepino-DKP **C** is driven biogenetically from intermediate **B**. However, the presence of the oxepine core makes it a challenge to be installed. Meanwhile, because of the presence of this oxepine core, other post-oxidations could be possible and generate more complex natural products (*e.g.* varioxepine A).

During this research project, two different intermediates DKP (**A**) and quinazolino-DKP (**B**) were installed initially, assembled from various amino acids (**Chapter II**). Then the oxepino-DKP (**C**) was attempted to be achieved by chemical and biological oxidation on scaffold **B**. In the meantime, we could have a first insight of the possible transformations of simple precursors **A** and **B** to natural products by late-stage C-H functionalizations. In parallel, we envisaged a synthetic methodology toward 2,5-dihydrooxepine via oxa-Cope rearrangement, which provides an alternative pathway to prepare intermediate **C** (**Chapter III**). All attained results allowed us to build up the final synthetic strategies toward the total synthesis of related natural products: such as gliocladrin A, aurantiomides, cinereain and varioxepine A, and even benzoxepine natural products as a direct application of our oxa-Cope methodology

---

<sup>121</sup> B. M. Stoltz, S. A. Loskot, D. K. Romney, F. H. Arnold, *J. Am. Chem. Soc.* **2017**, *139*, 10196–10199.

(Chapter IV).

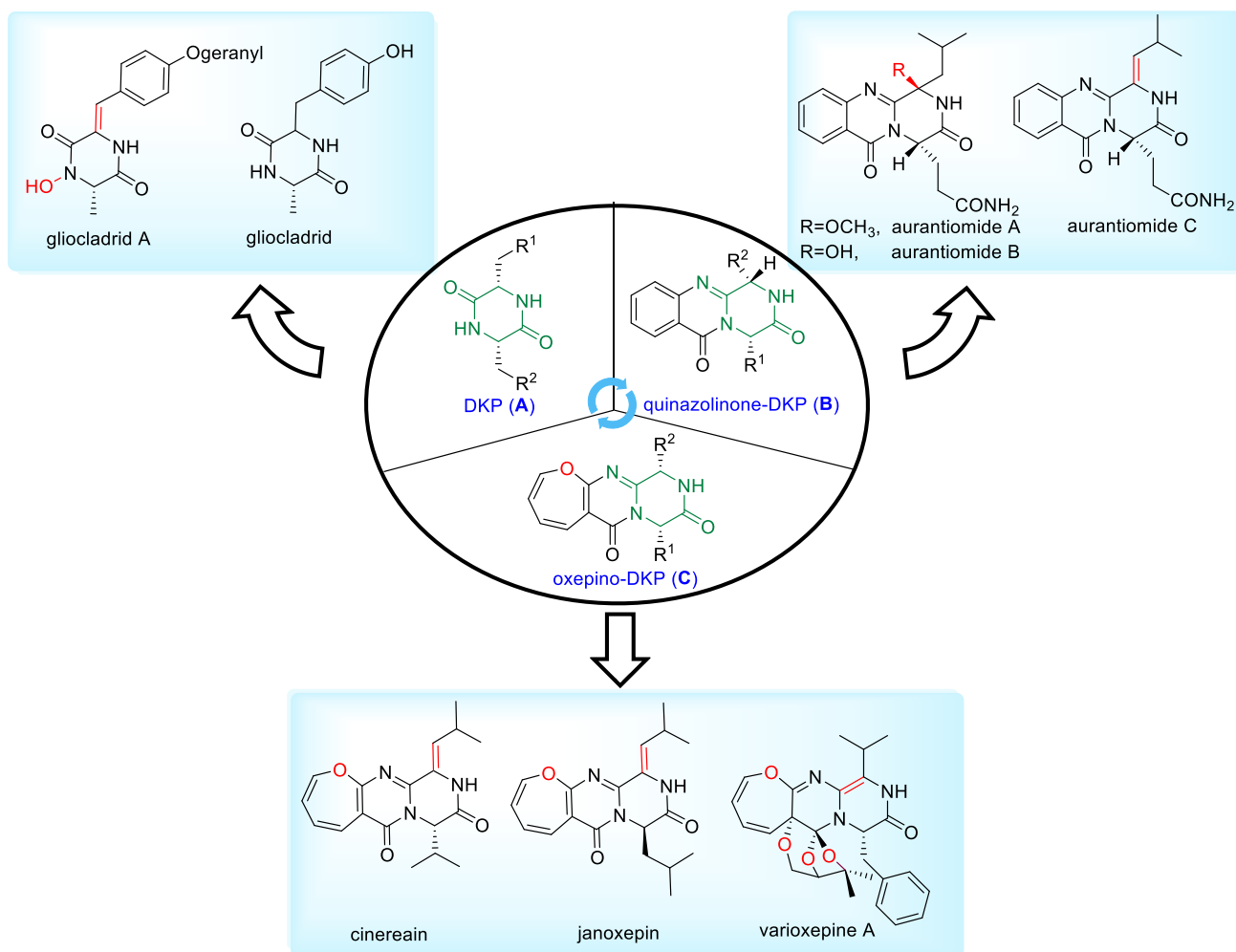


Figure I-11 The aim of the doctoral research

**CHAPTER II. INSTALLATION BIOMIMETIC  
GLIOCLADRIDE AND QUINAZOLINO-DKP SCAFFOLDS  
AND THEIR FUNCTIONALIZATION**

---

“Simple can be harder than complex. You have to work hard to get your  
thinking clean to make it simple.”

--- Steve Jobs

---

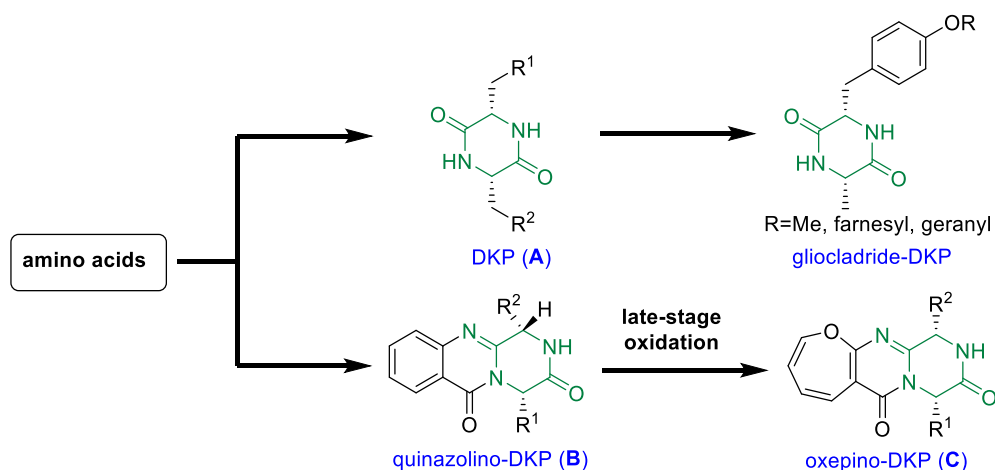




## Chapter II. Installations of Biomimetic Gliocladrine and Quinazolino-DKP Scaffolds and their Functionalizations

### 1. Synthetic works on gliocladrine and quinazolino-DKP scaffolds

The first part of this chapter consists of the synthesis of two biomimetic intermediates: DKP and quinazolino-DKP (Scheme II-1). The gliocladrine DKP analogs were then after synthesized by different substitutions on the phenol. Their synthesis is similar to that supposedly occurring in biosynthetic pathways, and follows prior chemical methods reported in the literature. The third intermediate scaffold oxepino-DKP was supposed to be obtained from late-stage oxidations, which are described in the second part of this chapter.



Scheme II-1 First synthetic goal of the project

#### 1.1. Gliocladrine DKPs

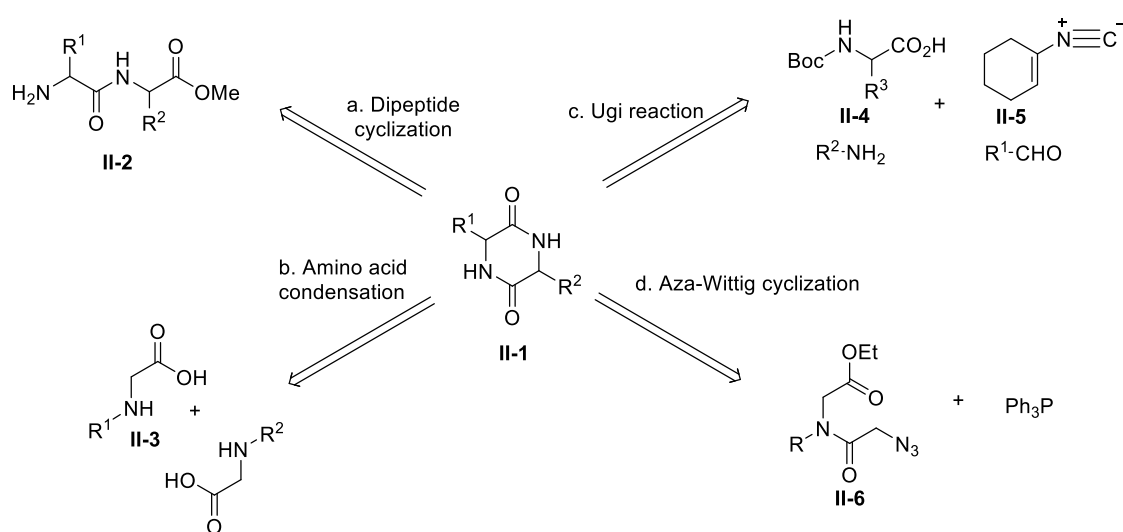
##### 1.1.1. Short literature review on approaches to the DKP motif

The synthesis of 2,5-diketopiperazine core could be achieved via four general pathways: amide bond formation, *N*-alkylation, tandem cyclization and *C*-acylation.<sup>40</sup> Among them, amide bond formation has been mostly applied in total synthesis.

The majority of synthetic methods are based on dipeptides, which are easily prepared from  $\alpha$ -amino acids by appropriate coupling reagents.<sup>122</sup> Dipeptides with an amine at one terminus

<sup>122</sup> a) G. A. Weisenburger, J. R. Dunetz, J. Magano, *Org. Process Res. Dev.* **2016**, *20*, 140–177; b) F. Albericio, A. El-Faham, *Chem. Rev.* **2011**, *111*, 6557–6602; c) T. I. Al-Warhi, H. M. A. Al-Hazimi, A. El-Faham, *Journal of Saudi Chemical Society* **2012**, *16*, 97–116; d) E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606–631.

and an ester at the other can cyclize to form a 2,5-DKP by acid- (e.g. AcOH)<sup>123</sup> or base-catalysis (e.g. Et<sub>3</sub>N, NH<sub>3</sub>)<sup>124</sup> (Scheme II-2a). The rate of cyclization is good only if the amide bonds are in *s-cis*-orientation. For this reason, thermal conditions (e.g. refluxing in toluene/*sec*-BuOH)<sup>125</sup> are sometimes required for sterically-demanding or electronically-disfavored substrates. In the past twenty years, one-pot microwave conditions have become attractive to produce desired 2,5-DKP in short time, independently of the amino acid sequence.<sup>126</sup> These reactions are developed to achieve intramolecular cyclizations or direct intermolecular cyclizations of two amino acids (Scheme II-2b). However, racemization is sometimes observed.



Scheme II-2 Synthetic approaches leading to the DKP core in the literature

Multicomponent reactions like the Ugi reaction is the fastest way to get trisubstituted DKPs, which can bring various substitutions on amino groups (Scheme II-2c).<sup>127</sup> This one-pot reaction can be produced without the use of expensive coupling reagents, but the main disadvantage is that chiral centers are difficult to be controlled.<sup>128</sup> Besides, an intramolecular aza-Wittig reaction followed by hydrolysis has also been used to synthesize the 2,5-DKP core

<sup>123</sup> K. Suzuki, Y. Sasaki, N. Endo, Y. Mihara, *Chem. Pharm. Bull.* **1981**, *29*, 233.

<sup>124</sup> S. J. Danishefsky, K. M. Depew, S. P. Marsden, D. Zatorska, A. Zatorski, W. G. Bornmann, *J. Am. Chem. Soc.* **1999**, *121*, 11953–11963.

<sup>125</sup> R. W. Woodard, *J. Org. Chem.* **1985**, *50*, 4796.

<sup>126</sup> M. Tullberg, M. Grøtli, K. Luthman, *Tetrahedron* **2006**, *62*, 7484–7491.

<sup>127</sup> R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, *29*, 123–131.

<sup>128</sup> I. Carvalho, M. B. Martins, *Tetrahedron* **2007**, *63*, 9923–9932.

(Scheme II-2d).<sup>129</sup> Total syntheses involving aza-Wittig as a key step usually require significant protecting group manipulation, and so less applications have been developed.

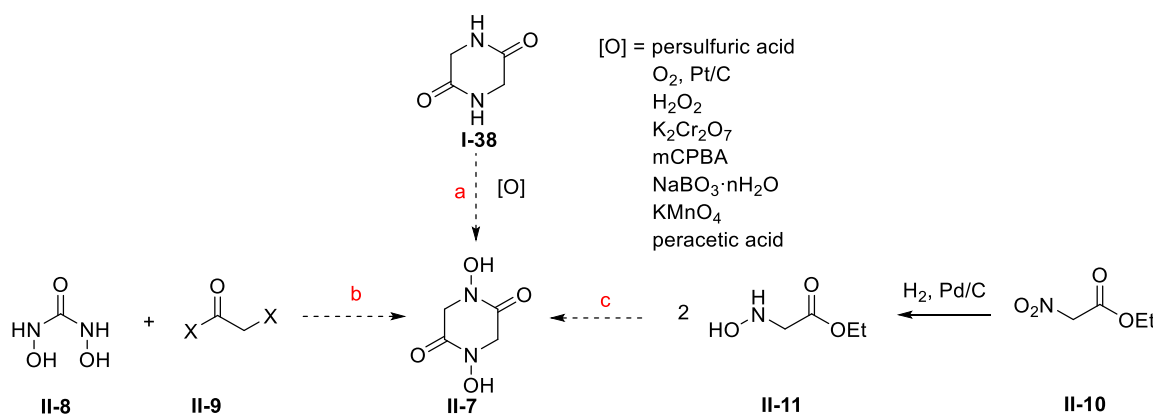
### 1.1.2. Short literature review on approaches to the total synthesis of gliocladrine-DKP alkaloids

As the only known example of hydroxamic DKP, the total synthesis of mycelianamide **I-43** (double oxidative form of gliocladrine-DKP) has attracted lots of attention since 1963. Brantley attempted three different approaches to synthesize the 1,4-dihydroxy-2,5-diketopiperazine core, yet without success (Scheme II-3):<sup>130</sup>

a) direct oxidation of 2,5-DKP **I-38**;

b) condensation methods utilizing hydroxylamine **II-8** and  $\alpha$ -halo acid halides **II-9**;

c) reduction of nitroesters **II-10** to  $\alpha$ -hydroxylamino esters **II-11** and subsequent bimolecular condensation of these compounds. None of these approaches was successful to provide **II-7**.



Scheme II-3 Synthetic approaches of 1,4-dihydroxy-2,5-diketopiperazine by Brantley

However, after his huge synthetic studies, Brantley accomplished the first total synthesis of deoxymycolianamide **I-44** by Knoevenagel condensation of *p*-hydroxybenzaldehyde **II-14** and diketopiperazine **II-13** (Scheme II-4a). Inspired by approach c (Scheme II-3c), the first total synthesis of mycelianamide **I-43** was achieved in 1980 by the condensation of hydroxylamino ester **II-16** with free hydroxylamine in methanol (Scheme II-4b).<sup>131</sup> The saturated form like phomamide **I-46** was synthesized in 2014 by direct cyclization of

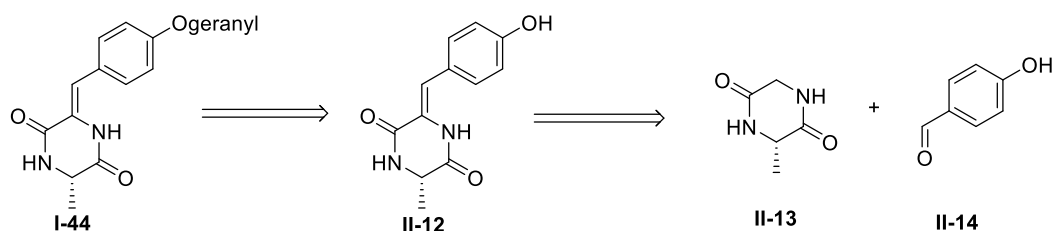
<sup>129</sup> K. C. Majumdar, K. Ray, S. Ganai, *Synlett*. **2010**, 14, 2122-2124.

<sup>130</sup> R. K. Brantley, "The synthesis related to mycelianamide", Ph.D. thesis, Georgia Institute of Technology, **1963**.

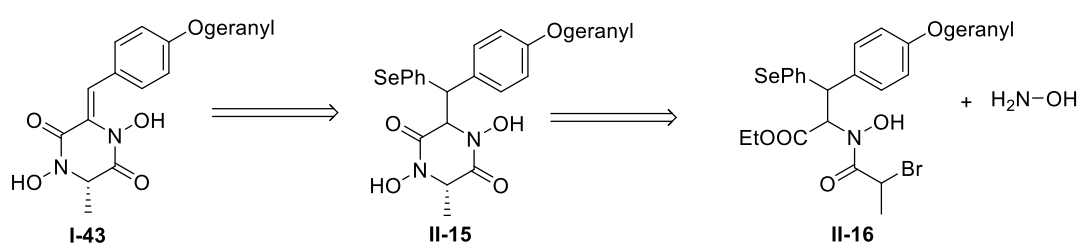
<sup>131</sup> M. P. Cava, N. Shinmon, R. F. C. Brown, *J.C.S. Chem. Commun.* **1980**, 1020-1021.

substituted dipeptide **II-18** (Scheme II-4c).<sup>62</sup> Although the gliocladrone natural products have a relatively simple structure, their synthesis still remains problematic due to their high density of functionalities. During our project, our aim was to find alternative divergent synthetic strategies, making use of biomimetic approaches and late-stage oxidations.

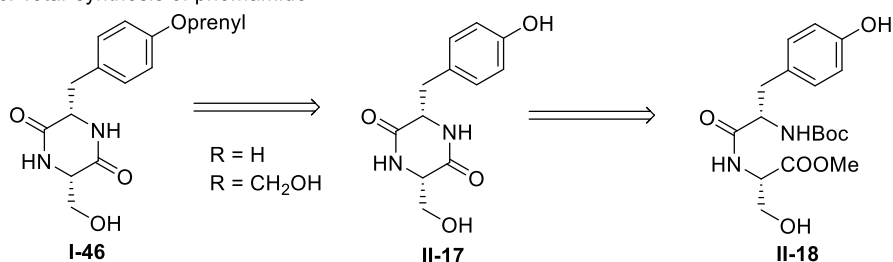
a. Total synthesis of (±)- deoxymycelianamide



b. Total synthesis of (±)- mycelianamide



c. Total synthesis of phomamide



Scheme II-4 Total synthesis of gliocladrone-DKPs in literature

### 1.1.3. Synthesis of the gliocladrone DKP scaffold

Cyclizations of the corresponding linear dipeptides were envisaged to make this scaffold. In general, the formation of a peptide bond in solution needs the interaction between two amino acids properly protected and activated at their *N*- or *C*-termini, which define a correct coupling direction. The process of amino acid coupling can be performed through the use of various families of coupling reagents such as EDC, CDI, BOP, DEPBT, HBTU, CDMT and EEDQ (Figure II-1).<sup>122</sup> Sometimes, undesired racemization can occur at the *C*-terminal amino acid residue in the course of a coupling reaction. In that case, 1-hydroxybenzotriazole (HOBT) or *N*-hydroxysuccinimide (HOSu) can be used as racemization suppressants to minimize this side reaction or even eliminate it completely.

As the DKP core of the gliocladrine family is made of L-tyrosine and L-alanine, the synthesis began with a coupling reaction between L-Boc-tyrosine (or *O*-alkyl protected L-Boc-tyrosine) and L-alanine methyl ester. Two different retrosynthetic routes are resumed below, depending on the stage of phenol alkylation (Scheme II-5). From a synthetic perspective, pathway **a** is biomimetic.

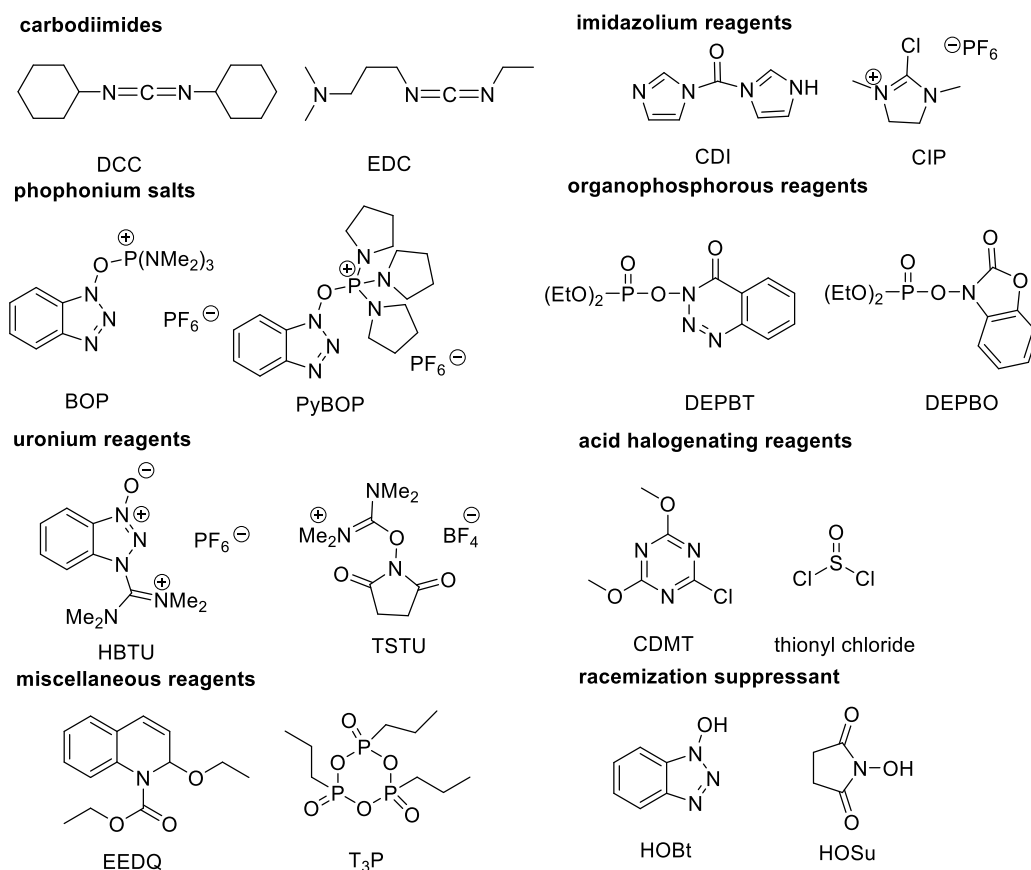
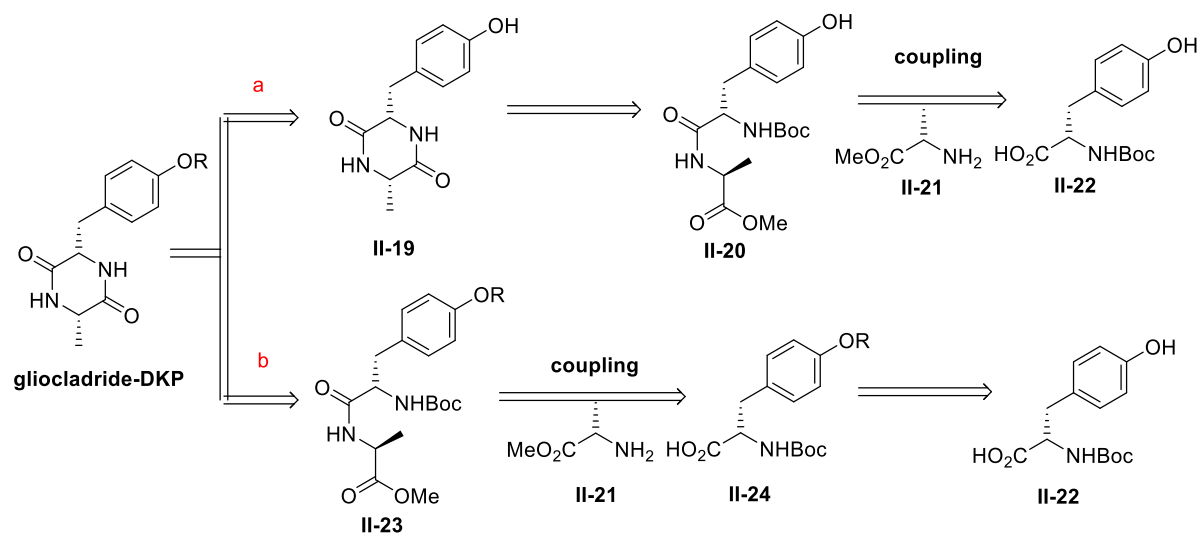


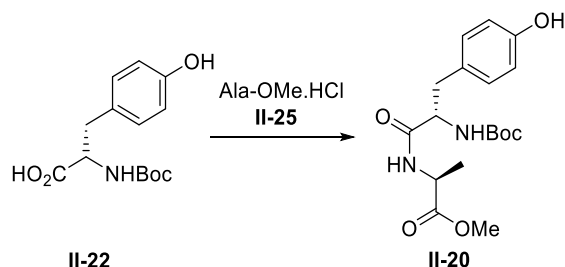
Figure II-1 Some examples of coupling reagents and racemization suppressants



Scheme II-5 Retrosynthetic strategies for gliocladrine DKP scaffold synthesis

Several coupling reagents were tested at first. The combination of HBTU and HOBt gave the best yield for reactions of free phenol derivative **II-21** (Table II-1, entry 5).

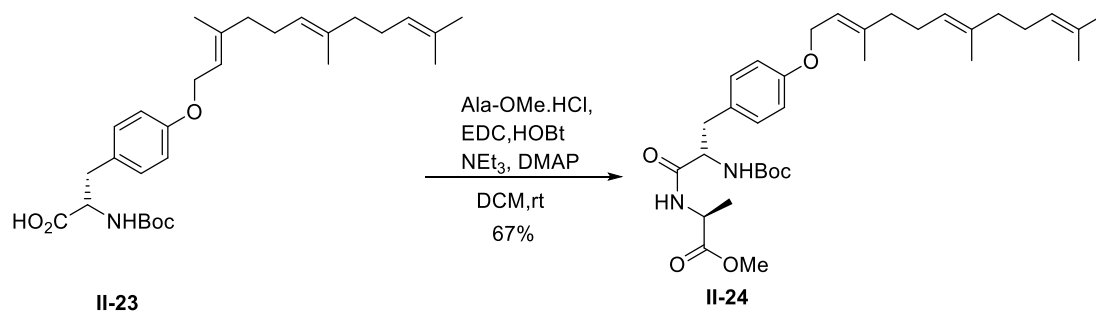
Table II-1 Screening of coupling conditions



Entry	Conditions	Results
1	EDC, HOBt, Et <sub>3</sub> N, DMF, rt, 2days	<b>II-20</b> (trace)
2	BOP, Et <sub>3</sub> N, DMF, 0°C, rt, 18h	NR
3 <sup>132</sup>	CuBr/HOBt (10%), DCM, rt, 24h <sup>a</sup>	<b>II-20</b> (21%)
4	HBTU, Et <sub>3</sub> N, DMF, rt, 2h	<b>II-20</b> (78%)
5	HBTU, HOBt, Et <sub>3</sub> N, DMF, rt, 2h	<b>II-20</b> (97%)

a: reagent was imidazole-Ala-OMe instead of Ala-OMe.HCl

In order to facilitate the purification, farnesylation of phenol was first tested for pathway **b**. As farnesylated substrate **II-23** successfully reacted in the presence of EDC and HOBt (Scheme II-6), the nucleophilic reactivity of the free phenol may be the main cause of the decrease of the yield when using other coupling reagents than HBTU in the case of Boc-tyrosine **II-22**.



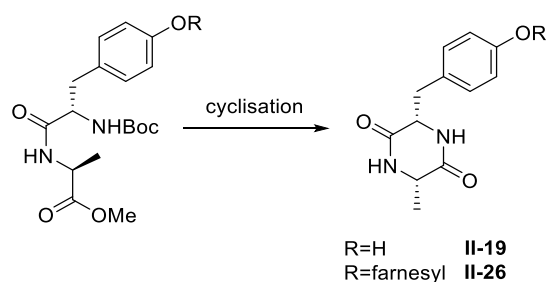
Scheme II-6 Substituted dipeptide synthesis

The dipeptide cyclization was carried out under three different conditions: base-catalyzed, thermal heating and microwave conditions. The microwave-assisted heating for 5 min in

<sup>132</sup> J. Suppo, G. Subra, M. Bergs, R. M. de Figueiredo, J. M. Campagne, *Angew. Chem. Int. Ed.* **2014**, *53*, 1–6.

water was the most efficient method, causing *N*-Boc deprotection and cyclization at the same time and yielding 98% of 2,5-DKPs (Table II-2, entry 4). However, 5% epimerization was observed according to NMR. Because of the difficult separation of the two diastereoisomers, the base-catalyzed condition (Table II-2, entry 1) was used in the synthesis of **II-19**. For farnesylated dipeptide **II-24** (entry 5), only degradation was observed upon cyclisation attempts, which may be explained by the weak stability or high reactivity of the farnesyl group under these harsh conditions.

Table II-2 Screening of conditions for dipeptide cyclization



Entry	Conditions	Results
1	TFA, DCM, rt; NH <sub>4</sub> OH, MeOH, rt, 16h	<b>II-19</b> (85%)
2	TFA, DCM, rt; toluene/ <i>sec</i> -BuOH, reflux, 16h <sup>133</sup>	<b>II-19</b> (71%)
3	TFA, DCM, rt; toluene, reflux	<b>II-19</b> (65%)
4	Microwave, 200°C, H <sub>2</sub> O, 5 min <sup>134</sup>	<b>II-19</b> (98%, d.r. 95:5)
5	Microwave, 200°C, H <sub>2</sub> O, 5 min	degradation

The *O*-alkylation of DKP **II-19** was then performed under classical Williamson S<sub>N</sub>2 conditions by using sodium hydride or Cs<sub>2</sub>CO<sub>3</sub> in DMF. The use of a carbonate as a base minimized the competition with *N*-alkylation or alkylation of the α-C-H position of the amide, yielding moderate yield (Table-II-3, entry 2). The conversion of farnesyl bromide into an iodide entailed by TBAI improved the yield to 52% (entry 3). The yield decreased when it was performed in DMSO at 60°C, but only *O*-farnesylated product **II-26** was obtained (entry 4). No better yields could be achieved when using a trichloroacetimidate alkylating agent under acidic condition or the Tsuji-Trost reaction.

<sup>133</sup> J. Aubé, Y. Zeng, Q. Li, R. P. Hanzlik, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3034-3038.

<sup>134</sup> M. Y. Rios, L. Pérez-Picasso, J. Escalante, H. F. Olivo, *Molecules* **2009**, *14*, 2836-2849.



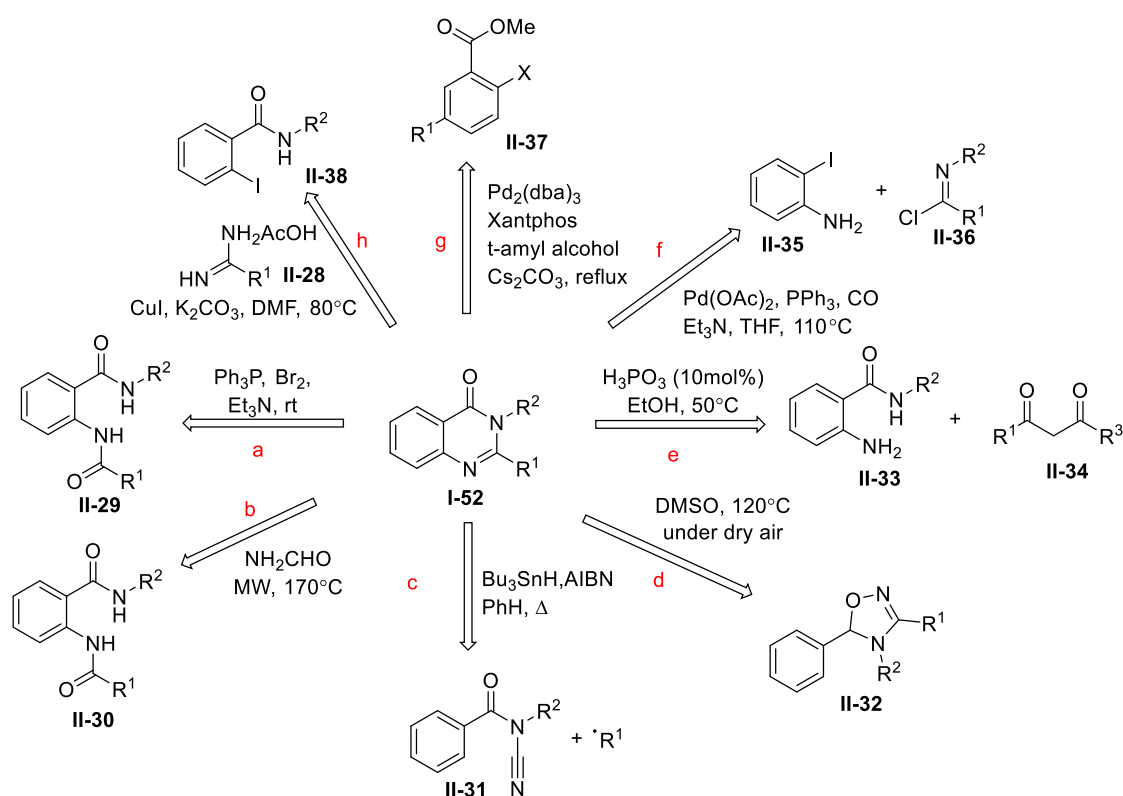


this farnesylated compound, it may indicate that the efficiency is not only controlled by the length of terpenoid chain.

## 1.2. Synthesis of quinazolino-DKP intermediates

### 1.2.1. Literature review on approaches to the 2,3-disubstituted quinazolinone motif and some examples of total syntheses of quinazolino-DKP alkaloids

A number of synthetic approaches have been developed to construct the 2,3-disubstituted quinazolinone core, such as condensations (a, b, e), radical cyclization (c<sup>135</sup>, d) and transition-metal-catalyzed C-N bond formation (f-h) (Scheme II-8).<sup>65</sup> These methods were further developed to make quinazolinones fused with a DKP core and applied to total syntheses with varying degrees of success.



Scheme II-8 Synthetic approaches to construct the 2,3-disubstituted quinazolinone core

The 2,3-disubstituted quinazolinone system is the key structural fragment of quinazolino-DKP

<sup>135</sup> M. Larraufie, C. Courillon, C. Ollivier, E. Lacôte, M. Malacria, L. Fensterbank, *J. Am. Chem. Soc.* **2010**, *132*, 4381-4387; b) M. Larraufie, C. Ollivier, E. Lacôte, M. Malacria, L. Fensterbank, *Angew. Chem.* **2010**, *122*, 2224-2227.

alkaloids. The total synthesis of the simplest members, such as gyantrypine, (-)-fumiquinazoline G and (-)-fiscalin B, resulting from double cyclodehydration of linear tripeptides, have been largely studied for decades (Scheme II-9).<sup>136</sup> As the majority of synthetic methods developed are substrate-dependent, the most universal and straightforward route to synthesize these 2,3-disubstituted quinazolinones is still to use the intramolecular dehydrative cyclization of suitably substituted diamides. The direct double condensation attempts of diamides were achieved by exploring the peptide assembly on Sasrin® resin, which afforded anacine, verrucine A and verrucine B with a low yield.<sup>137</sup>

Snider's synthesized (-)-fumiquinazoline G by using an intramolecular aza-Wittig annulation developed by Eguchi<sup>138</sup>. The transformation of quinazoline-4-one **II-39** to an amide was initiated by the deprotection of the dimethoxybenzyl group (Scheme II-9a).<sup>139</sup> As requiring many judicious manipulations of protecting groups, the application of this method was not expanded to other quinazolinone-DKPs.

The cyclodehydration of *N*-acylanthranilamides **II-42** to iminobenzoxazines **II-43** has also been a frequent approach for the synthesis of quinazolino-DKPs by employing Ph<sub>3</sub>P/Br<sub>2</sub>/Et<sub>3</sub>N conditions developed by Mazurkiewicz,<sup>140</sup> or HMDS/I<sub>2</sub> developed by Argade<sup>141</sup> through dehydration of β-keto amides to oxazine (Scheme II-9b). After removal of Fmoc group with piperidine, the oxazine-quinazoline rearrangement was mediated by silica or refluxing conditions and ended with an intramolecular cyclization to get the DKP core. This approach was then successfully applied to the synthesis of (-)-fumiquinazoline G and (-)-fiscalin B,<sup>142</sup> but failed for fumiquinazoline F and *ent*-alantrypinone.<sup>143</sup> This work demonstrates that this method is sensitive to steric hindrance and not applicable to highly functionalized quinazolinones.

Liu developed a microwave-promoted, three-component, one-pot reaction to provide access to the quinazolino-DKP core (Scheme II-9c).<sup>144</sup> By starting with different Boc-amino acids **II-46**

---

<sup>136</sup> C. Avendano and J. C. Menendez, *Current Organic Chemistry* **2003**, 7, 149-173.

<sup>137</sup> H. Wang, M. M. Sim, *J. Nat. Prod.* **2001**, 64, 1497-1501.

<sup>138</sup> S. Eguchi, H. Takeuchi, S. Hagiwara, *Tetrahedron* **1989**, 45, 6375-6386.

<sup>139</sup> B. B. Snider, F. He, *Synlett* **1997**, 483-484.

<sup>140</sup> a) R. Mazurkiewicz, *Chem.* **1989**, 120, 973-980; b) P. Wipf, C. P. Miller, *J. Org. Chem.* **1993**, 58, 3604-3606.

<sup>141</sup> N. P. Argade, U. A. Kshirsagar, S. B. Mhaske, *Tetrahedron Lett* **2007**, 48, 3243-3246.

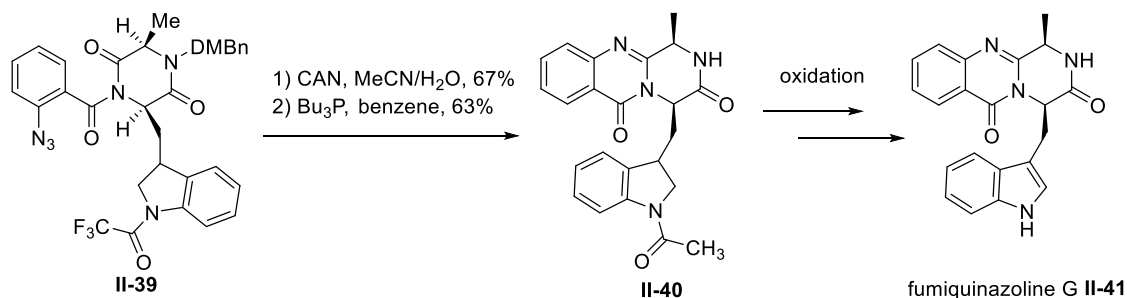
<sup>142</sup> A. Ganesan, H. Wang, *J. Org. Chem.* **1998**, 63, 2432-2433.

<sup>143</sup> N. A. Magomedov, D. J. Hart, *J. Am. Chem. Soc.* **2001**, 123, 5892-5899.

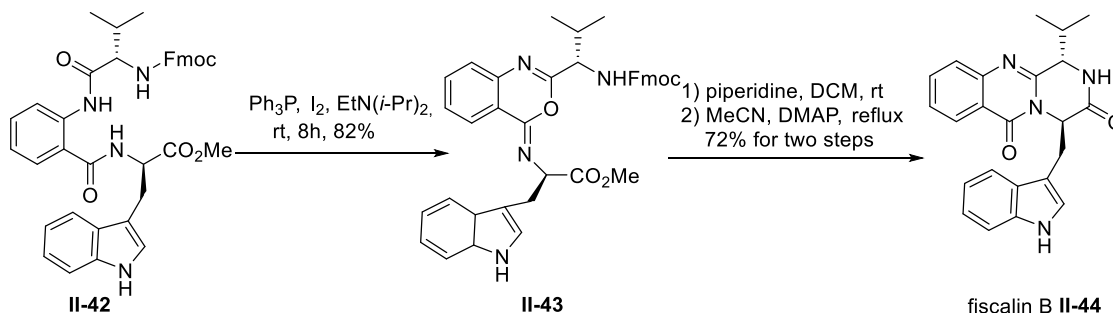
<sup>144</sup> J. F. Liu, B. Zhang, G. Bi, K. Sargent, L. Yu, D. Yohannes, C. M. Baldino, *J. Org. Chem.* **2005**, 70, 6339-

and amino acid esters **II-47**, he accomplished the total syntheses of gyantrypine, fumiquinazoline F and fiscalin B with overall yields 55%, 39% and 20% respectively.

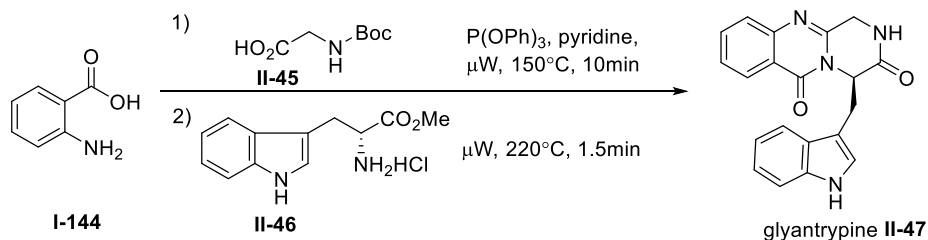
a. Total synthesis of (+)-fumiquinazoline by aza-Wittig approach



b. Total synthesis of fiscalin B through dehydrative oxazine to quinazoline route



c. Total synthesis of gyantrypine by microwave irradiation approach



Scheme II-9 Examples of total synthesis of quinazolinone-DKPs

Based on these first stage quinazolino-DKP core synthesis, the total synthesis of spiroquinazolinones (±)-lapatin,<sup>145</sup> (±)-alantrypinone,<sup>146</sup> (-)-serantrypinone<sup>147</sup> were achieved by combining aza-Diels-Alder or oxidative cyclizations. However, the synthesis of quinazolino-DKPs with unsaturated appendages has not been yet reported.

6345.

<sup>145</sup> K. N. Houk, D. Leca, F. Gaggini, J. Cassayre, O. Loiseleur, S. N. Pieniazek, J. A. R. Luft, *J. Org. Chem.* **2007**, *72*, 4284-4287.

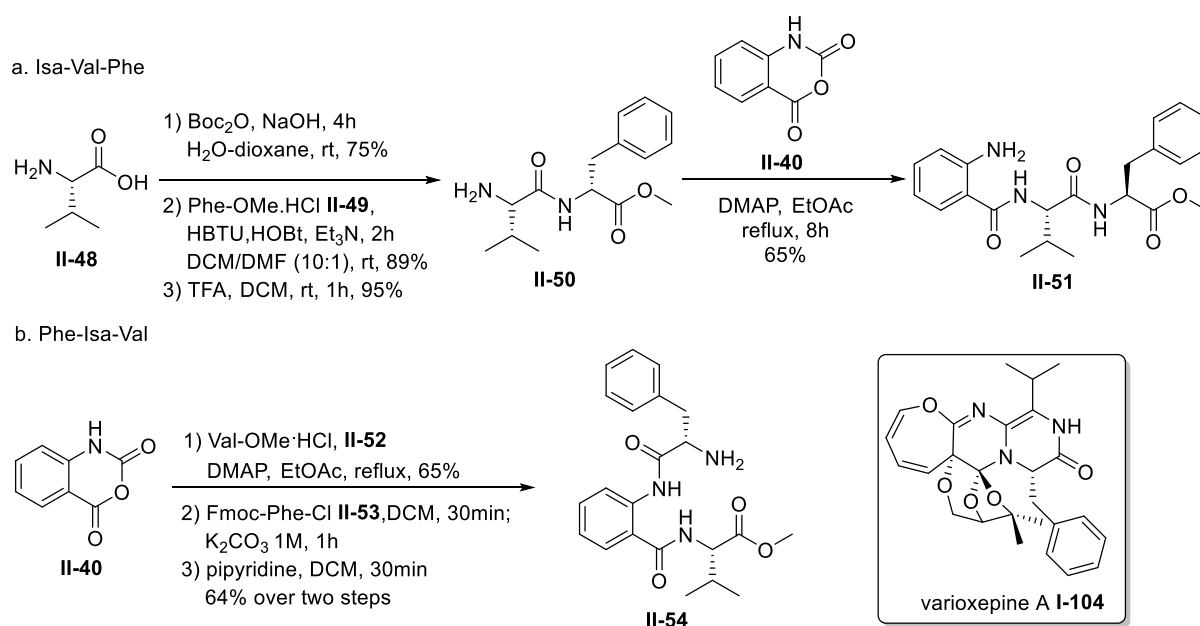
<sup>146</sup> A. S. Kende, J. Fan, Z. Chen, *Org. Lett.* **2003**, *5*, 3205-3208.

<sup>147</sup> D. J. Hart, G. Oba, *Tetrahedron Lett.* **2007**, *48*, 7069-7071.

## 1.2.2. Biomimetic synthesis of the quinazolino-DKP scaffold

From a structural perspective, the first design of our quinazolino-DKP intermediate was based on a linear assemblage of three amino acids: anthranilic acid **I-114**, valine and phenylalanine, which allowed getting biomimetic precursors (**II-51** and **II-54**) of varioxepine A. The 3,6,8-trioxabicyclo[3.2.1]octane motif contained in the varioxepine A is indeed more attractive and challenging for late-stage functionalization studies.

Two different assemblages of tripeptides Isa-Val-Phe or Phe-Isa-Val were initially prepared from isatoic anhydride **II-52** (Isa) by standard methods, as shown in Scheme II-10.



Scheme II-10 Synthesis of two different tripeptide assemblages: Isa-Val-Phe or Phe-Isa-Val

Isa-Val-Phe **II-51** was synthesized by a sequence of peptide coupling reactions mediated by HBTU, HOBt and DMAP. The synthesis of dipeptide **II-54** began with the acylation of isatoic anhydride with valine methyl ester, followed by a coupling reaction with Fmoc-Phe acyl chloride under Schotten-Baumann conditions. The Fmoc-Phe acyl chloride **II-53** had previously been prepared from Fmoc-Phe in the presence of thionyl chloride according to Carpino's protocol.<sup>148</sup> Dipeptides **II-51** and **II-54** were obtained successfully with an overall yield of 41% for both of them.

Unfortunately, the classical acid- or base-catalyzed conditions and microwave conditions did

<sup>148</sup> L. A. Carpino, J. R. Williams, *J. Org. Chem.* **1979**, *44*, 1175-1177.

not lead to the expected double cyclodehydration of the two tripeptides (Table II-4). It could be found from the literature that, for a sequence containing an isatoic acid moiety at the *N*-terminus (like **II-51**), the only successful cyclization cases also incorporated a proline residue.<sup>149</sup> This may indicate that the structural pre-organization of the linear tripeptide imposed by proline would help achieving the double cyclization, explaining why it failed in our case.

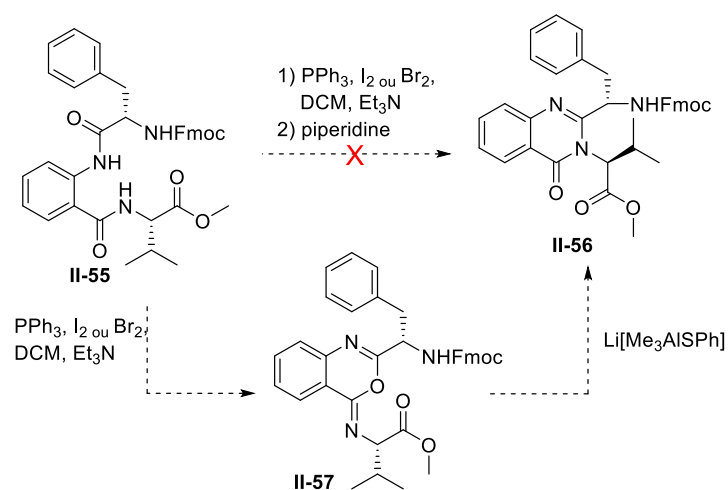
Table II-4 Acid- or base catalyzed cyclization conditions for the two assemblages

Entry	Conditions	Results
1	Sc(OTf) <sub>3</sub> , DMF, 140°C, 48h <sup>150</sup>	NR
2	Sc(OTf) <sub>3</sub> , DMF, 160°C, 24h	degradation
3	Zn(OTf) <sub>2</sub> , DMF, 140°C, 48h	NR
4	Zn(OTf) <sub>2</sub> , 140°C DMF, 160°C, 24h	NR
5	acetic acid (cat.), dioxane, rt, 24h	NR
6	NaHCO <sub>3</sub> , Dioxane, rt, 24h	NR
7	DMAP, MeCN, microwave, 200°C, 5min	epimerization

Compound **II-55** was then submitted to alternative cyclization conditions by using PPh<sub>3</sub>/I<sub>2</sub> or Br<sub>2</sub>, inspired by Ganesan's and Magomedov's approaches. Various bases like Et<sub>3</sub>N or DIPEA and heating reactions were tested, no intermediate oxazine **II-57** or pyrimidinone **II-56** could be identified.

<sup>149</sup> P. Cledera. Ph. D. Thesis, Universidad Complutense, **2002**.

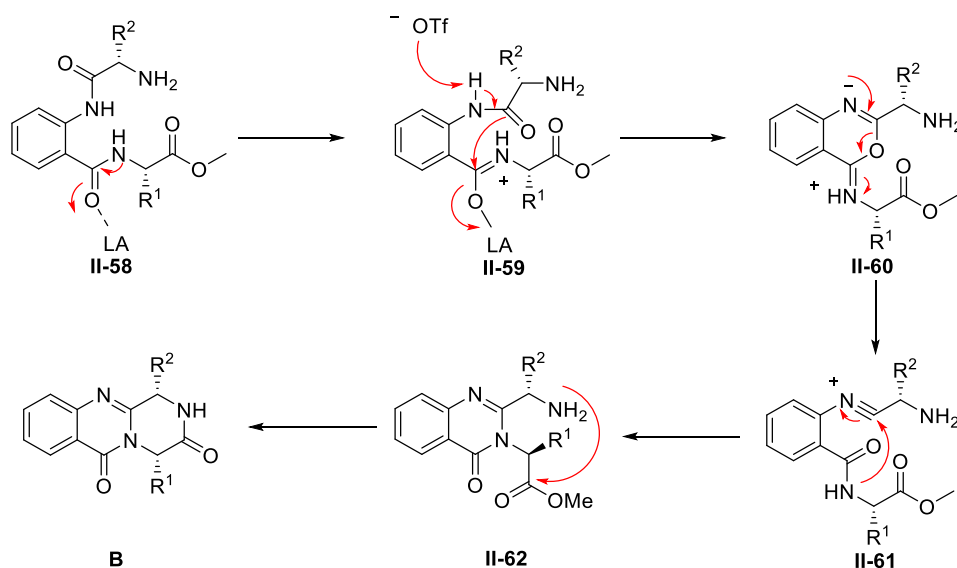
<sup>150</sup> Y. H Chu, M. C. Tseng, H. Y. Yang, *Org. Biomol. Chem.* **2010**, *8*, 419-427.



Scheme II-11 Dipeptide cyclization by using Ganesan's approach

Despite the unsuccessful outcome of metal triflate-catalyzed cyclodehydrations with our substrates (Table II-5), such methods have been successfully used to synthesize several other pyrazino[2,1-b]quinazolin-3,6-diones on solid support (Wang resin).<sup>151</sup> Therefore, we decided to synthesize alternative analogs of **II-54** by using the same synthetic route, starting from various combinations of amino acids (similar as Scheme II-10b, global yields in Table II-5), and tested their cyclization under microwave conditions in the presence of zinc or scandium triflate. To our delight, four out of five linear tripeptide precursors were cyclized in these conditions at 140°C, but with low yields compared to solid-phase peptide synthesis. The mechanism of the Lewis acid catalyzed double cyclodehydration is proposed below (Scheme II-12). Coordination between the metal triflate and the carbonyl group of anthranilate **II-58** would lead to the first dehydration and afford a benzoxazine structure **II-60**. Then, an intramolecular rearrangement of the oxazine cycle would result in an amidine intermediate **II-62**, followed by final amide formation to close the DKP ring, and afford the quinazolino-DKP **B** as final product.<sup>151</sup>

<sup>151</sup> Y. H. Chu, M. C. Tseng, *Tetrahedron* **2008**, *64*, 9515-9520.



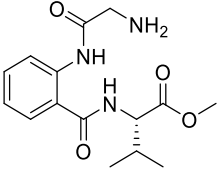
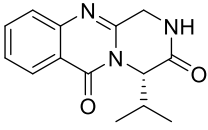
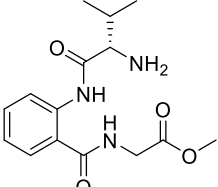
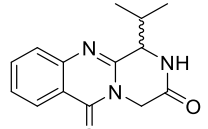
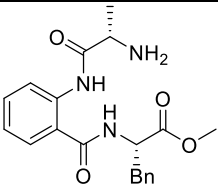
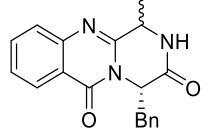
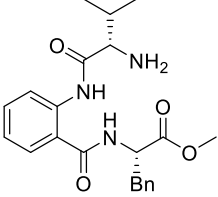
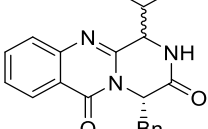
Scheme II-12 Mechanism of metal triflate-catalyzed cyclodehydration

Reactions were optimized in sealed tubes and results are listed below. Between the two metal triflates,  $\text{Sc}(\text{OTf})_3$  and  $\text{Zn}(\text{OTf})_2$ , zinc triflate was established to be the most effective catalyst to make the double cyclodehydration (Table II-5). Increasing the Lewis acid loading or reaction concentration lowered yields. Besides, for cyclotripeptides containing two chiral centers, like **II-70** and **II-71**, two diastereoisomers were isolated in each case in favor of the *trans* isomer. As triflic acid is produced as a by-product of the cyclization, it is suspected to cause the epimerization at stereogenic center C1.<sup>137</sup>

Table II-5 Substrate screening under  $\text{Zn}(\text{OTf})_2$  and  $\text{Sc}(\text{OTf})_3$  catalyzed conditions (\* Lewis acid (1 equiv.), conc. 0.03M, DMF, sealed tube, 140 °C)

Tripeptide precursors (overall yield of their synthesis)	Quinazoline-DKP products	Yields according to both catalysts ( <i>cis/trans</i> ratio)*	
		$\text{Sc}(\text{OTf})_3$	$\text{Zn}(\text{OTf})_2$
 <b>II-54</b> (41%)	 <b>II-67</b>	NR	NR

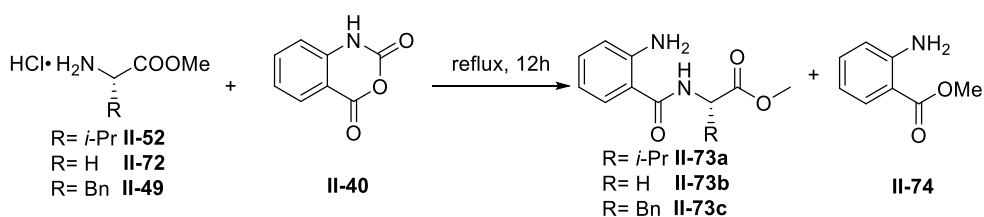


 <p><b>II-63</b> (38%)</p>	 <p><b>II-68</b></p>	30%	56%
 <p><b>II-64</b> (80%)</p>	 <p><b>II-69</b></p>	26%	36%
 <p><b>II-65</b> (17%)</p>	 <p><b>II-70</b></p>	22% (36/64)	32% (38/62)
 <p><b>II-66</b> (33%)</p>	 <p><b>II-71</b></p>	17% (42/58)	25% (39/61)

Aiming at getting rapidly an intermediate for late-stage functionalization studies, we decided to use the combination of valine and glycine (**II-68** and **II-69**) as oxidation models. The optimization of their synthesis was thus investigated before larger-scale productions.

The first step of linear tripeptide synthesis consists in a direct coupling of isatoic anhydride with the amino acid methyl ester, under base-catalyzed conditions. The optimization of this step was based on solvent and base screening under reflux condition (Table II-6). The methanolysis of isatoic anhydride observed in entry 4 indicated that the reaction is sensible to protic solvents, which led us to use distilled ethyl acetate to get a better yield for valine coupling in the presence of DMAP. Of three amino acids tested —valine, glycine and phenylalanine— the less sterically hindered coupling partner (glycine) gave the best yield (91%), leading us to choose compound **II-69** as final synthetic intermediate.

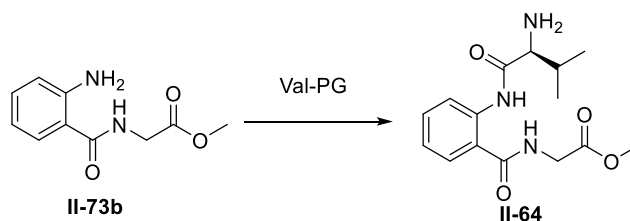
Table II-6 Optimization of the coupling reaction between isatoic anhydride and amino acid methylester



Entry	R	Solvent	Base (1.1 equiv.)	Results (yields)
1	<i>i</i> -Pr	EtOAc	no base	NR
2	<i>i</i> -Pr	EtOAc	Et <sub>3</sub> N	<b>II-73a</b> (21%)
3	<i>i</i> -Pr	distilled EtOAc	Et <sub>3</sub> N	<b>II-73a</b> (59%)
4	<i>i</i> -Pr	MeOH	Et <sub>3</sub> N	<b>II-73a</b> (14%) <b>II-74a</b> (49%)
5	<i>i</i> -Pr	MeCN	Et <sub>3</sub> N	<b>II-73a</b> (27%)
6	<i>i</i> -Pr	DMF	Et <sub>3</sub> N	<b>II-73a</b> (44%)
7	<i>i</i> -Pr	distilled EtOAc	DMAP	<b>II-73a</b> (76%)
8	<i>i</i> -Pr	DMF	DMAP	degradation
9	<i>i</i> -Pr	DCM	DMAP	<b>II-73a</b> (28%)
10	<i>i</i> -Pr	distilled EtOAc	DMAP (0.2 equiv.) Et <sub>3</sub> N (1 equiv.)	<b>II-73a</b> (49%)
11	H	distilled EtOAc	DMAP	<b>II-73b</b> (91%)
12	Bz	distilled EtOAc	DMAP	<b>II-73c</b> (42%)

The peptide coupling reaction between **II-66** and protected valine was optimized by changing the protecting groups (as well as deprotection conditions) and coupling reagents (Table II-7). Both Fmoc and Boc protecting groups gave satisfying results. The Boc group was finally preferred due to better purification results. In addition, the coupling efficiency of the tripeptide was improved by replacing HBTU by EEDQ as a coupling reagent.<sup>152</sup>

Table II-7 Tripeptide formation by using different protecting groups and coupling reagents

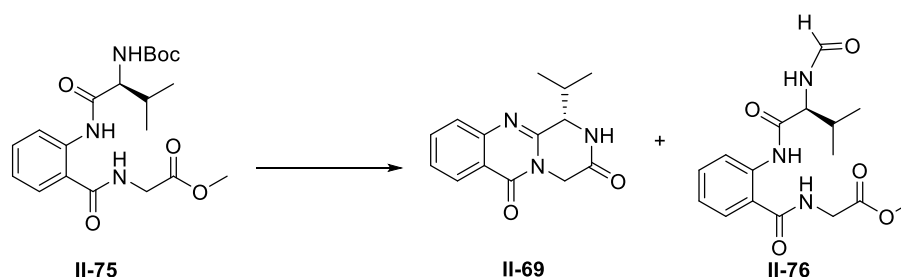


<sup>152</sup> B. Zacharie, T. P. Connolly, C. L. Penney, *J. Org. Chem.* **1995**, *60*, 7072–7074.

Entry	PG	conditions/coupling reagents	Results (yields)
1	Fmoc	(1) DCM, K <sub>2</sub> CO <sub>3</sub> (1M); (2) 20% piperidine, DCM	(1) 90%; (2) 57%
2	Boc	(1) HBTU, HOBT, Et <sub>3</sub> N, DCM; (2) TFA, DCM	(1) 54%; (2) 80%
3	Boc	(1) EEDQ, Et <sub>3</sub> N, DCM; (2) TFA, DCM	(1) 89%; (2) 80%

During the optimization of double cyclization into quinazolino-DKP, a by-product was always isolated, supposedly **II-76** formed from the Vilsmeier-Haack-type formylation of amine-deprotected tripeptide **II-64** with DMF under Lewis acid catalyzed condition. Thus, the Boc-protected intermediate **II-75** was directly engaged in the cyclodehydration, giving better yields. Surprisingly, higher yields and shorter reaction times were observed when the reaction proceeded in water, especially under microwave conditions (Table II-8). In absence of Lewis acid, the epimerization observed during the formation of cyclotripeptide **II-69** in water-catalyzed conditions was also eliminated and proved by chiral chromatography analysis.

Table II-8 Optimization of double cyclodehydration

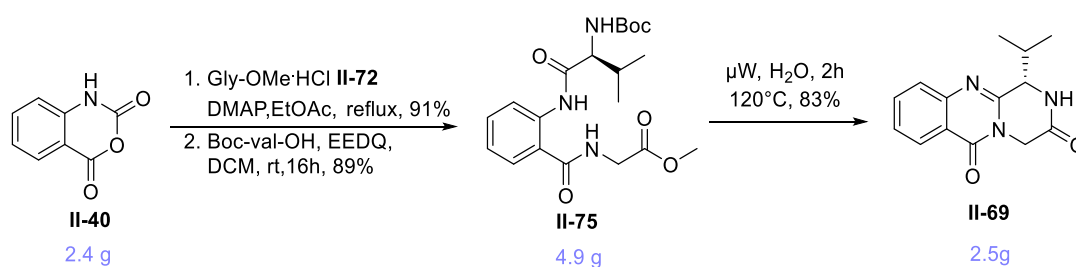


Entry	Conditions	Results
1*	Zn(OTf) <sub>2</sub> (1 equiv.), 0.03M, DMF, sealed tube, 140 °C, 16 h	<b>II-69</b> (36%) <b>II-76</b> (20%)
2	Zn(OTf) <sub>2</sub> (1 equiv.), 0.03M, DMF, sealed tube, 140 °C, 16 h	<b>II-69</b> (58%)
2	0.03M, DMF, sealed tube, 140°C, 16 h	NR
3	0.03M, H <sub>2</sub> O, microwave, 150°C, 30 min	<b>II-69</b> (51%)
7	0.03M, H <sub>2</sub> O, microwave, 120°C, 2 h	<b>II-69</b> (83%)
8	0.1M, H <sub>2</sub> O, microwave, 120°C, 2 h	<b>II-69</b> (73%)

\* Compound **II-64** was used here

To summarize, after optimizing protecting groups, coupling reagents and double cyclodehydration conditions, a biomimetic quinazolino-DKP intermediate (**II-69**) could be achieved in three steps with an overall yield of 67%. It was also prepared in gram-scale for

further modification studies (Scheme II-13).

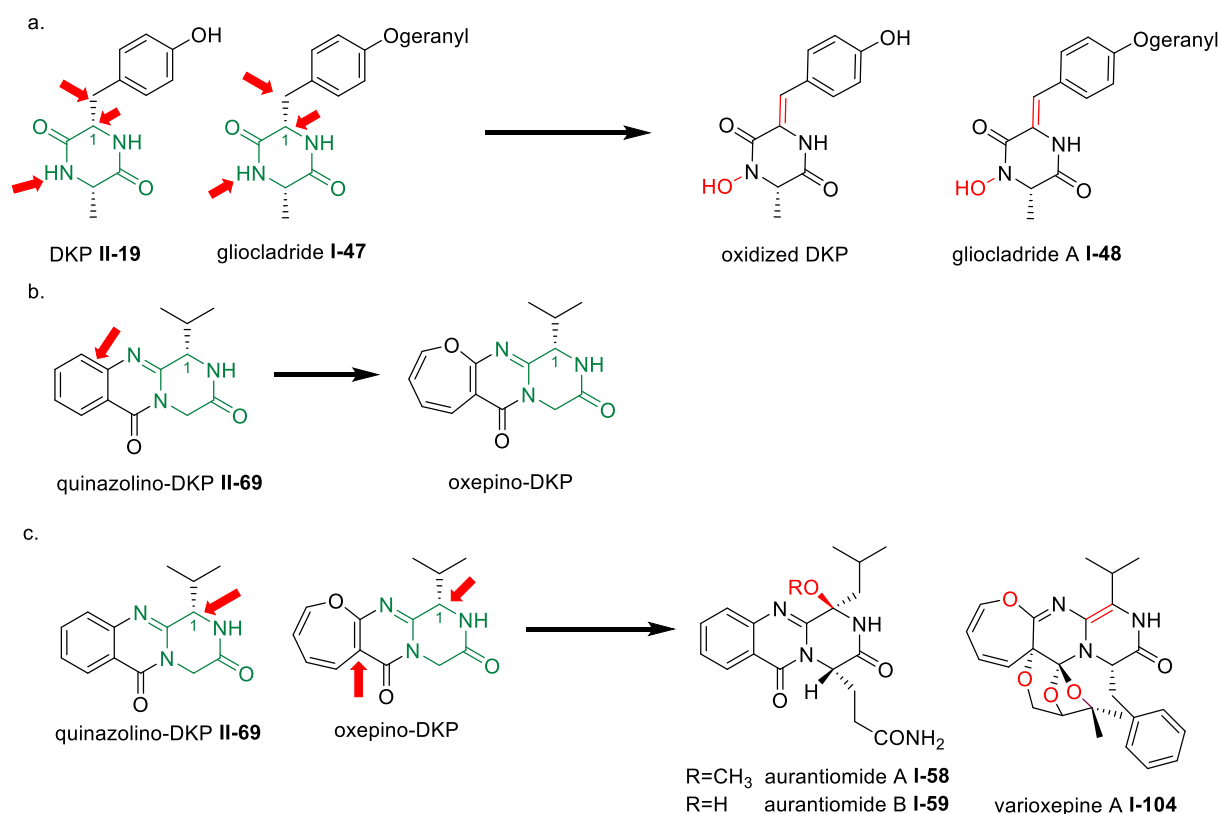


Scheme II-13 Gram-scale synthesis of quinazolino-DKP II-59

## 2. Post-functionalization attempts of biomimetic DKP scaffolds

With the three precursors in hand (DKP II-19, gliocladrone I-47 and quinazolino-DKP II-69), we began to study late-stage functionalization strategies. Three main goals were expected to be achieved in this part (Scheme II-14):

- Selectively oxidizing the amide functional group and the benzylic position for DKP and gliocladrone-type DKP, then accessing various biologically relevant natural products (anticancer compounds in particular) by oxidative divergent conception.
- Finding a rapid access to install advanced oxepino-DKP intermediate from quinazolino-DKP by epoxidation of the aromatic ring, which is also a process inspired by biogenesis. This epoxidation may be problematic by chemical means but might be selectively performed through biotransformation.
- Selectively oxidizing the  $\alpha$ -C-H position of the amide group to synthesize several families of natural products or advanced oxidized precursors, which could be diversified by adding different appendages at a later stage.



Scheme II-14 The main goals of late-stage functionalization of DKP intermediates

In the following parts, chemical and microbial oxidation studies on these substrates will be described.

## 2.1. Chemical oxidations

### 2.1.1. Oxidation attempts of DKPs and gliocladrone-type DKP scaffolds

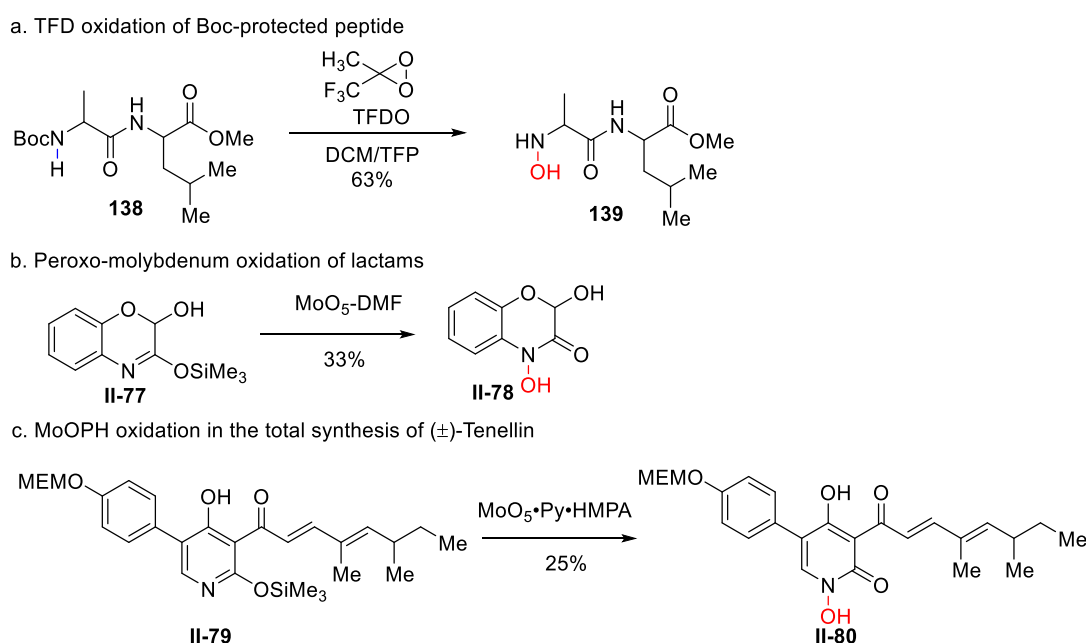
Most of the hydroxamic acid derivatives isolated from nature show potential therapeutic uses as inhibitors of siderophores.<sup>153</sup> Acting as powerful metal ion chelators, cyclic hydroxamic acids can scavenge iron and interact with iron-containing metalloproteinases,<sup>154</sup> thus being useful for the treatment and prevention of cancer metastasis, inflammation and immune diseases.<sup>155</sup> The development of a general method to get rapidly *N*-substituted hydroxamic acids would thus be useful for drug discovery.

<sup>153</sup> a) R. Codd, *Coordination Chemistry Reviews* **2008**, 252, 1387-1408; b) N. Saban, M. Bujak, *Cancer Chemotherapy and Pharmacology* **2009**, 64, 213-221.

<sup>154</sup> B. Kurzak, H. Kozłowski, E. Farkas, *Coordination Chemistry Reviews* **1992**, 114, 169-200.

<sup>155</sup> K. P. Roberts, R. A. Iyer, G. Prasad, L. T. Liu, R. E. Lind, P. E. Hanna, *Prostate* **1998**, 34, 92-99.

Linear terminal hydroxamic acid derivatives are easily accessible by generating amide bonds from hydroxylamine and carboxylic acids. Cyclic hydroxamic acids are *N*-hydroxy lactams, which are difficult to synthesize directly from amide groups. Very few successful examples are found in the literature. DMDO and TFDO could be used to oxidize the C<sup>Boc</sup>-N bond of linear *N*-Boc protected peptides **I-138** (Scheme II-15a).<sup>156</sup> Peroxo-molybdenum complex MoO<sub>5</sub>•DMF is reported to oxidize the aromatic lactam **II-77** to cyclic hydroxamic acid **II-78** in the presence of DMF (Scheme II-15b).<sup>157</sup> Diperoxo-oxo(hexamethylphosphoramide) molybdenum(VI) pyridine complex (MoO<sub>5</sub>•Py•HMPA or MoOPH) was developed to oxidize *N*-trimethylsilylamides to furnish the corresponding hydroxamic acids, which was also applied to the synthesis of (±)-tenellin (Scheme II-15c).<sup>158</sup> However, in most cases, yields are usually low, showing the difficulties of this oxidation.



Scheme II-15 Hydroxylation of *N*-H bonds in amide functions in the literature

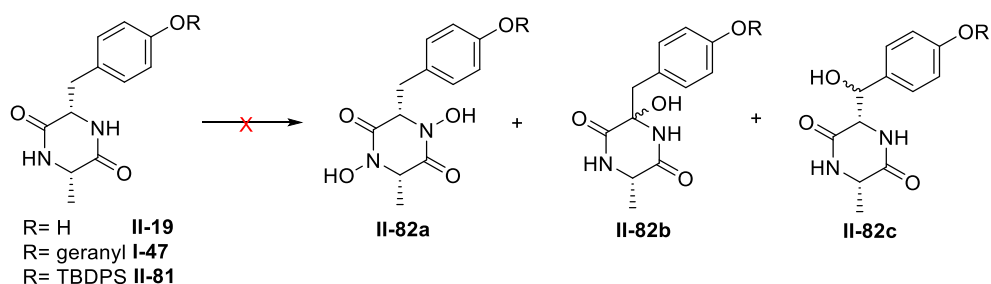
Inspired by these limited works, we decided to start with a screening of oxidants to determine the reactivity of our DKP intermediates under various oxidative conditions. Some of them are listed below (Table II-9).

Table II-9 Oxidant screening for DKP oxidation

<sup>156</sup> M. R. Rella, P. G. Williard, *J. Org. Chem.* **2007**, *72*, 525-531.

<sup>157</sup> S. A., Matlin, P. G. Sammes, R. M. Upton, *J. Chem. Soc. Perkin Trans. 1* **1979**, *10*, 2481-2487.

<sup>158</sup> J. H. Rigby, M. Qabar, *J. Org. Chem.* **1989**, *54*, 5852-5853.



Entry	R	Conditions	Results
1	H	H <sub>2</sub> O <sub>2</sub> , MeOH, 0°C → 50°C, 16h	NR
2	H	mCPBA, NaHCO <sub>3</sub> , MeOH, rt, 18h	NR
3	H	SiO <sub>2</sub> , oxone, MeOH, 80°C, 5h <sup>159</sup>	NR
4	H	oxone, acetone, aq NaHCO <sub>2</sub> , rt, 24h	NR
5	H	DMDO, acetone, rt, 2 days	NR
6	H	cerium ammonium nitrate, MeOH, rt, 2 days	complex mixture
7	H	TPP, CAN, hv, air, DMSO, rt, 18h	degradation
8	H	TPP, O <sub>2</sub> , MeCN, hv, FeCl <sub>3</sub> , rt, 18h	NR
9	H	NaOCl, TBAI, DCM/DMF, 0°C, 3h	degradation
10	H	DDQ, DMF, rt, 16h <sup>160</sup>	NR
11	TBDPS	mCPBA, NaHCO <sub>3</sub> , DCM, 0°C → rt, 6h	NR
12	geranyl	TMSCl, Et <sub>3</sub> N; MoOPH, MeCN, rt→50°C, 24h	NR
13	geranyl	MoOPH, MeCN, rt→50°C, 24h	NR

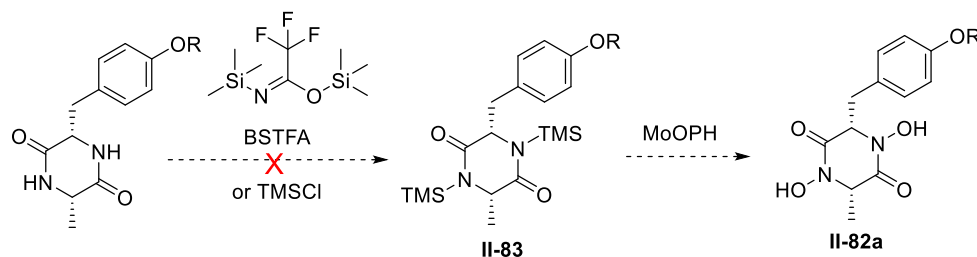
Peroxides (H<sub>2</sub>O<sub>2</sub>, mCPBA, oxone, DMDO), transition metal-catalyzed oxygenation through singlet oxygen (TPP/hv/O<sub>2</sub>) and molybdenum oxide reagents were unsuccessful to oxidize DKPs. Cerium ammonium nitrate (CAN) resulted in total degradation, which may be explained by a CAN-catalyzed oxidative coupling between electron-rich amino acids (tyrosine or tryptophan) as reported by Francis<sup>161</sup>. As unprotected DKPs have a very low solubility in the usual solvent used, silylated and geranylated DKP were also subjected to similar oxidative conditions, but no encouraging results were obtained. In particular, the silylation of DKPs proved difficult, despite successful reports for cyclo-(L-Gly-L-Gly)

<sup>159</sup> P. J. Kropp, J. D. Fields, *J. Org. Chem.* **2000**, *65*, 5937-5941.

<sup>160</sup> J. Xu, W. Zhang, H. Ma, L. Zhou, Z. Sun, Z. Du, H. Miao, *Molecules* **2008**, *13*, 3236-3245.

<sup>161</sup> K. L. Seim, A. C. Obermeyer, M. B. Francis, *J. Am. Chem. Soc.* **2011**, *133*, 16970-16976.

peptide found in the literature by employing BSTFA<sup>162</sup> or TMSCl (Scheme II-16), so that we could not test an oxidation in the presence of MoO<sub>5</sub>·Py·HMPA (MoOPH).<sup>163</sup>



Scheme II-16 Silylation and oxidation of DKPs

### 2.1.2. Oxidation attempts of the quinazolino-DKP scaffold

Much work has been reported in the literature on the reactivity of 2,3-disubstituted quinazolinone.<sup>164</sup> The position C1 can be deprotonated by strong bases, and the generated anions **II-84** could undergo stereoselective alkylations, acylations and Michael reactions (Scheme II-17a).<sup>165</sup> The tertiary acyliminium species **II-86** could also be generated at position C1 by using Koser's reagent or free-radical bromination, leading to hydroxyl, alkoxy, acyloxy and aryl derivatives.<sup>166</sup> The oxidation with PCC could also generate a tertiary acyliminium cation in order to give 1-oxo derivatives **II-87**.<sup>167</sup> Regarding position C4, only nucleophilic reactions have been developed after deprotonation with LiHMDS in the presence of R<sup>1</sup> substituent at position C1 (Scheme II-17b).<sup>168</sup> During the synthesis of (±)-lapatin B, the imidate-protected diketoperazine core could be aromatized by DDQ, affording **II-91** as intermediate, which involved in fact a C1 oxidation.<sup>145</sup>

<sup>162</sup> S. Muhammad, A. R. Bassindale, P. G. Taylor, L. Male, S. J. Coles, M. B. Hursthouse, *Organometallics* **2011**, *30*, 564–571.

<sup>163</sup> a) E. Vedejs, D.A. Engler, J. E. Telschow, *J. Org. Chem.* **1978**, *43*, 188-196; b) P.G. Sammes, S.S. Matlin, *J.C.S. Chem. Comm.* **1972**, 1222-1223.

<sup>164</sup> a) C. Avendaño, E. de la Cuesta, *Current Organic Synthesis* **2009**, *6*, 143-168; b) C. Avendaño, E. de la Cuesta, *Current Organic Chemistry* **2003**, *7*, 149-173.

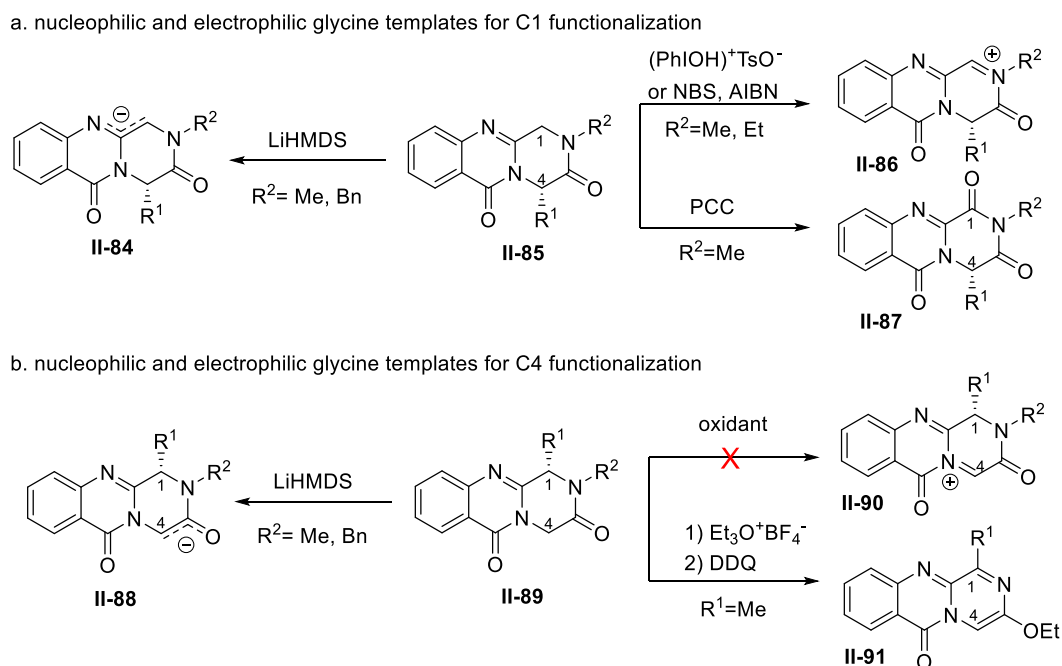
<sup>165</sup> S. M. Santamaría, F. L. Buenadicha, M. Espada, M. Söllhuber, C. Avendaño, *J. Org. Chem.* **1997**, *62*, 6424-6428.

<sup>166</sup> a) A. Santamaría, N. Cabezas, C. Avendaño, *Tetrahedron* **1999**, *55*, 1173-1186; b) E. Caballero, J. C. Menéndez, C. Avendaño, *Tetrahedron* **1999**, *55*, 14185-14198.

<sup>167</sup> M. L. Heredia, E. de la Cuesta, C. Avendaño, *Tetrahedron : Asymmetry* **2001**, *12*, 2883-2889.

<sup>168</sup> F. L. Buenadicha, C. Avendaño, M. Söllhuber, *Tetrahedron : Asymmetry* **2001**, *12*, 3019-3026.





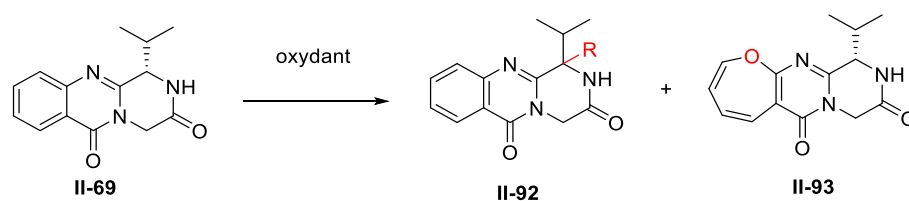
*Scheme II-17 Nucleophilic and electrophilic glycine templates for C1 and C4 functionalizations (literature examples)*

Avendaño's work has demonstrated that there was an intrinsic reactivity difference between position C1 and C4 vis-à-vis oxidations (the formation of the tertiary acyliminium species **II-90** is disfavored). Thus, it is expected that appropriate oxidants could also selectively functionalize the substituted position C1 in our case.

The transformation of the aromatic ring into arene oxides and oxepines is expected to be very difficult in the laboratory. The energy barrier for the transfer of oxygen onto benzene is estimated to 33-35 kcal/mol, which is a high barrier for typical laboratory oxidants.<sup>169</sup> The direct aromatic epoxidation of quinazolino-DKPs may be possible thanks to substitutions on the aromatic ring.<sup>118</sup> With these possibilities in mind, we set up at first oxidant screenings (Table II-10). Among peroxides, halogenation reagents, transition metal catalysts and biomimetic catalyst systems (entry 6 and 7), we were delighted that DDQ could selectively functionalize the substituted position C1 (entry 16 and 17), providing methyl ether **VI-85a** in 77% yield or alcohol **VI-85b** in 39% yield, depending on the condition used.

<sup>169</sup> C. W. Charles, P. George, J. J. Stezowski, J. P. Glusker, *Structural Chemistry* **1990**, *1*, 33-39.

Table II-10 Oxidant screening for quinazolino-DKPs



Entry	Conditions	Results
1	H <sub>2</sub> O <sub>2</sub> , NaHCO <sub>3</sub> , DCM, rt → reflux, 16h	NR
2	H <sub>2</sub> O <sub>2</sub> , NaOH, DCM, 60°C, 6h	no isolable product
3	mCPBA, NaHCO <sub>3</sub> , DCM, rt, 6h <sup>170</sup>	NR
4	TPP, O <sub>2</sub> , hv, MeCN, rt, 16h	NR
5	IBX, DCM, 0°C → rt, 7 days	NR
6	FeCl <sub>3</sub> , O <sub>2</sub> , (porphyrin), DCM, rt, 20h	NR
7	FeCl <sub>3</sub> , H <sub>2</sub> O <sub>2</sub> , porphyrin, DCM, rt, 20h	complex mixture
8	VO(acac) <sub>2</sub> , TBHP, acetone, 80°C, 2days	NR
9	CrO <sub>3</sub> , H <sub>2</sub> SO <sub>4</sub> , acetone/H <sub>2</sub> O, 80°C, 2days	NR
10	Br <sub>2</sub> , NaHCO <sub>3</sub> , py, MeOH, 0°C → 90°C, 24h	NR
11	Molybdate, H <sub>2</sub> O <sub>2</sub> , TBACl, DMF, rt → 90°C, 3 days	NR
12	MoOPH, MeCN, rt→50°C, 24h	NR
13	SeO <sub>2</sub> , dioxane/H <sub>2</sub> O, rt, 7 days <sup>171</sup>	<b>II-92b</b> (trace)
14	Oxone, acetone/H <sub>2</sub> O, 0°C, rt, 7days	<b>II-92b</b> (trace)
15	DMDO, acetone, rt, 6 days	<b>II-92b</b> (trace)
16	DDQ, MeOH, 50°C, 16h	<b>II-92a</b> (77%) R=OMe
17	DDQ, wet DCM, rt, 24h	<b>II-92b</b> (39%) R=OH
18	NaOCl, TBAI, DCM, 0°C, 3h	complex mixture

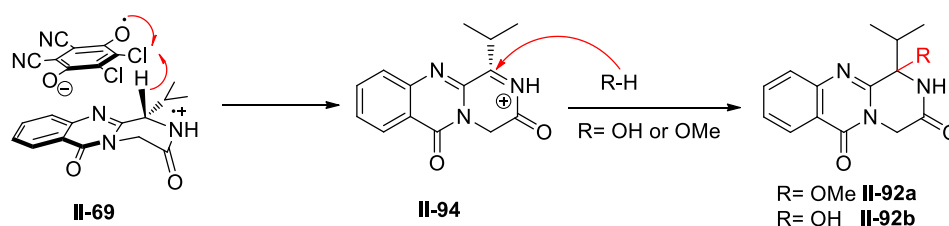
The reaction would proceed by quinone-mediated hydride abstraction (Scheme II-18).<sup>172</sup> The different nucleophiles (H<sub>2</sub>O or MeOH) in the reaction medium would finally quench the generated cation intermediate to afford the products. These products (**II-92a** and **II-92b**) are the result of a C-H functionalization of the  $\alpha$  position of amide functions, with no protection

<sup>170</sup> G.W. Griffin, K. Ishikawa, H. C. Charles, *Tetrahedron* **1977**, *5*, 427-430.

<sup>171</sup> R. G. Doveston, R. Steendam, S. Jones, R.J. K. Taylor, *Org. Lett.* **2012**, *14*, 1122-1125.

<sup>172</sup> S.S. Stahl, A.E. Wendlandt, *Angew. Chem. Int. Ed.* **2015**, *54*, 14638-14658.

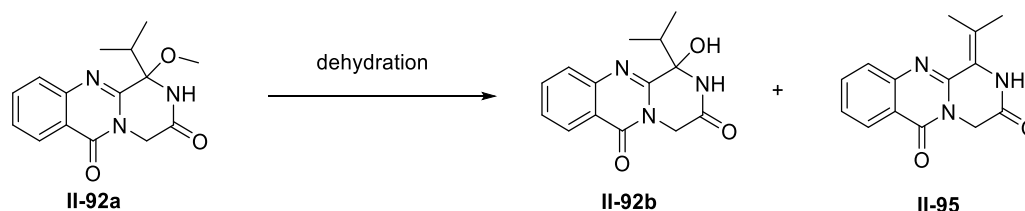
needed, and would be meaningful in a late-stage oxidation for some quinazolino-DKP natural product synthesis (such as aurantiomide A and B in Scheme II-14). As mentioned before, these conditions cannot functionalize simple DKP substrates, showing the importance of the quinazoline part, probably involved in  $\pi$ -stacking with DDQ (Scheme II-18). Besides, the generation of tertiary acyliminium species **II-94** during the mechanism resulted in a racemic hydroxylated or methoxylated products **II-92**.



Scheme II-18 Mechanism of DDQ mediated C-H oxidation

Elimination conditions were also investigated on compound **II-92a** (Table II-11), with a total synthesis perspective towards cinereain and janoxepin. Microwave conditions showed again good efficiency, affording a yield of 82% of **II-95** (entry 4). It was also observed that the nucleophilic addition of the hydroxide or methoxide anions occurred quickly to produce compound **II-92** when put **II-95** to protic solvent medium (such as water and MeOH), which indicated that the generated double bond may not be very stable.

Table II-11 Screening of conditions for the elimination of the methoxy group

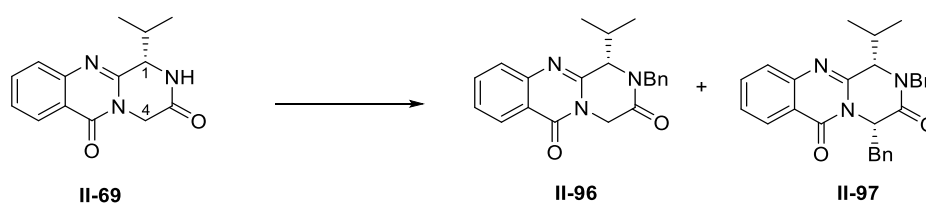


Entry	Conditions	Results
1	DBU, DCM, 0°C, 2h	<b>II-95</b> (trace)
2	HCl (aq), DCM, rt, 16h	<b>II-92b</b> (73%)
3	acetic acid, reflux, 3h	NR
4	<b>microwave, MeCN, 80°C, 20 min</b>	<b>II-95 (82%)</b>
5	APTS, MeOH, molecular sieve, reflux, 20min	<b>II-95 (25%)</b>

Finally, the C-benylation of **II-69** was tested as well. NaH was not basic enough to deprotonate position C4, only performing NH benzylation to afford benzyl amide **II-89** (Table

II-12, entry 2). With LiHMDS and LDA, no desired benzylation product (**II-97**) was observed either. Avendaño and co-workers have studied the deprotonation of the C4 center for unprotected ketopiperazines, the related alkylation required a large excess of base (10 equiv. LiHMDS) and long reaction times, while the alkylation to a *N*-protected ketopiperazine could be achieved with less base but with only moderate yields. In addition, the alkylation of C1 and dialkylation of C4 sometimes competed, which indicated that a selective benzylation at C4 requires more investigations.<sup>173</sup>

Table II-12 Benzylation trials on position C-4



Entry	Conditions	Results
1	K <sub>2</sub> CO <sub>3</sub> (1 equiv.), TBAI, BnBr, acetone, reflux, 18h	<b>II-96</b> (30%)
2	NaH (2 equiv.), TBAI, BnBr, THF/DMF, rt, 16h	<b>II-96</b> (69%)
3	LiHMDS (1.1 equiv.), BnBr, THF, -78°C, 3h*	complex mixture
4	LDA (1.1 equiv.), BnBr, THF, -78°C, 3h*	complex mixture

\* Boc-protected form **II-97** was used as substrate

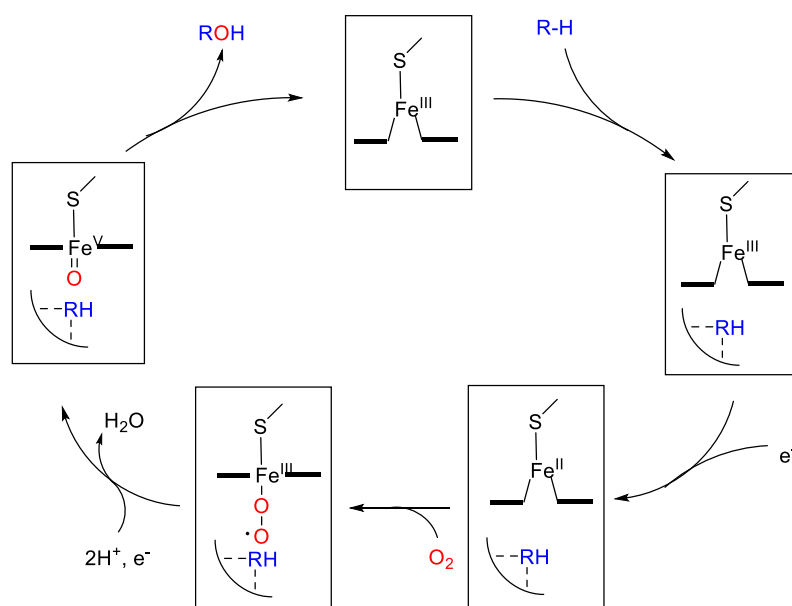
## 2.2. Biotransformation attempts

Enzyme- and microorganism-catalyzed transformations are considered as complementary approaches to the chemical C-H oxidations, and more generally to chemical synthetic reactions. Chemists attempt selective reactions based on the intrinsic reactivity of functional groups depending on reagents, media and conditions, while biologists could attempt selective reactions by using the intrinsic reactivity of enzymes through their catalytic activity naturally shaped within active sites.

The hydroxylation of N-H and oxidation of aromatic cycle are two unachieved goals by traditional chemical methods, although they are common biological processes *in vivo*,

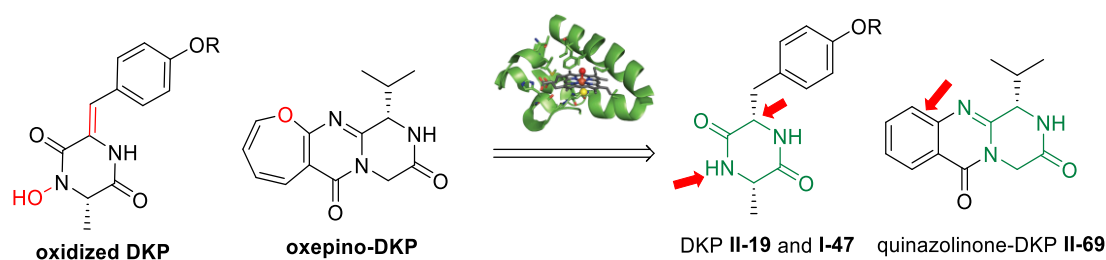
<sup>173</sup> F. L. Buenadicha, C. Avendaño, M. Söllhuber, *Tetrahedron: Asymmetry* **2001**, *12*, 3019–3028.

referring to monooxygenases, specially cytochrome P450 (Scheme II- 19).<sup>174</sup>



Scheme II- 19 Mechanism of cytochrome P450 catalyzed oxidations<sup>175</sup>

Therefore, the biotransformations of our two DKP intermediate scaffolds were envisaged in this part, trying to take benefit of microbial biosynthetic processes (Scheme II- 20).



Scheme II- 20 Retrosynthesis presentation of biotransformation goals

### 2.2.1. A short state of the art on biotransformations

In organic synthesis, the term bioconversion refers to as the specific modification of a compound (natural or non-natural) into a distinct product, using biological catalysts. The involved biological catalysts could be an enzyme, a cell lysate or a whole microorganism, like bacteria, yeast and fungi.<sup>176</sup> Enzymes, such as oxidoreductases, could perform chemical reactions in a regio-, chemo- and stereo-selective manner, thereby dramatically simplifying

<sup>174</sup> D. Mansuy, *Comparative Biochemistry and Physiology Part C* **1998**, *121*, 5–14.

<sup>175</sup> F. P. Guengerich, *J. Biochem. Mol. Toxicol.* **2007**, *21*, 163-168.

<sup>176</sup> M. F. Hegazy T. A. Mohamed, A. I. Elshamy, A. H. Mohamed et al., *J. Adv. Res.* **2015**, *6*, 17–33.

synthesis schemes.

Biocatalytic oxidations can be divided mechanistically in two categories: dehydrogenation (*e.g.* flavin-dependent oxidases, copper-dependent oxidases, amine oxidases and lacases) and oxyfunctionalisations (*e.g.* flavin-dependent monooxygenases, heme-dependent monooxygenase and peroxygenase).<sup>177</sup> As the cofactors (such as metal ions or prosthetic groups) and adequate media are sometimes determinants for catalytic processes (Scheme II-19), the direct use of isolated enzymes brings very often practical challenges.

The whole-cell biotransformation is another biocatalytic approach. The use of whole active cells, containing all the necessary factors of metabolism, will guarantee the correct stability and activity of enzymatic systems, which was preferred during this project. However, there are also some disadvantages, for example, the presence of other enzymes that may catalyze the substrate through undesired reactions; the transport of substrates or products in and out the cell can also be problematic; the toxicity of products, whose concentration increases during the reaction, may also limit the enzyme production and process efficiency.<sup>178</sup>

The efficiency of generation of the desired products depends as well as on the culture conditions and incubation conditions of microorganism. For example, the oxidative activity of cytochrome P450 in *Streptomyces platensis* could be induced by soybean peptones.<sup>179</sup> Concerning incubation conditions, especially in the case of oxygenases, pH, the presence of sustainable supply of O<sub>2</sub> and electron sources are important parameters for the enzymatic activity.<sup>180</sup>

As the enzymes needed for the oxidation of our compounds **II-19** and **II-69** have not been studied and each enzyme has its limited substrate scope, we decided to perform at first a screening of microbial strains for each substrate. The first insights of strain tolerances and reactivities to our precursors would further help us to select the best fermentation systems.

The biotransformation of the two biomimetic precursors followed a general procedure developed in our laboratory, illustrated in Scheme II-21. Strains were cultured at first in

---

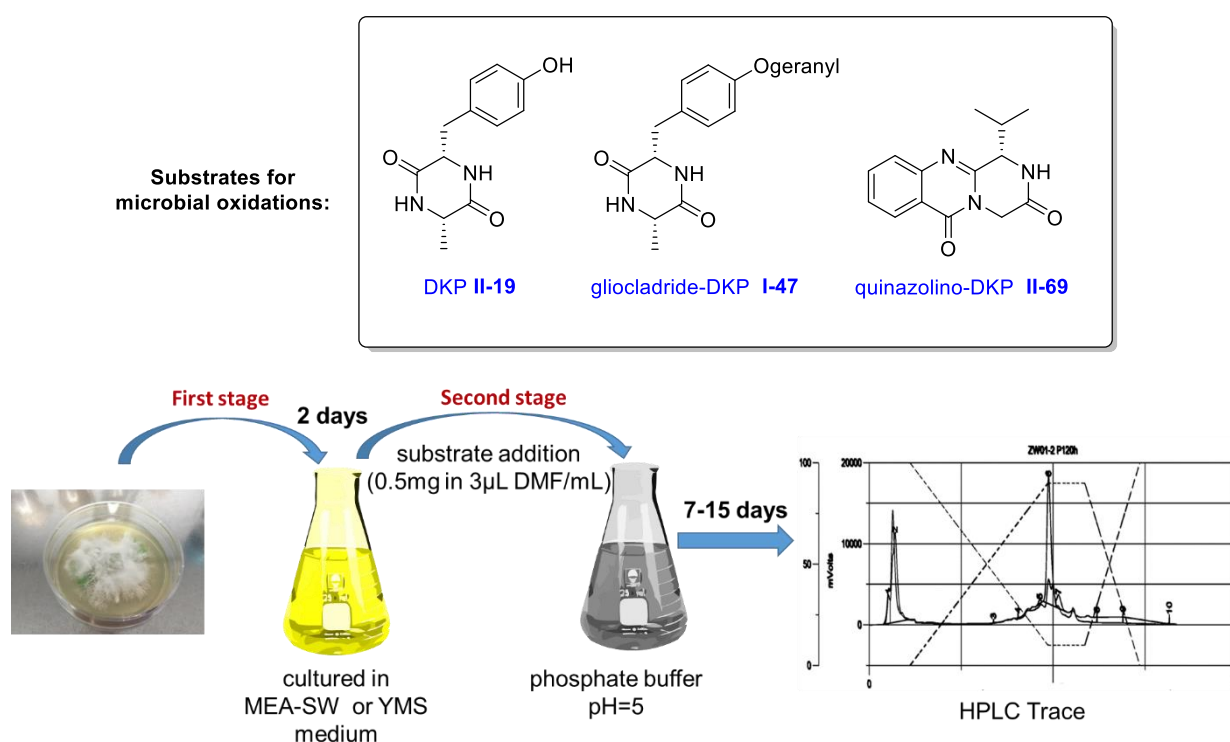
<sup>177</sup> J. J. Dong, E. Fernández-Fueyo, F. Hollmann, C. E. Paul, M. Pesic, S. Schmidt, Y. Wang, S. Younes, W. Zhang, *Angew. Chem. Int. Ed.* **2018**, *57*, 9238–9261.

<sup>178</sup> W.A. Loughlin, *Bioresource Technology* **2000**, *74*, 49-62.

<sup>179</sup> a) C. Mazier, M. Jaouen, M. A. Sari, D. Buisson, *Bioorganic & Medicinal Chemistry Letters* **2004**, *14*, 5423–5426.; b) A. El Ouarradi, M. Lombard, D. Buisson, *Journal of Molecular Catalysis B: Enzymatic* **2010**, *67*, 172–178

<sup>180</sup> T. Hudlicky and J. W. Reed, *Chem. Soc. Rev.* **2009**, *38*, 3117–3132.

different culture media, such as yeast malt soy extract (YMS), potato dextrose agar (PDA), potato dextrose broth (PDB), artificial sea water-added malt extract agar (MEA-SW), to select the adequate medium that allows the production of the maximum biomass during 2 days (first stage, also called fermentation) and sometimes helps to induce the increase of some oxidoreductases. The MEA-SW was selected for marine strain culture, while YMS was selected for other microbial species. Then, the obtained biomass was transferred to a pH-controlled phosphate buffer (second stage, also called incubation), which usually stops the microorganism growth, together with the substrate to be transformed. The biotransformations were then monitored by subjecting sonicated sample to HPLC every day during one or two weeks. The corresponding strain screening and interesting results are detailed and discussed in following two parts.



*Scheme II-21 General procedure of biotransformations and substrate structures*

### 2.2.2. Microbial oxidations for gliocladrine-type DKPs

Introduced in the first chapter, all gliocladrine DKPs are natural products isolated from marine strains.<sup>60</sup> Thus, it was logical to screen a selection of marine fungal species from the collection of the MCAM unit of the National Natural History Museum and some known bacteria and fungi species for oxidoreductions, as potential biotransformation strains (Table II-13).

Table II-13 List of microorganisms tested for the biotransformation of the DKP scaffolds

<b>Marine fungal species</b>			
<b>N°</b>	<b>Type</b>	<b>N°</b>	<b>Type</b>
LD 8H	<i>Hypocrea lixii</i>	SL 428H	<i>Melanconis stilbotoma</i>
LD 155H	<i>Dendryphiella</i>	LD 13H	<i>Chaetomium sp</i>
LD 330H	<i>Penicillium sp</i>	LD 150F	<i>Tolypocladium inflatum</i>
LD 450H	<i>New species</i>	LD 144H	<i>marine ascomycete</i>
LD 447H	<i>Chaetomium sp</i>	LD 53H	<i>Paraconiothyrium sporulosum</i>
LD 535H	<i>Botryotinia fuckeliana</i>	LD 326H	<i>Pleosporales sp</i>
AN 130T	<i>Verticillium cf biguttatum</i>	SL 539T	<i>New species</i>
AN 397T	<i>Dendryphiella. arenaria</i>	LD 448H	<i>Pleosporales sp</i>
PC 398R	<i>Phoma sp</i>	LD 12H	<i>Chaetomium sp</i>
SL 411T	<i>New species</i>	LD 149H	<i>Beauveria brongiartii</i>
SL 468T	<i>Embellisia sp</i>	LD 131H	<i>Trametes versicolor</i>
SL 473T	<i>Diaporthe sp</i>	LD 331H	<i>Pyrenochaetopsis</i>
SL 469T	<i>Cladosporium cucumerinum</i>		
<b>Bacteria</b>			
NRRL B150	<i>Streptomyces griseus</i>	ATCC 11861	<i>Streptomyces vinaceus</i>
NRRL 2364	<i>Streptomyces platensis</i>	NRRL 5449	<i>Streptomyces candidus</i>
ATCC 29607	<i>Pseudomonas putida</i>	ATCC 4276	<i>Nocardia opaca</i>
ATCC 4055	<i>Rhodospirillum rubrea</i>	DSM 43198	<i>Rhodococcus rhodochrous</i>
<b>Other fungi</b>			
ATCC 11145	<i>Rhizopus oryzea</i>	BO	<i>Mucor racemosus</i>
NRRL 1757	<i>Mortierella isabellina</i>	ATCC 9142	<i>Aspergillus niger</i>
NRRL 315	<i>Aspergillus alliaceus</i>	LCP 863480	<i>Absidia corymbifera</i>
ATCC 7159	<i>Beauveria bassiana</i>	CBS 110-16	<i>Mucor plumbeus</i>
ATCC 42838	<i>Absidia blakesleeana</i>	CBS 416-74	<i>Mucor rouxii</i>
ATCC 9245	<i>Cunninghamella echinulata</i>	CBS 144-88	<i>Geotrichum candidum</i>
LCP 763122	<i>Apophysomyces elegans</i>	NRRL 3628	<i>Mucor janssenii</i>
ATCC 984199	<i>Aspergillus niger</i>	ATCC 36-112	<i>Cladosporium elegans</i>
ATCC 1009	<i>Aspergillus ochraceus</i>	ATCC 11542	<i>Botrytis cinerea</i>



The chromatographic signal of the DKP precursor cyclo-(L-Ala-L-Tyr) **II-19** was found to disappear after one week (Figure II-2) for all 25 tested marine fungal strains. Especially in the case of LD 8H and PC 398R, no more signal of starting material was detected at the end of two days. However, no other attractive product could be identified from these experiments. As cyclo-(L-Ala-L-Tyr) is a simple cyclodipeptide, it is possible that it plays as a source of amino acids by hydrolysis for the micro-organism during the incubation phase, which may explain the non-specific consumption of our biomimetic intermediate **II-19**.

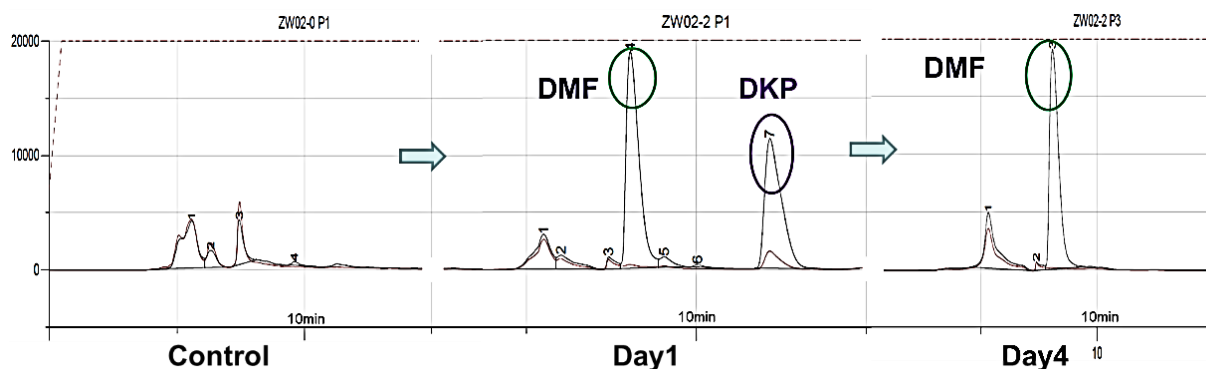


Figure II-2 Bioconversion HPLC trace of DKP intermediate **II-19**

The geranylated DKP **I-47** was therefore submitted to biotransformations with the marine strains. No change in compound concentration was observed in the incubation medium (from HPLC analysis), possibly indicating the difficulty of substrate transport into the cells, or the substrate may inhibit any biotransformation.

Finally, the biotransformation of DKP and geranylated DKP were carried out with the other listed fungal and bacterial species (Table II-13). No bioconversion was detected in these cases, suggesting that precursor **II-19** could be specifically metabolized by the marine species. However, this phenomenon still requires to be investigated.

### 2.2.3. Microbial oxidation of quinazolino-DKP substrates

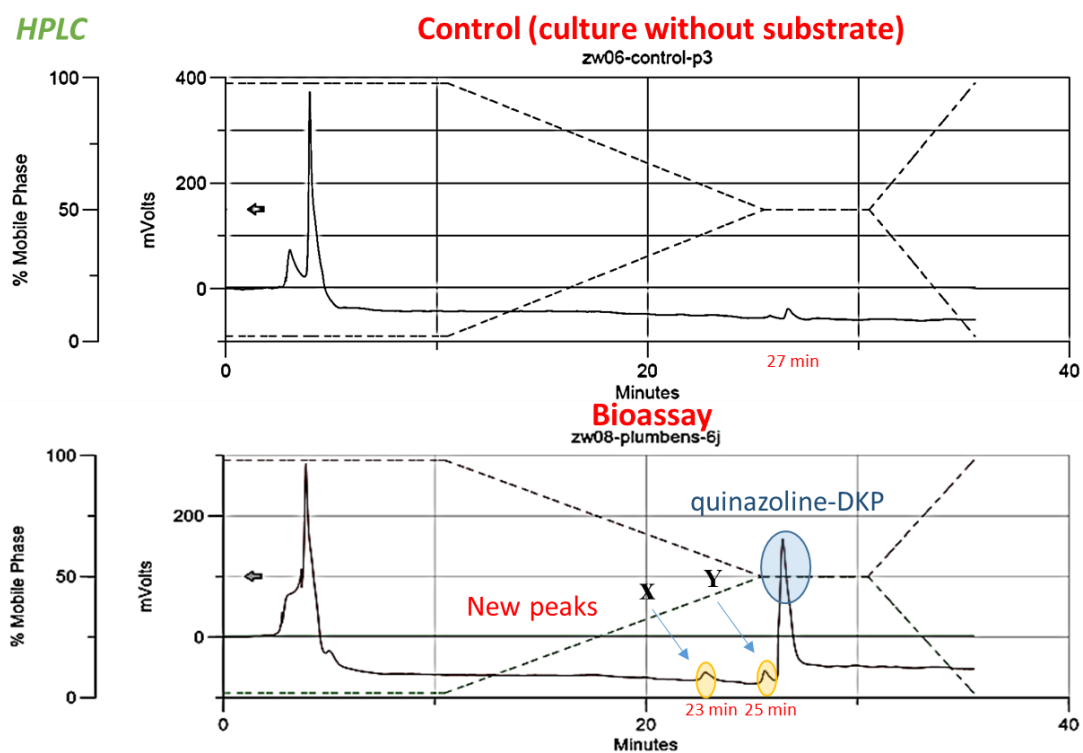
Oxepine-containing DKPs were mostly isolated from *Aspergillus* species and cinereain was isolated from *Botrytis cinerea*.<sup>181</sup> Thus, the screening of potential strains for biotransformation was predominantly carried out with *Botrytis cinerea*, some *Aspergillus* species and some usual bacterial and fungal species present in our laboratory collection (Table II-14).

<sup>181</sup> See resume in chapter I, p19-22

Table II-14 List of microorganism strains involved in the biotransformation of quinazolino-DKP

N°	Type	N°	Type
NRRL B 1193	<i>Streptomyces pradiae</i>	DSM 44541	<i>Rhodococcus ruber</i>
NRRL 8167	<i>Streptomyces antibioticus</i>	ATCC 4056	<i>Rhodococcus rubra</i>
ATCC 101486	<i>Absidia blakesleana</i>	BO	<i>Mucor racemosus</i>
CCP 752296	<i>Aspergillus teuveus</i>	CBS 204-74	<i>Mucor sinensis</i>
ATCC20023	<i>Aspergillus candidus</i>	MMP 430	<i>Mucor plumbeus</i>
NRRL 3655	<i>Cunninghamella echinulata</i>	MUCL 31324	<i>Penicillium islandicum</i>
ATCC 984199	<i>Aspergillus niger</i>	ATCC 36-112	<i>Cladosporium elegans</i>
ATCC 1009	<i>Aspergillus ochraceus</i>	ATCC 11542	<i>Botrytis cinerea</i>
ATCC 9142	<i>Aspergillus niger</i>	NRRL 315	<i>Aspergillus alliaceus</i>

Unfortunately, the oxidation of the aromatic ring of substrate **II-69** into an oxepine was neither observed under *Botrytis cinerea* nor under *Aspergillus* biotransformation conditions. However, the fungus *Mucor plumbeus* interestingly showed some promising results. Two new compounds **X** and **Y** were detected by HPLC after six days incubation (Figure II-3).

Figure II-3 HPLC chromatogram of the bioconversion of quinazolino-DKP **II-59**

One of the products, compound **Y**, was identified by comparing its LC-MS profile with synthetic alcohol **II-92b** reference (MW= 273) previously obtained by the reaction of **II-69** with DDQ. With the same retention time (12 min) and the same  $m/z$  value ( $m/z = 256$ ), compound **Y** and compound **II-92b** might be the same products (Figure II-4). Compound **Y** could be formed by the enzymatic C-H oxidation at position C1, displaying an  $[M-OH]^{+}$  ion at  $m/z$  256 formed from hydroxyl elimination. As enzymatic hydroxylation is usually selective, we could expect that compound **Y** might be formed stereoselectively, which still needs confirmation.

The difference of  $m/z$  value between compound **X** ( $[M+H^{+}]^{+}$  ion at  $m/z = 274$ ) and the starting material ( $[M+H^{+}]^{+}$  ion at  $m/z = 258$ ) is 16, which also matched another O-incorporation (could be an oxepine) on quinazolino-DKP **II-59**.

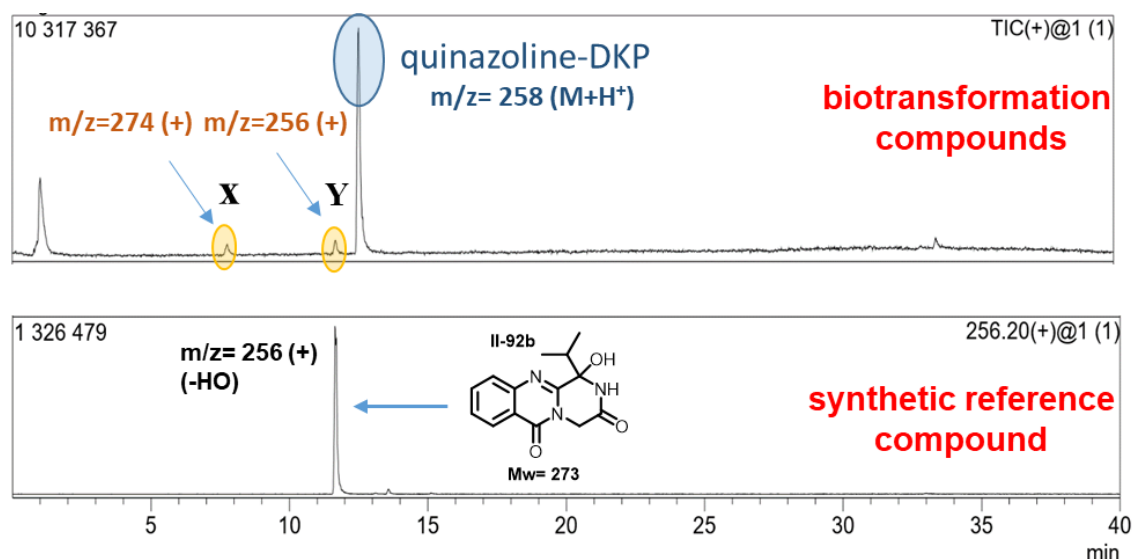


Figure II-4 LC-MS chromatograms for identifications of compound **X** and **Y**

To identify this potentially interesting unknown product, an optimization of biotransformation conditions was carried out. Parameters like substrate concentration, DMF concentration, the age of strain culture and pH of the phosphate buffer were investigated.<sup>182</sup> A major improvement was observed at pH 5, where the bioconversion into compound **X** reached 10% (Figure II-5) at the end of two weeks (calculation based on the HPLC ratio between product and starting material).

<sup>182</sup> B. Nidetzky, R. Kratzer, J. M. Woodley, *Biotechnology Advances* **2015**, *33*, 1641-1652.

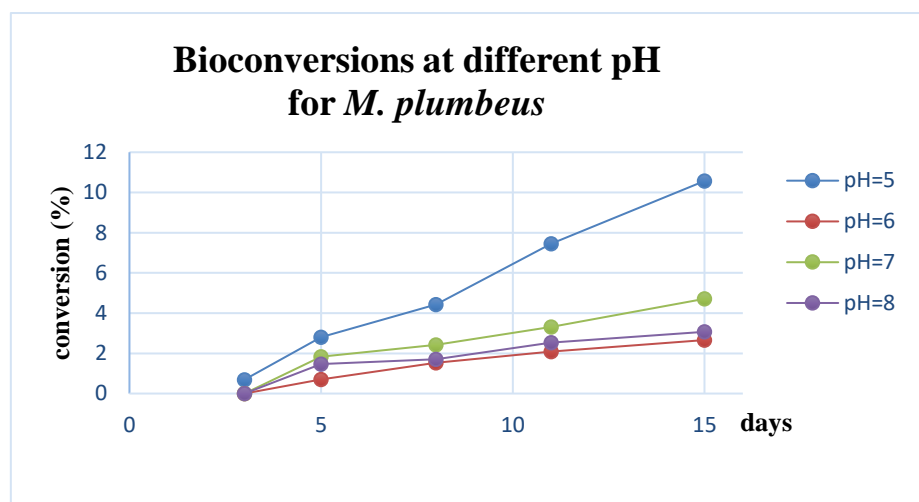


Figure II-5 Bioconversion ratio at different pHs for *M. plumbeus*

Unfortunately, on a larger scale, the same conversion was not achieved, and compound **X** could not be identified for the moment. As O<sub>2</sub> incorporation is crucial for oxidation,<sup>183</sup> we supposed that the aeration difference between the small and larger scales may be the main cause of failure. Appropriate biotransformation conditions are thus still needed in order to isolate and identify these interesting products.

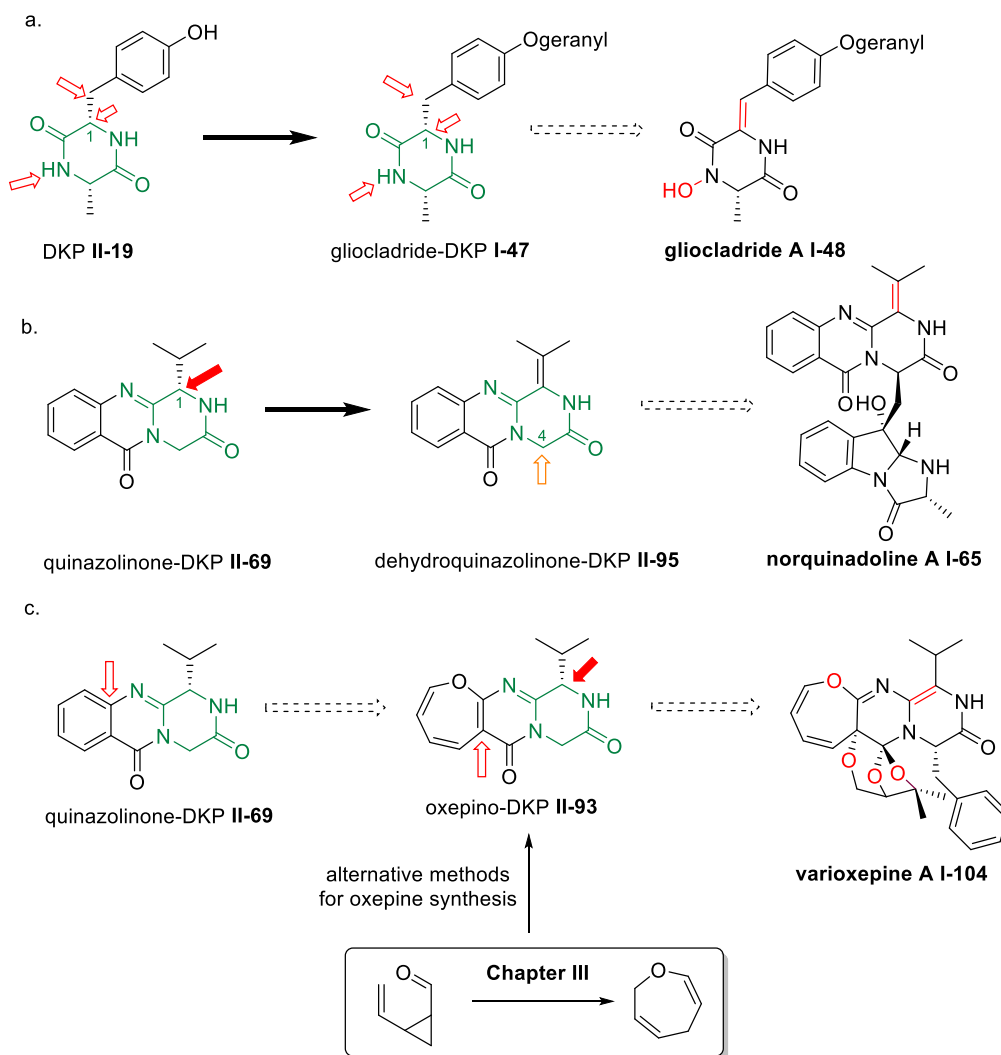
### 3. Conclusion and perspectives

Two simple biomimetic intermediates DKP and quinazolinone-DKP were successfully synthesized. The late-stage *O*-alkylation (phenol) and C-H oxidation led to two advanced intermediates, gliocladrone **I-47** and dehydroquinazolinone-DKP **II-95**, respectively (Scheme II-22a and b). The selective functionalization of amides is still challenging, and so is the biomimetic synthesis of gliocladrone A (**I-48**). However, the DDQ-mediated C-H oxidation of **II-69** brought us close to target natural products like norquinadolone A (**I-65**). A straightforward synthetic strategy would end up with one more late-stage C-H alkylation at position C4. Obviously, the most difficult challenge will be to find an access to an advanced intermediate oxepino-DKP (Scheme II-22c). Although biotransformations have reached some encouraging results, applying them to practical natural product synthesis will not be that simple. All biotransformation parameters should be well studied prior to any scale-up to optimize enzyme efficiency. Sometimes, to improve efficiency, recombinant enzymatic

<sup>183</sup> J. B. Park, *J. Microbiol. Biotechnol.* **2007**, *17*, 379–392.

production may be needed,<sup>184</sup> which requires the identifications of the functional enzymes and also corresponding encoding protein sequences.

As an alternative to this costly and challenging task, we decided to design a new synthetic strategy towards dihydrooxepines. This was realized during my thesis project and will be detailed in next chapters, on the practical, theoretical and application points of view.



Scheme II-22 Resume of Chapter II

<sup>184</sup> M. Adamczak, S. H. Krishna, *Food Technol. Biotechnol.* **2004**, 42, 251–264.



## **CHAPTER III. FROM TANDEM CYCLOPROPANATION/ OXA-COPE REARRANGEMENT STUDIES TO THE TOTAL SYNTHESIS OF OXEPIN-BASED NATURAL PRODUCTS**

---

*“In chemistry, one’s ideas, however beautiful, logical, elegant, imaginative they may be in their own right, are simply without value unless they are actually applicable to the one physical environment we have – in short, they are only good if they work! I personally very much enjoy the challenge which this physical restraint on fantasy presents.”*

*---Robert Burns Woodward*

---





## Chapter III. From Tandem Cyclopropanation/Oxa-Cope Rearrangement Studies to the Total Synthesis of Oxepin-Based Natural Products

### 1. Literature review

#### 1.1. Synthetic methods towards oxepins

The occurrence of oxepine rings in a large variety of interesting natural products has raised many efforts to generate this oxacyclic system.<sup>185</sup> Because of entropic factors that impede ring closure, less synthetic methods have been developed compared with five- and six-membered ring systems.<sup>186</sup> The main approaches to the formation of seven-membered heterocyclic systems are annulation processes,<sup>187</sup> such as [4 + 3] and [5 + 2]<sup>188</sup> annulations, which generate two single bonds in the cyclic product, by reacting two acyclic precursors.

The intramolecular synthetic methods of three subtypes of unsaturated seven-membered tetrahydrooxepine have been reviewed by Snyder and coworkers in 2006.<sup>189</sup> They summarized all strategies by two kinds of bond connections: C-O bond forming reactions and C-C bond forming reactions, shown in Figure III-1.

Most of these cyclization methods give access to enol ether oxepines **III-3**. The Lewis acid-mediated nucleophilic cyclization methods through hydroxyl group nucleophiles (such as a, b and f) have been primarily developed to achieve the C-O connections. The ring closing metathesis dominates the double C-C bond forming strategies, which has been used to generate all three types of 'oxepines'. Beyond these mentioned methods, intramolecular Horner-Wadsworth-Emmons reactions,<sup>190</sup> acetal-alkene Prins reactions,<sup>191</sup> alkyne

---

<sup>185</sup> J. B. Bremner, S. Samosorn, *A critical review of the 2005 literature preceded by two chapters on current heterocyclic topics* **2007**, 402-429.

<sup>186</sup> G. Illuinati, L. Mandolini, *Acc. Chem. Res* **1981**, *14*, 95-102.

<sup>187</sup> a) G. A. Molander, *Acc. Chem. Res* **1998**, *31*, 603-609; b) L. Yet, *Chem. Rev.* **2000**, *100*, 2963-3007; c) J. O. Hoberg, *Tetrahedron* **1998**, *54*, 12631-12670.

<sup>188</sup> J. M. Stryker, K. E. O. Ylijoki, *Chem Rev* **2013**, *113*, 2244-2266.

<sup>189</sup> N. L. Snyder, H. M. Haines and M. W. Peczuh, *Tetrahedron* **2006**, *62*, 9301-9320.

<sup>190</sup> a) C. J. Moody, E. H. B. Sie, *Tetrahedron* **1992**, *48*, 3991-4004; b) C. J. Moody, E. H. B. Sie, *Tetrahedron Letters* **1991**, *32*, 6947-6948.

<sup>191</sup> a) C. Taillier, B. Gille, V. Bellosta, J. Cossy, *J. Org. Chem.* **2005**, *70*, 2097-2108; b) D. Berger, L. E. Overman, P. A. Renhowe, *J. Am. Chem. Soc.* **1997**, *119*, 2446-2452; c) D. Berger, L. E. Overman, P. A. Renhowe, *J. Am. Chem. Soc.*, **1993**, *115*, 9305-9306.

cyclizations<sup>192</sup> and sigmatropic rearrangements<sup>193</sup> have been investigated as well, but with limited synthetic significant developments.

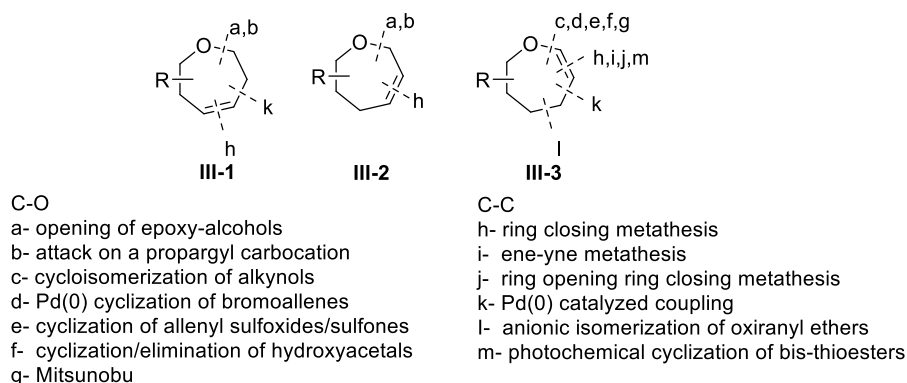
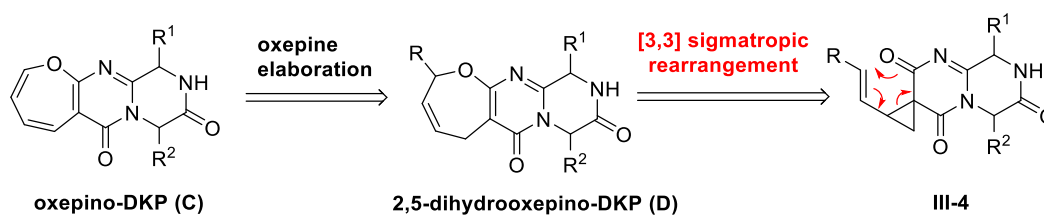


Figure III-1 Synthetic methods of unsaturated seven-membered oxacycles

During our project, we were interested in the development of a new method to synthesize rapidly the oxepine ring, which could be further applied to the preparation of advanced oxepino-DKP intermediate and, hopefully, also to the total synthesis of cinereain and janoxepin.

From a retrosynthetic perspective, the oxepino-DKP (**C**) could be generated by oxidation of a 2,5-dihydrooxepino-DKP (**D**). Efficient synthetic methods are thus desired to prepare such functionalized 2,5-dihydrooxepines. The generated seven-membered oxacycle possesses an allyl vinyl ether pattern, which suggests that a retro-Claisen (or oxa-Cope) reaction could be an alternative synthetic solution. Therefore, we could imagine that the 2,5-dihydrooxepine core **D** may result from a [3,3]-sigmatropic rearrangement of acylvinylcyclopropane derivative **III-4**.



Scheme III-1 Design of the alternative methodology

To implement this idea in practice, a brief review of [3,3]-sigmatropic rearrangements and

<sup>192</sup> L. D. M. Lolkema, H. Hiemstra, C. Semeyn, W. N. Speckamp, *Tetrahedron* **1994**, *50*, 7115-7128.

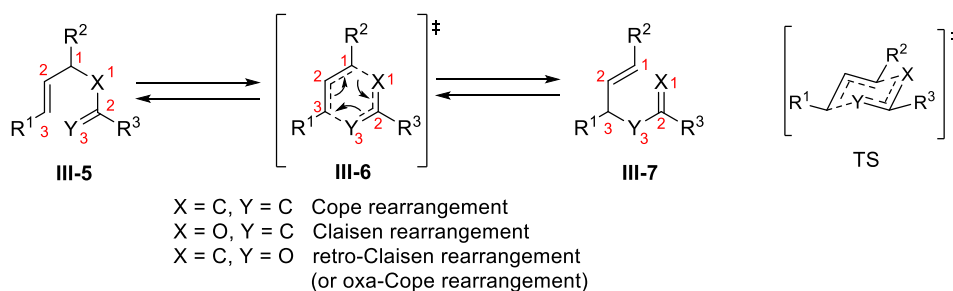
<sup>193</sup> W. N. Chou, J. B. White, *Tetrahedron Letters* **1991**, *32*, 157-166.

some well-developed approaches will be resumed in the first part of this chapter. Inspired by these works, our methodology design and experimental and computational results will be detailed in following parts.

## 1.2. [3,3]-Sigmatropic rearrangements for the formation of carbocycles

### 1.2.1. Definitions

A sigmatropic rearrangement is a pericyclic reaction wherein the result is the migration of one  $\sigma$ -bond and two  $\pi$ -bonds in an uncatalyzed intramolecular process.<sup>194</sup> The locations of  $\sigma$ -bonds and  $\pi$ -bonds get reorganized, but the total number remain unchanged. Sigmatropic rearrangements are classified according to the number of bonds separating the migration origin and the migration terminus in each component. Number 1 is assigned to both of the atoms involved in the broken bond, followed by the other atoms up to the atoms where a new  $\sigma$ -bond is formed.<sup>195</sup> [3,3]-Sigmatropic shifts are well-studied sigmatropic rearrangements, which are illustrated below (Scheme III-2).<sup>196</sup>



*Scheme III-2 General presentation of [3,3]-sigmatropic rearrangements*

These reactions are generally used for stereocontrolled formation of carbon-carbon bonds due to the six-membered chair-like cyclic transition states (Scheme III-2), in which 1,3-diaxial interactions are minimized.<sup>2</sup> The most widely used [3,3]-sigmatropic rearrangements are Cope rearrangements and Claisen rearrangements (Scheme III-2). While the former concerns the rearrangement of all-carbon chains, the latter involves allyl vinyl ether. Since its discovery by Ludwig R. Claisen in 1912,<sup>197</sup> the Claisen rearrangement has become a powerful synthetic tool for the construction of unsaturated ketones and aldehydes with a high degree of

<sup>194</sup> E. M. Greer et C. V. Cosgriff, *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **2013**, 109, 328-350.

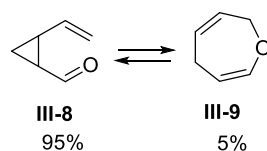
<sup>195</sup> P. Knochel, G. A. Molander, *Comprehensive Organic Synthesis II*, Elsevier Limited, Amsterdam, **2014**

<sup>196</sup> S. J. Rhoads, N. R. Raulins, *Organic reaction*, John Wiley & Sons, **1975**, 22, 2-60.

<sup>197</sup> L.R. Claisen, *Chem. Ber.*, **1912**, 45, 3157.

regiochemical and stereochemical control.<sup>2</sup> This reaction is also under thermodynamic control with respect to reactants and products.

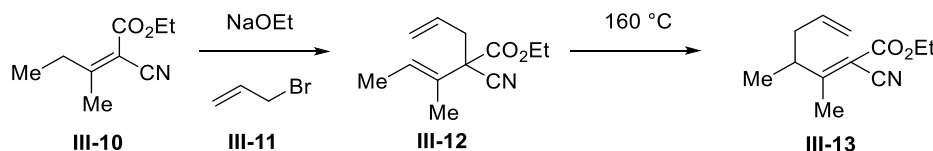
Both rearrangements being thermally allowed reversible process, a mixture of compounds can be obtained if the reactant and the product are comparable in stability. However, factors such as ring strain or conjugation could favor one product over the other. The final equilibrium is thus governed by the relative stability of the starting material and the product.<sup>2</sup> Consequently, retro-Claisen rearrangements, equivalent to oxa-Cope rearrangements, can be occasionally observed, as we shall see later. The 2-vinylcyclopropanecarboxaldehyde systems have been shown to exist in equilibrium with their oxa-Cope isomers at room temperature (Scheme III-3). This will be detailed in part 1.3 as an important reaction for the purpose of our total synthesis project.



*Scheme III-3 Equilibrium of oxa-Cope rearrangement at room temperature*

### 1.2.2. Cope rearrangements

In 1940, the first “Cope” rearrangement was reported by Arthur C. Cope and co-workers, during the distillation of allylated malonic cyanoester **III-12** (Scheme III-4).<sup>198</sup>

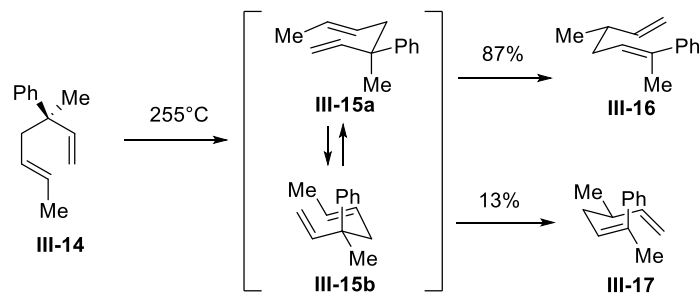


*Scheme III-4 The first “Cope” rearrangement*

These kinds of [3,3]-sigmatropic rearrangements were afterwards mainly studied in the 1,5-hexadiene systems. The equilibrium depends highly on the interaction between substituents. In particular, the presence of substituents (*e.g.* **III-14**) which are capable to conjugate the generated double bond system (like carbonyl groups, a phenyl ring or a double bond) help to shift the equilibrium to the rearranged product. The stereochemical outcome of the Cope rearrangement is mainly controlled by chair transition states, which results into *E*-configured

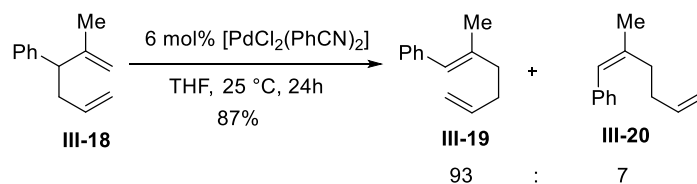
<sup>198</sup> A. C. Cope, E. M. Hardy, *J. Am. Chem. Soc.* **1940**, 62, 441–444.

Cope products (the bulkiest group at equatorial position), like compound **III-16** (Scheme III-5).<sup>199</sup>



Scheme III-5 The stereochemical control of Cope rearrangements

Although the stabilized product could be favored, request of high temperature is still a big drawback of the Cope rearrangement. Catalyzed versions, like palladium-catalyzed Cope rearrangements, have thus been developed to accelerate the reaction. For example, treatment of 1,5-diene **III-18** with  $[\text{PdCl}_2(\text{PhCN})_2]$  as a catalyst in THF could give 1,5-dienes **III-19** and **III-20** at room temperature (Scheme III-6).<sup>200</sup>



Scheme III-6 Palladium-catalyzed Cope rearrangements

When the 1,5-diene is substituted by a hydroxy (or alkoxy) group at C-3 like **III-13**, this [3,3]-sigmatropic shift is referred to as the oxy-Cope rearrangement, which converts the allylic alcohol (or ether) to the corresponding aldehyde or ketone.<sup>201</sup> The discovery of anionic oxy-Cope rearrangements by using the potassium alkoxides has gained more attention in stereocontrolled natural product synthesis. These reactions are significantly accelerated (up to  $10^{15}$  times higher compared with normal Cope rearrangement), due to the fact that the deprotonated form of the alcohol has a higher-energy ground state than the alcohol and undergoes rearrangement easily at or near room temperature.<sup>202</sup> The mild reaction conditions and high level of stereocontrol exhibit considerable tolerance toward functional groups

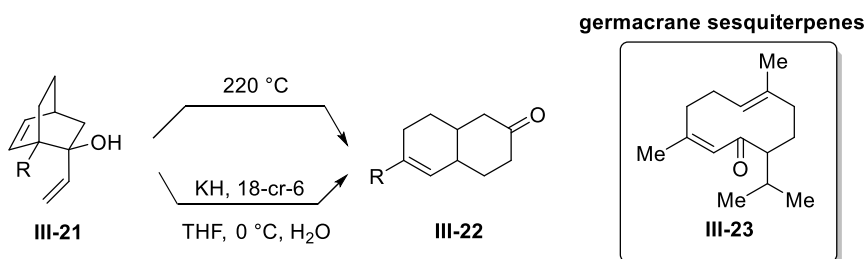
<sup>199</sup> R. K. Hill, N. W. J. Gilman, *Chem. Soc. Chem. Commun.* **1967**, 619–620.

<sup>200</sup> a) L. E. Overman, *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 579; b) R. P. Lutz, *Chem. Rev.* **1984**, 84, 205-247.

<sup>201</sup> L. A. Paquette, *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 609-626.

<sup>202</sup> L. A. Paquette, *Tetrahedron* **1997**, 53, 13971-14020.

present in valuable synthetic method.<sup>203</sup> For example, the rearrangement of potassium salt of the 3-hydroxy-1,5-diene **III-21** is a key step in the synthesis of germacrene sesquiterpenes (Scheme III-7).<sup>204</sup>



*Scheme III-7 Oxy-Cope rearrangements*

### 1.2.3. Rearrangements of vinylcyclopropanes and divinylcyclopropanes into cyclopentenes and cycloheptadienes

The bond angles in cyclopropanes are 22° smaller than the ideal 109.5°.<sup>205</sup> This angular strain as well as the torsional strain from eclipsed carbon-hydrogen bonds has benefited many synthetic methodologies toward complex molecules.<sup>2</sup>

In the case of vinyl- or divinyl-cyclopropanes, their activation energy is lowered from 59-66 kcal/mol to 34-55 kcal/mol in the presence of conjugated substituents.<sup>206</sup> The use of ring strain and the vicinal electron-donating effect make vinylcyclopropanes (VCPs) useful building blocks to construct complex systems under efficient and mild conditions. Vinyl or divinylcyclopropanes could undergo four fundamental types of bond-reorganization processes:<sup>207</sup>

- 1) *cis-trans* isomerization;
- 2) ring-opening reactions;
- 3) ring enlargement;
- 4) cycloadditions.

<sup>203</sup> Y. Zou, L. Zhou, C. Ding, Q. Wang, P. Kraft, A. Goeke, *Chem. Biodiv.* **2014**, *11*, 1608-1628.

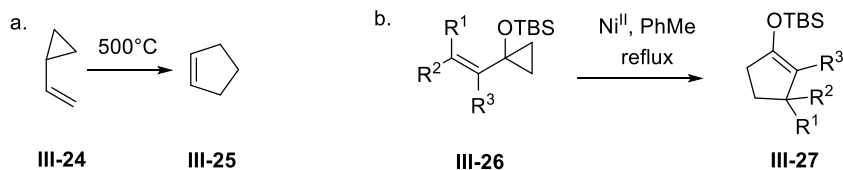
<sup>204</sup> a) D. A. Evans, J. V. Nelson, *J. Am. Chem. Soc.* **1980**, *102*, 774-782; b) A. J. Minnaard, J. B. Wijnberg, A. de Groot, *Tetrahedron* **1999**, *55*, 2115-2146.

<sup>205</sup> H. N. C. Wong, M. Y. Hon, C. W. Tse, Y. C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.* **1989**, *89*, 165-198

<sup>206</sup> a) T. Hudlicky, T. M. Kutchan, Naqvi, S. M. Naqvi, *The Vinylcyclopropane-cyclopentene Rearrangement. In Organic Reactions*, Wiley New York, **1985**, *33*, 247-335; b) A.F. Plate et al., *Russ. Chem. Rev. (Engl. Transl.)* **1976**, *45*, 469-478.

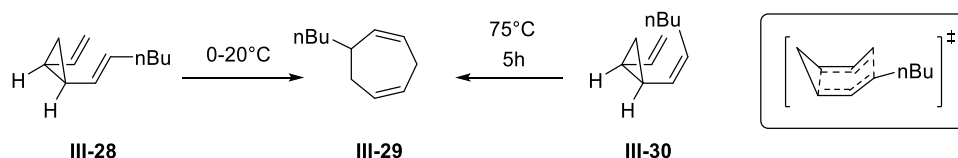
<sup>207</sup> a) B. Crammer, Z. Goldschmidt, *Chem. Soc. Rev.* **1988**, *17*, 229-267; b) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 5504-5523.

The thermal rearrangement of vinylcyclopropanes to cyclopentenenes, discovered by Neureiter in 1959, is the most recognized reaction (Scheme III-8a).<sup>208</sup> Metal-catalyzed versions (ex. Ni<sup>II</sup>, Et<sub>2</sub>AlCl, SnCl<sub>4</sub>) were afterwards developed to make this rearrangement applicable to diverse synthetic schemes (Scheme III-8b).<sup>209</sup> In addition, the presence of electron donating substituents geminal to the vinyl group is usually beneficial to the reaction. Possibly occurring with all VCP-containing compounds, this rearrangement is related to [1,3]-sigmatropic rearrangement with a high biradicaloid character.



Scheme III-8 Vinylcyclopropane-cyclopentene type rearrangements

The Cope rearrangement of divinylcyclopropanes is an effective method to synthesize seven-membered rings, which rearrange through a boat-shaped six-membered-ring transition state with very predictable stereochemistry.<sup>210</sup> The barrier for the rearrangement of *cis*-divinylcyclopropanes is strongly exothermic, calculated at 18.8 kcal/mol,<sup>211</sup> indicating that the *cis*-divinylcyclopropane can rearrange experimentally near room temperature or even below. For example, *cis*-1,2-divinylcyclopropane **III-28**, isolated at -20°C, rearranges to 1,4-cycloheptadiene in 90 seconds at 35°C.<sup>212</sup> Reaction conditions may vary, depending on the substitution pattern or conformations of divinylcyclopropanes (Scheme III-9).



Scheme III-9 Rearrangements of substituted *cis*-1,2-divinylcyclopropane

In most cases, divinylcyclopropanes are transient species that cannot be isolated. As the stereoselective synthesis and isolation of *cis*-divinylcyclopropanes are often challenging, the

<sup>208</sup> N. P. Neureiter, *J. Org. Chem.* **1959**, *24*, 2044-2046.

<sup>209</sup> a) M. Meazza, H. Guo, R. Rios, *Org. Biomol. Chem.* **2017**, *15*, 2479-2490; b) S. C. Wang, D. J. Tantillo, *Journal of Organometallic Chemistry* **2006**, *691*, 4386-4392.

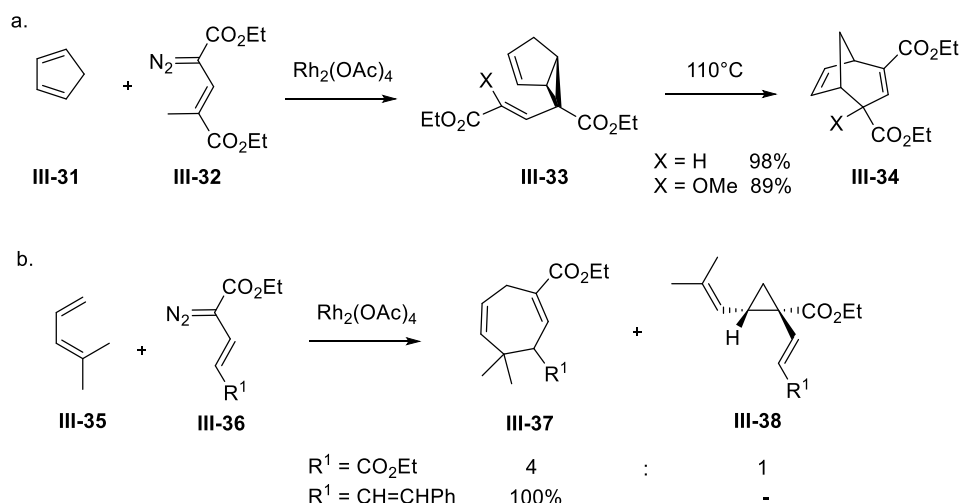
<sup>210</sup> W. Carruthers, *Modern Methods of organic synthesis* Cambridge University Press, **2004**

<sup>211</sup> J. Fabien, D. Sperling, H.U. Reißig, *Liebigs Ann. /Recueil* **1997**, 2443-2449.

<sup>212</sup> Vogel, E. *Angew. Chem. Int. Ed.* **1960**, *72*, 4-26.

tandem stereoselective cyclopropanation/Cope rearrangement offers a general entry to highly functionalized seven-membered rings.<sup>213</sup>

In 1987, Davies reported the rhodium(II) acetate-catalyzed reactions between vinyl diazomethane containing two EWGs with cyclopentadiene, which resulted in the *endo* bicyclic product **III-34** with good yield (Scheme III-10a).<sup>214</sup> This *endo* stereochemistry was rationalized by a tandem cyclopropanation/Cope rearrangement mechanism via a well-defined boat transition state of the divinylcyclopropane rearrangement. The reaction of vinylcarbenoids with unsymmetrical dienes resulted in a mixture of cycloheptadienes **III-37** and the *trans*-divinylcyclopropanes **III-38**.<sup>215</sup> As the cyclopropanation is sensitive to steric hindrance, the reaction with bulky vinylcarbenoids resulted in the formation of seven-membered rings exclusively without evidence of the formation of *trans*-divinylcyclopropanes (Scheme III-10b).



Scheme III-10 Tandem stereoselective cyclopropanation/Cope rearrangement reported by Davies

The intramolecular version of this reaction was also investigated in the Davies group. Interestingly, the isolated products are highly dependent on the reaction conditions (Scheme III-11).<sup>216</sup> At 0 °C, cyclopropane form **III-40** was isolated in 48% yield, which undergoes a Cope rearrangement to afford cycloheptadiene **III-41** at 25 °C. When the rhodium catalyzed

<sup>213</sup> a) H. M. L. Davies, *Tetrahedron* **1993**, *49*, 5203-5223; b) T. Gaich, S. Krüger, *Beilstein Journal of Organic Chemistry* **2014**, *10*, 163-193.

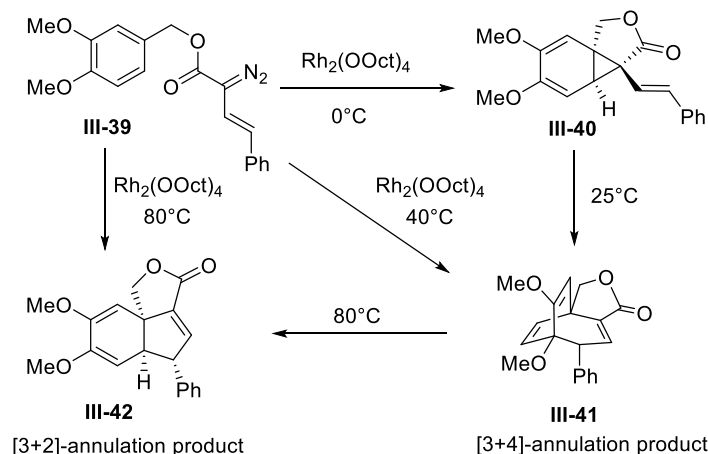
<sup>214</sup> H. M. L. Davies, H. D. Smith, O. Korkor, *Tetrahedron Letters* **1987**, *28*, 1853-1856.

<sup>215</sup> H. M. L. Davies, T. J. Clark, H. D. Smith, *J. Org. Chem.* **1991**, *56*, 3817-3824.

<sup>216</sup> H. M. L. Davies, H. D. Smith, B. Hu, S. M. Klenzak, F. J. Hegner, *J. Org. Chem.* **1992**, *57*, 6900-6903.



reaction was carried out at 40 °C, [3+4] annulation product **III-41** was isolated in 76% yield, whereas the [3+2] annulation product **III-42** became predominant at 80°C. It has also been found that [3+2] annulation product **III-42** was favored in polar solvent system and that the [3+4] annulation products have limited stability, leading to the [3+2] annulation products over several days at room temperature.



Scheme III-11 [3+4] vs [3+2] annulations of divinylcyclopropanes under different reaction conditions

These examples of divinylcyclopropane rearrangements, as many others, highlight the predominant role of the temperature on the reaction outcome. We shall encounter this problem during our work on the oxa-Cope rearrangement.

### 1.3. Hetero-Cope-type rearrangements for the synthesis of heterocycles, especially 2,5-dihydro-1-heterocycloheptenes

#### 1.3.1. Oxa-Cope rearrangements (= retro-Claisen rearrangements)

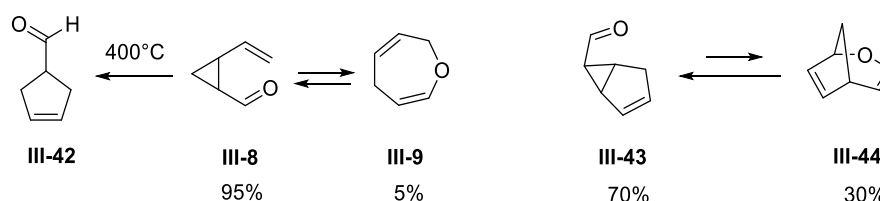
##### 1.3.1.1. From *cis*-2-vinylcyclopropanecarboxaldehydes to 2,5-dihydrooxepines

The reversible oxa-Cope-type rearrangement of vinylcyclopropanecarbaldehyde **III-8** to 2,5-dihydrooxepine **III-9** was proposed by Vogel in 1963.<sup>217</sup> In 1965, the first reaction of this kind of equilibrium was observed by Rey (Scheme III-12).<sup>218</sup> It was reported that during the preparation of bicyclo[3.1.0]hex-2-en-6-yl-*endo*-formaldehyde **III-43**, 30% of valence isomer 2-oxa-bicyclo-[3.2.1]octa-3,6-diene **III-44** was formed according to <sup>1</sup>H-NMR spectra. In 1968, Cockroft successfully synthesized compound **III-8** from *cis*-2-

<sup>217</sup> E. Vogel, *Angew. Chem. Intern. Ed. Engl.* **1963**, 2, 1-52

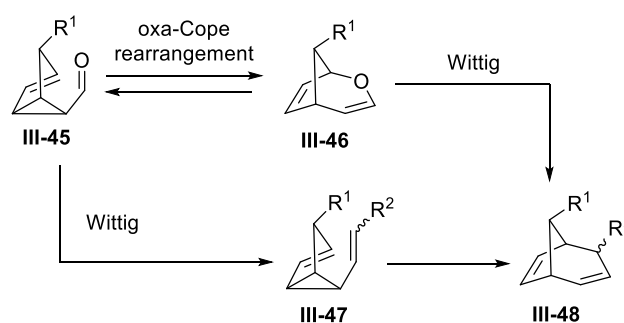
<sup>218</sup> M. Rey, *Helvetica Chimica Acta* **1965**, 48, 1985-1986.

vinylcyclopropanecarboxylic acid chloride.<sup>219</sup> Compound **III-9** was obtained by the slow distillation of compound **III-8** (yield > 95%), as confirmed by infrared and 100-MHz <sup>1</sup>H-NMR spectra. At room temperature, **III-9** slowly reverts to **III-8** to form a mixture in a ratio of 95:5 ( $t_{1/2}$  = 1 day). This kind of facile tautomerization was also demonstrated by the equilibrium between **III-43** and **III-44**.



*Scheme III-12 Rearrangement of cis-2-vinylcyclopropanecarboxaldehydes*

The oxa-Cope rearrangement was also observed later during the preparation of substituted bicyclo[3.2.1]octane skeletons **III-48** by using the Cupas-Watts-Schleyer synthesis.<sup>220</sup> Based on IR and NMR evidence, the aldehyde substrate **III-45** could undergo the oxa-Cope rearrangement to afford compound **III-46** (Scheme III-13). As this intermediate was not stable, the Wittig product **III-48** was only isolated.



*Scheme III-13 Cupas-Watts-Schleyer synthesis of bicyclo[3.2.1]octanes*

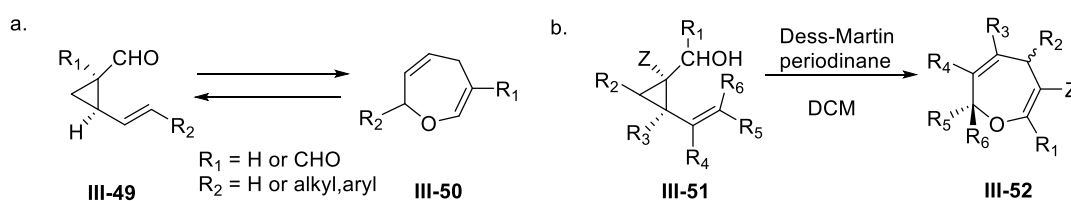
Motivated by these pioneering works, Boeckman and coworkers began to study synthetically and mechanistically the oxa-Cope rearrangement of vinylcyclopropane and vinylcyclobutane carboxaldehydes in the 1980s'.<sup>221</sup> Their studies suggested that the equilibrium favors the vinylcyclopropyl aldehyde isomer **III-49** ( $K_{\text{eq}}=0.05$ ) (Scheme III-14a). However, the dihydrooxepines **III-50** and **III-52** can be favored in presence of  $\pi$ -conjugated stabilizing

<sup>219</sup> R. D. Cockroft, S. J. Rhoads, *J. Am. Chem. Soc.* **1969**, 2815-2816.

<sup>220</sup> G. W. Klumpp, J. W. F. K. Barnick, A. H. Veeffkind, F. Bickelhaupt, *Recueil* **1969**, 88, 766-778.

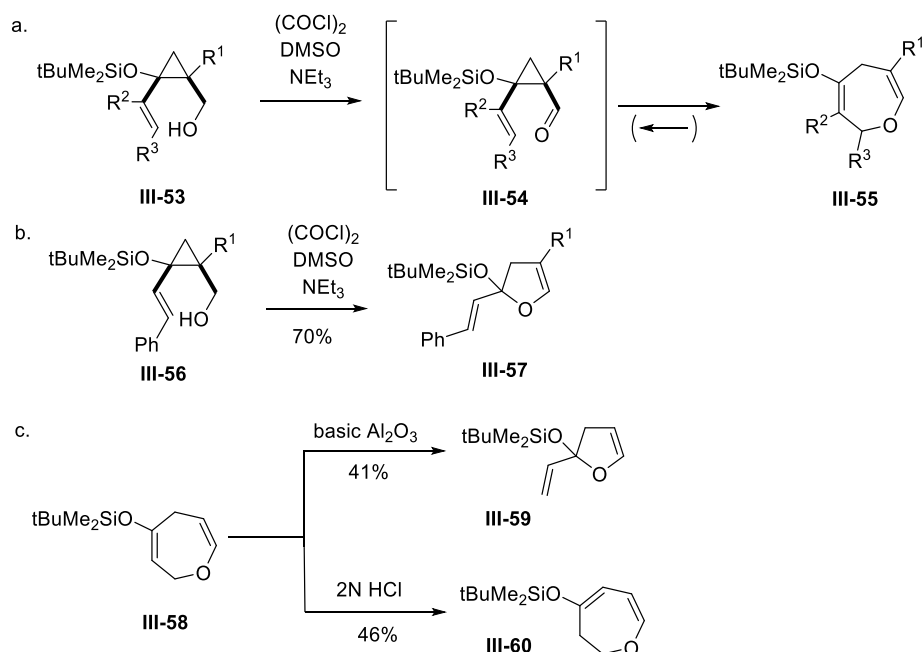
<sup>221</sup> R. K. Boeckman, C.J. Flann, K. M. Poss., *J. Am. Chem. Soc.* **1985**, 107, 4359-4362.

group Z such as CHO, CN and SO<sub>2</sub>Ph (Scheme III-14b).<sup>222</sup> These results inspired Boeckman and coworkers to perform a retro-Claisen rearrangement on functionalized chiral vinylcyclobutenes as key elements to construct eight-membered rings and then achieve the total synthesis of (+)-laurenyne.<sup>223</sup>



Scheme III-14 Substitution effects on oxa-Cope rearrangements

The rearrangement of functionalized cyclopropyl aldehyde was studied by Reissig and Hofmann in 1992. The Swern oxidation of 2-silyloxy-2-vinylcyclopropyl methanols **III-53** provided directly 2,5-dihydrooxepine derivatives **III-55** in excellent yield (Scheme III-15a). The cis location of the aldehyde and alkenyl groups allowed a concerted Cope type [3,3]-sigmatropic rearrangement, with concomitant release of the ring strain. Moreover, donor-acceptor substitutions on vinylcyclopropane **III-54** could weaken the central C-C bond in the cyclopropane ring and further stabilize the product, thus shifting the equilibrium to the formation of 2,5-dihydrooxepin **III-55**.



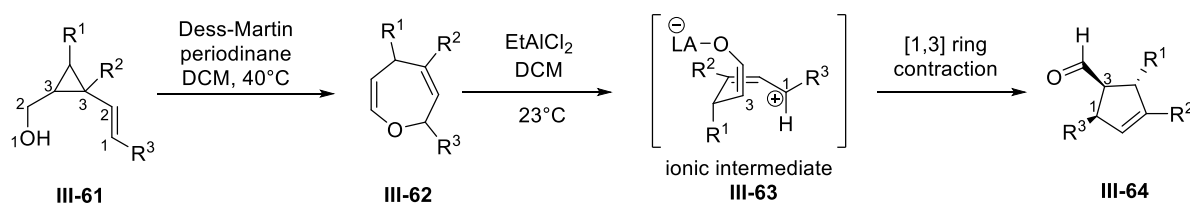
Scheme III-15 Rearrangements of 2-silyloxyvinylcyclopropyl aldehydes

<sup>222</sup> R. K. Boeckman, M. D. Shair, J. R. Vargas, L. A. Stolz, *J. Org. Chem.* **1993**, *58*, 1295-1297.

<sup>223</sup> R. K. Boeckman, J. Zhang, M. R. Reeder, *Org. Lett.* **2002**, *4*, 3891-3894.

In the meantime, alcohols bearing a 2-styryl substituent yielded dihydrofuran derivatives **III-57** in 70% yield (Scheme III-15b).<sup>47</sup> This five-membered product **III-59** was also observed during the purification of 2,5-dihydrooxepines over basic alumina, whereas treatment with 2N HCl allowed the isomerization of 2,5-dihydrooxepine into 2,3-dihydrooxepin (Scheme III-15c), demonstrating that the instability of dihydrooxepines may cause isolation problems.

Rovis took advantage of this instability to stereoselectively synthesize polysubstituted cyclopentenes by the Lewis acid mediated [1,3]-ring contraction of 2,5-dihydrooxepines.<sup>224</sup> The requisite 2,5-dihydrooxepines **III-62** were prepared by a one-pot oxidation/oxa-Cope rearrangement (Scheme III-16). Then the stereoselective [1,3]-ring contraction was performed in diluted DCM (which helps to prevent the formation of oligomeric products) in the presence of EtAlCl<sub>2</sub> at ambient temperature.



Scheme III-16 Lewis acid mediated [1,3] ring contraction of 2,5-dihydrooxepines.

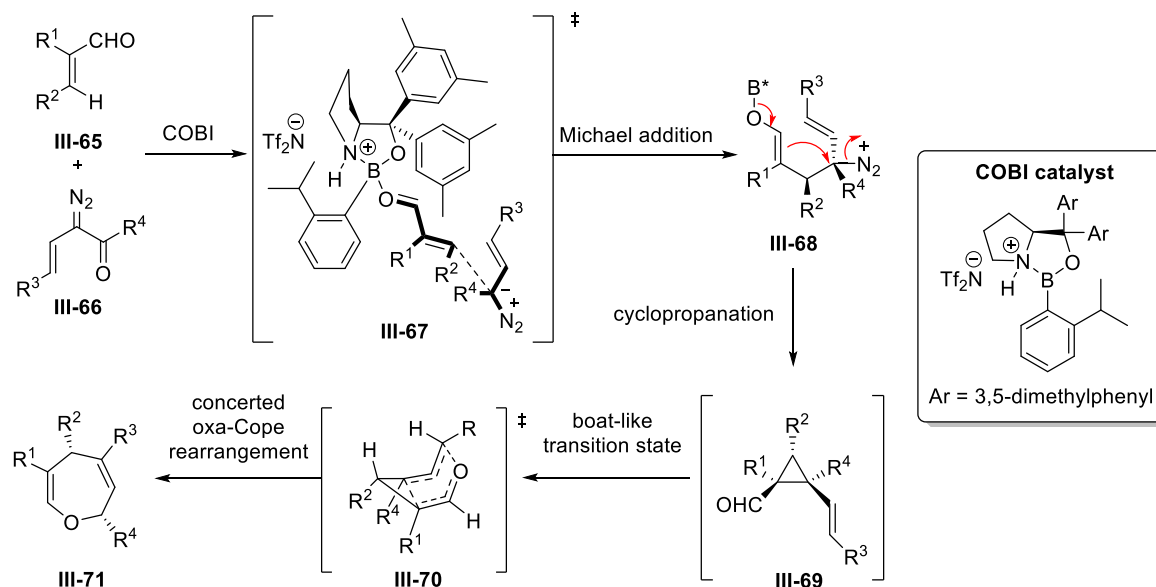
The rearrangement was also achieved by directly using vinylcyclopropylaldehydes, indicating that the formation of the dihydrooxepin is not necessary. The plausible explanation of this transformation could be that the Lewis acid accelerates the Claisen/retro-Claisen equilibrium, so that an intramolecular metalloenolate–allylic cation ion pair **III-63** is formed from either the 2,5-dihydrooxepine or the cyclopropyl aldehyde, which is then converted to the vinylcyclopentene product **III-64**.

Inspired by all previous studies, Ryu et al. have recently developed a remarkable catalytic enantioselective synthesis of highly substituted 2,5-dihydrooxepines (Scheme III-17).<sup>225</sup> A Michael addition between substituted acroleins **III-65** and vinyl diazoesters **III-67**, initiating the cyclopropanation in the presence of the chiral oxazaborolidinium ion (COBI) as a Lewis acid catalyst, afforded enantioselectively *cis*-1-formyl-2-vinylcyclopropanes **III-69** (up to 82% yield, 96% ee), which could subsequently undergo the oxa-Cope rearrangement to

<sup>224</sup> C. G. Nasveschuk, T. Rovis, *Angewandte Chemie* **2005**, *117*, 3328-3331.

<sup>225</sup> S. Y. Shim, S.M. Cho, A. Venkateswarlu, D. H. Ryu, *Angew. Chem. Int. Ed. Engl.* **2017**, *56*, 8663-8666.

generate optically pure functionalized 2,5-dihydrooxepines **III-71**. Some resulting bromo-derivatives could be easily converted to other functional groups by Stille coupling, potentially applicable in the synthesis of complex molecules.



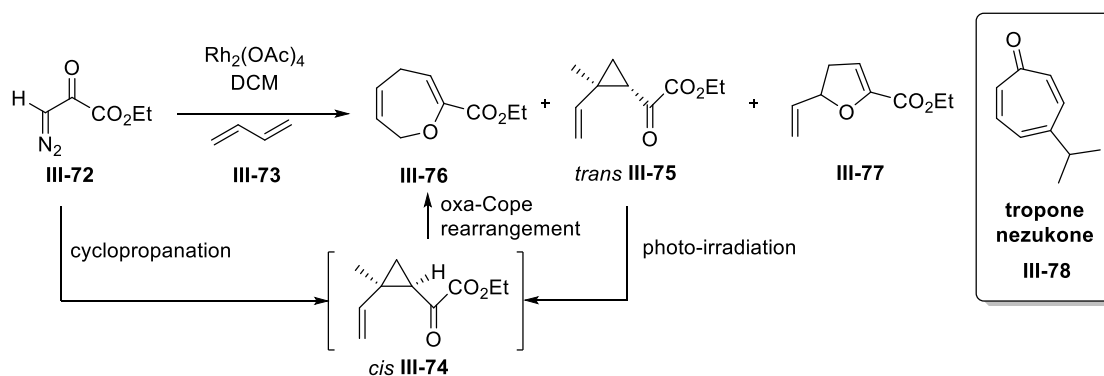
Scheme III-17 Catalytic enantioselective synthesis of highly substituted 2,5-dihydrooxepines

### 1.3.1.2. Rearrangements of *cis*-2-vinylcyclopropyl ketones

Compared with the valence tautomerization between *cis*-2-vinylcyclopropane-carboxaldehyde and 2,5-dihydrooxepine, the tautomerizations of other 2-vinylcyclopropane carbonyl compounds have been less studied.

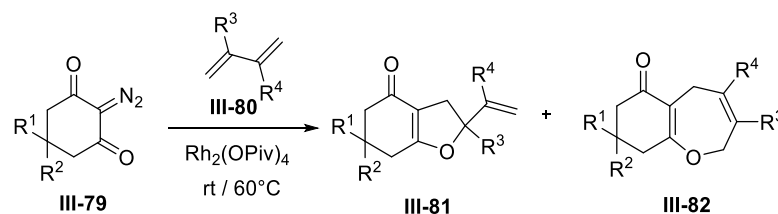
The Rh-catalyzed reaction of 1,3-butene with ethyl diazopyruvate not only provided an oxalycyclopropane **III-75** (Scheme III-18), but also 2,5-dihydrooxepine-7-carboxylate **III-76** and 2,3-dihydro-5-furoate **III-76**.<sup>226</sup> The *cis* isomer of cyclopropane **III-74** was totally transformed into dihydrooxepine, probably because of the coulombic repulsion of the  $\alpha$ -dicarbonyl system on the cyclopropane, which shifts the equilibrium to dihydrooxepines. The photo-isomerization of *trans* (**III-75**) to *cis* (**III-74**) isomer yielded 80% of dihydrooxepine **III-76**. The rearrangement of *cis*-1-acyl-2-vinylcyclopropane was afterwards applied to the synthesis of tropone nezukone **III-78**.

<sup>226</sup> a) R. S. Greenberg, H. S. Kim, E. Wenkert, *Helvetica Chimica Acta* **1987**, *70*, 2159-2165; b) M. E. Alonso, P. Jano, M. I. Hernandez, R. S. Greenberg, E. Wenkert, *J. Org. Chem.* **1983**, *48*, 3047-3050.



*Scheme III-18 Rh-catalyzed reaction of 1,3-butene with ethyl diazopyruvate*

Finally Lee et al. have investigated the rhodium(II)-catalyzed reactions of cyclic diazodicarbonyl compounds with conjugated dienes to prepare dihydrofurans and dihydrooxepines.<sup>227</sup> The reactions could be performed with various substituted dienes to get substituted five-membered rings **III-81** and seven-membered rings **III-82** (Scheme III-19). However, the main drawbacks of this method are that it always resulted in a mixture of compounds and non-substituted rings are difficult to obtain because of the volatility of butadiene.



*Scheme III-19 Rhodium(II)-catalyzed reactions of cyclic diazodicarbonyl compounds*

### 1.3.2. The Cloke-Wilson rearrangements to heterocyclopentenes

2-Vinyl-2,3-dihydrofurans are often observed as rearrangement products of 2-vinylcyclopropylcarbonyl compounds, defining the Cloke-Wilson rearrangement. The ring enlargements of cyclopropylimines and cyclopropylcarbaldehydes were first described by Cloke<sup>228</sup> and Wilson<sup>229</sup> in 1929 and 1947, respectively, forming the hetero-cyclopentenes under high temperature conditions. The presence of donor and acceptor substituents on cyclopropanes make the transformation of cyclopropylketones into dihydrofurans possible under mild conditions.<sup>2</sup> Besides, low-valent metal complexes could initiate the formation of

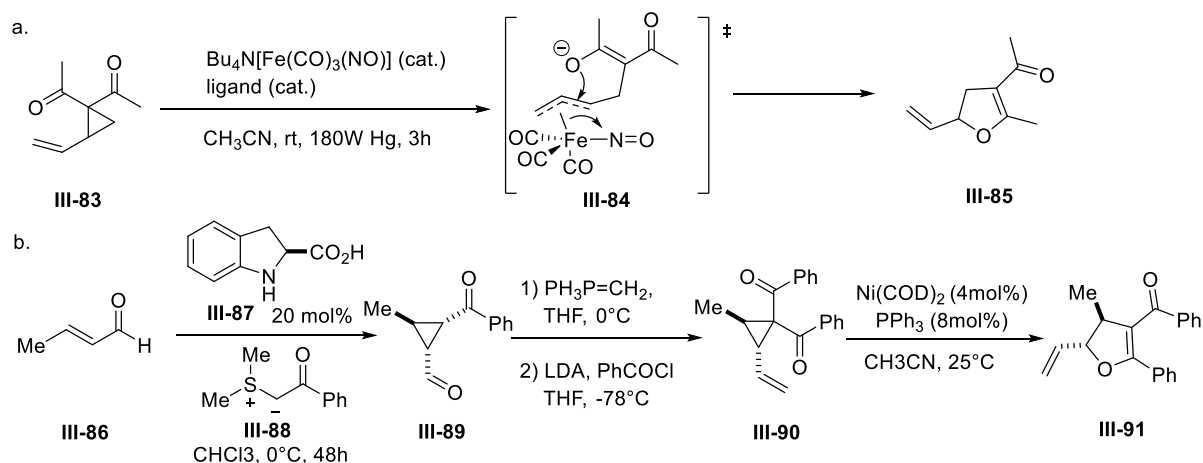
<sup>227</sup> Y. R. Lee, J. C. Hwang, *European Journal of Organic Chemistry* **2005**, 8, 1568-1577.

<sup>228</sup> J. B. Cloke, *J. Am. Chem. Soc.* **1929**, 51, 1174.

<sup>229</sup> C. L. Wilson, *J. Am. Chem. Soc.* **1947**, 69, 3002.

$\pi$ -allyl complex with suitably activated vinyl cyclopropanes to generate the corresponding vinyl or aryldihydrofurans in good yields. For example, the metal complex  $\text{Bu}_4\text{N}[\text{Fe}(\text{CO})_3(\text{NO})]$  (TBA[Fe]) catalyzes the rearrangement of vinylcyclopropane **III-83** under photochemical conditions at room temperature (Scheme III-20a).<sup>230</sup> Ni(0) not only catalyzed the rearrangement of 1-acyl-2-vinylcyclopropane **III-90** under mild reaction conditions with low catalyst loading, but also allowed a retention of configuration for chiral vinyl substitutions (Scheme III-20b).<sup>231</sup>

Beside the methodological achievements, the Cloke-Wilson rearrangement has been exemplified many times in the previous schemes of this section, standing as important side-products of the oxa-Cope rearrangement. It will also be discussed later with our results.



Scheme III-20 Cloke-Wilson rearrangements under mild conditions

### 1.3.3. A few words on 1-aza-Cope rearrangements (aza-retro-Claisen rearrangements)

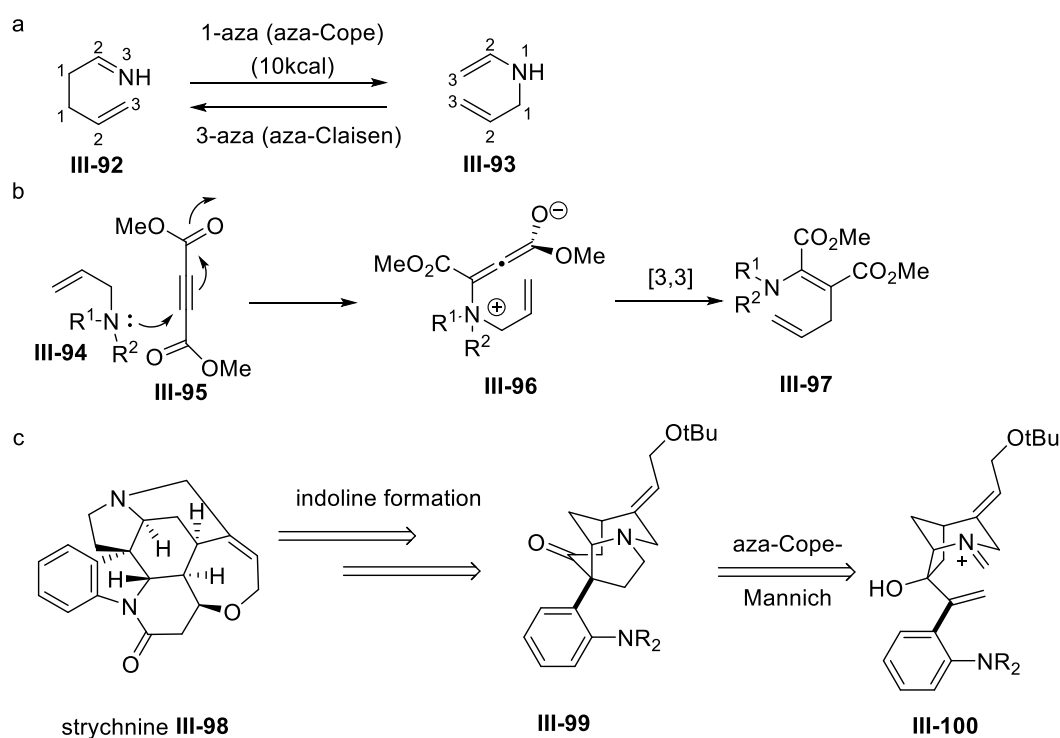
Aza-Cope rearrangements, together with the oxa-Cope rearrangements, are heteroatom variations of the Cope rearrangements. The 3-aza-Cope rearrangements (Scheme III-21a) were first developed in the 1960's and higher temperatures are required than the corresponding oxygen analogues.<sup>232</sup> Similar as the retro-Claisen rearrangement, the 1-aza-Cope rearrangement is endothermic, usually requiring 7-10 kcal/mol (Scheme III-21a). Uncatalyzed rearrangements of allyl vinyl amines undergo 3,3-sigmatropic conversion at about 250 °C. However, significant decrease of the reaction temperature could be achieved

<sup>230</sup> C. H. Lin, D. Pursley, J. E. M. N. Klein, J. Teske, J. A. Allen, F. Rami, A. Köhnc, B. Plietker, *Chem. Sci.* **2015**, *6*, 7034-7043.

<sup>231</sup> J. S. Johnson, R. K. Bowman, *Org. Lett.* **2006**, *8*, 573-576.

<sup>232</sup> S. Blechert, *Synthesis* **1989**, 71.

when the nitrogen is charged in the presence of a Brønsted or a Lewis acid, for example.<sup>233</sup> Henceforward, the effect of charged nitrogens on the kinetics of these rearrangements has been extensively exploited. The development of zwitterionic aza-Claisen and aza-Cope rearrangements, by lowering the activation energy barrier, allows the reactions to run at room temperature or below (Scheme III-21b).<sup>234</sup> In the meantime, this charge neutralization can serve as a highly efficient driving force.<sup>235</sup> A successful application of this rearrangement was the total synthesis of strychnine, taking the tandem aza-Cope-Mannich reaction as a key step. (Scheme III-21c).<sup>236</sup>



Scheme III-21 Aza-Cope rearrangements: a. General presentation; b. Cationic aza-Cope rearrangement; c. Synthesis of strychnine by Overman

## 2. Experimental studies for the synthesis of 2,5-dihydrooxepines through one-pot tandem cyclopropanation/oxa-Cope rearrangement

The pioneering work on the acyl-2-vinylcyclopropyl ketone rearrangement demonstrated its

<sup>233</sup> a) L. E. Overman, *Acc. Chem. Res.* **1992**, *25*, 352–359; b) L. E. Overman, L. T. Mendelson, E. J. Jacobsen, *J. Am. Chem. Soc.* **1983**, *105*, 6629–6637; c) R. J. Doedens, G. P. Meier, L. E. Overman, *J. Org. Chem.* **1988**, *53*, 685–690.

<sup>234</sup> J. F. Lavallée, G. Berthiaume, P. Deslongchamps, F. Grein, *Tetrahedron Lett.* **1986**, *27*, 5455–5458.

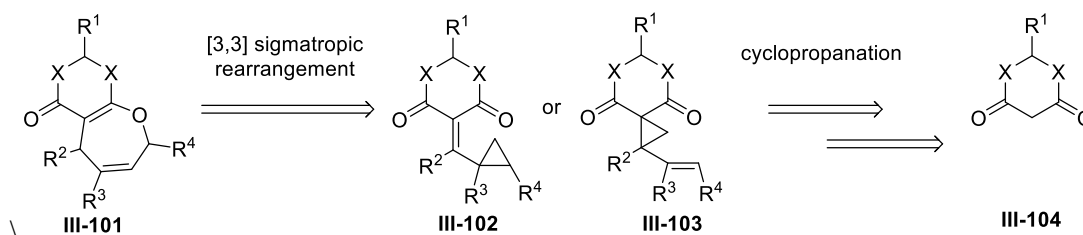
<sup>235</sup> U. Nubbemeyer, *Natural Products Synthesis II* **2005**, 149–213.

<sup>236</sup> S. D. Knight, L. E. Overman, G. Pairedeau, *J. Am. Chem. Soc.* **1993**, *115*, 9293–9294.



possible utility in the construction of seven-membered cyclic systems. However, unlike 2-vinylcyclopropanecarboxaldehydes, the rearrangement of 2-acylvinylcyclopropyl ketones has been neither well studied, nor applied to total synthesis. The development of an applicable oxa-Cope rearrangement became therefore attractive for ketone derivatives. Thus, we envisioned at first to synthesize 2-vinylcyclopropane 1,1-dicarbonyl derivatives, then to study their rearrangement as a new route toward the synthesis of functionalized 2,5-dihydrooxepines. In parallel of this work, a thorough theoretical work was performed and highlighted the peculiar reactivity of our oxa-Cope substrates (developed in Section 3). Eventually, this method could be applied to the synthesis of complex oxepine derivatives like cinereain-type and also benzoxepine natural products (**Chapter IV**).

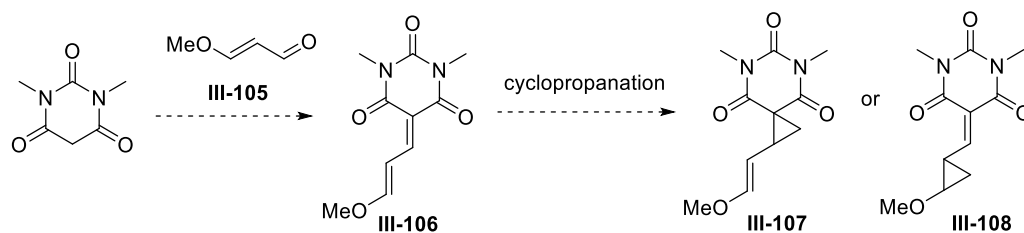
Two different precursors **III-102** and **III-103** (Scheme III-22) were first envisaged. Both of these two intermediates contain an acylvinylcyclopropane moiety, but differ from the position of the cyclopropane, one attached directly at the central position of a 1,3-dicarbonyl group, the other located at the terminal definite position. Different strategies have thus been examined initially to synthesize these intermediates and also test these hypotheses.



*Scheme III-22 New synthetic strategy*

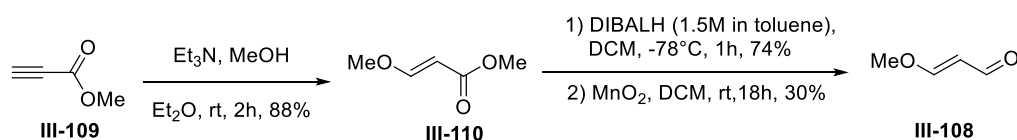
### 2.1. Attempts of Knoevenagel condensation followed by cyclopropanation

Discovered in 1894, the Knoevenagel condensation is an efficient type of carbon-carbon bond-forming reaction, particularly for the reaction between active methylene (especially malonate derivatives) and carbonyl compounds. Afterwards, a Simmons-Smith reaction could install the cyclopropane to the generated or an adjacent alkene. In a first attempt, we tried to condense dimethyl barbituric acid with 3-methoxyacrolein **III-105** to give **III-106** bearing a polarized diene (Scheme III-23). Then a cyclopropanation on one of the double bond in the presence of diiodomethane with zinc-copper couple would afford either **III-107** or **III-108**. These dimethyl barbituric acids were initially chosen due to their similarity with intermediate **III-4** (Scheme III-1), which was planned in our total synthesis of oxepino-DKP.



Scheme III-23 Precursors preparation through Knoevenagel condensation/ cyclopropanation/ oxa-Cope rearrangement

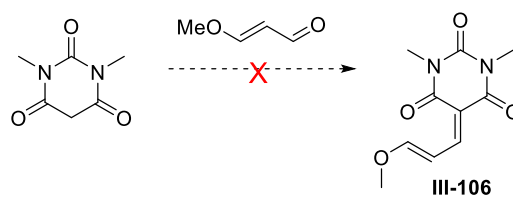
3-Methoxyacrolein was prepared according to a known procedure (Scheme III-24).<sup>237</sup> One equivalent of methanol was added to methyl propiolate **III-109** in the presence of triethylamine. Then the obtained methyl 3-methoxyacrylate **III-110** was reduced to alcohol with DIBALH and reoxidized with MnO<sub>2</sub> to get aldehyde partner **III-108**.



Scheme III-24 Preparation of 3-methoxyacrolein

The Knoevenagel condensation was afterwards attempted between dimethyl barbituric acid and aldehyde **III-108**. Unfortunately, no reaction happened under different basic conditions (Table III-1). The failure might result from the decrease electrophilicity of aldehyde partner **III-108**, which is strongly conjugated with an electron donating group.

Table III-1 Condition screening for Knoevenagel condensation of dimethyl barbituric acid

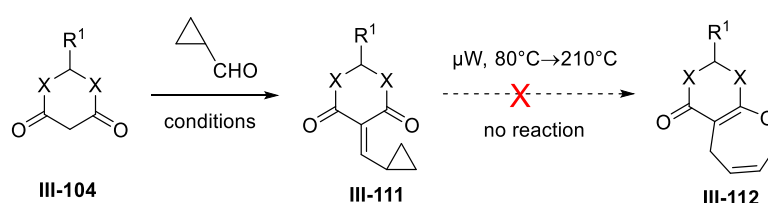


Entry	Conditions	Results
1	L-proline (0.1 equiv.), toluene, rt	NR
2	piperidine (0.06 equiv.), MS 4Å, DCM, rt or reflux	NR
3	K <sub>2</sub> CO <sub>3</sub> (1.0 equiv.), DCM, rt or 50°C	NR
4	K <sub>2</sub> CO <sub>3</sub> (1.0 equiv.), DMF, rt or 50°C	NR

<sup>237</sup> Y. V Quang, D. Marais, F. Le Goffic, *Tetrahedron Letters* **1983**, 24, 5209-5210.

The commercially available cyclopropanecarboxaldehyde could directly give several precursors **III-111** by the condensation with suitable 1,3-dicarbonyl substrates. Cyclic compounds such as 1,3-cyclohexanediones, Meldrum's acid and barbituric acids were tested at first. The Knoevenagel condensation successfully gave the desired intermediates (**III-113** to **III-115**) in 88, 85 and 78% yields, respectively (Table III-2). However, these intermediates were inert upon heating to perform the sigmatropic rearrangement. Hence, we concluded that the cyclopropane C-C bond was probably not polarized enough to drive the intramolecular cyclization. We turned our attention toward the synthesis of donor-acceptor cyclopropanes.

Table III-2 Knoevenagel condensation with commercial cyclopropanecarboxaldehyde



Entry	Substrates	Conditions	Results (isolated yield)
1		L-proline (0.1 equiv.), toluene, 18h, rt	 <b>III-111a</b> (78%)
2		L-proline (0.1 equiv.), toluene, 18h, rt	 <b>III-111b</b> (85%)
3		L-proline (0.1 equiv.), toluene, 18h, rt <sup>238</sup>	 <b>III-111c</b> (88%)

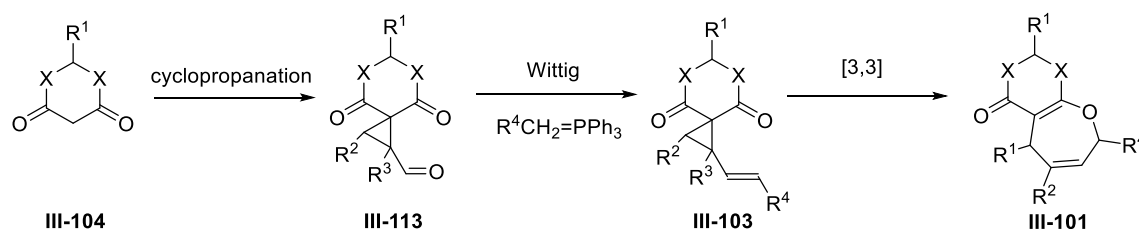
## 2.2. Attempts of cyclopropanation followed by Wittig reaction

The direct carbene transfer from free carbenes or diazo compounds onto olefins is a popular method to make cyclopropanes.<sup>239</sup> As the cyclopropyl model **III-103** would be ideal to realize

<sup>238</sup> X. Y. Tang, Y. Wei, M. Shi, *Org. Lett.* **2010**, *12*, 5120-5123.

<sup>239</sup> a) C. Ebner, E. M. Carreira, *Chem. Rev.* **2017**, *117*, 11651-11679; b) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981-10080.

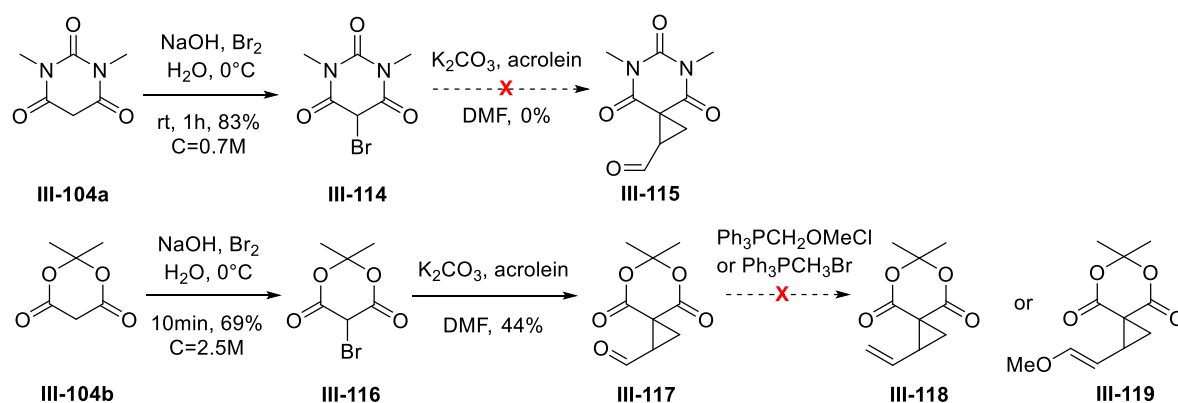
the oxa-Cope rearrangement, the direct cyclopropanation at the  $\alpha$ -position of dicarbonyl compounds could directly generate precursor **III-113**, which would be followed by the Wittig reaction, offering possibilities to diversify the targeted 2,5-dihydrooxepines **III-101** (Scheme III-25).



Scheme III-25 Strategy of Cascade Cyclopropanation / Wittig reaction/ Oxa-Cope rearrangement

### 2.2.1. Cyclopropanation with $\alpha$ -bromodicarbonyl compounds

$\alpha$ -Bromodicarbonyl compounds can generate in situ carbenes in basic medium.<sup>240</sup> Here bromobarbituric acids and bromo-Meldrum's acid are synthesized by using  $\text{Br}_2$  under highly concentrated basic reaction conditions. Then both monobromo-intermediates **III-114** and **III-116** were engaged in a reaction with acrolein in the presence of  $\text{K}_2\text{CO}_3$ , assuming to give the corresponding cyclopropane derivatives (Scheme III-26). Unfortunately, the cyclopropanation only worked with bromo-Meldrum's acid **III-116** to give compound **III-117** with a moderate yield after purification, although a 100% conversion was observed after 2 h of reaction (NMR titration in situ with dimethoxybenzene). This moderate yield might be a result of the poor stability of the product **III-117** in the work-up condition.



Scheme III-26 Preparations of monobromo-heterocycles and corresponding cyclopropanations

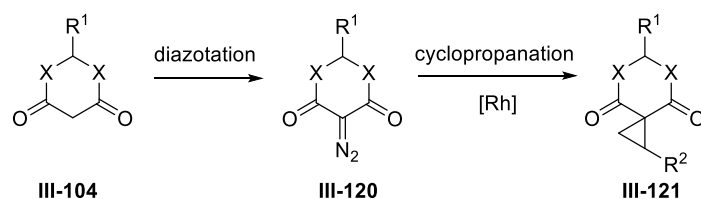
For the same reason, the Wittig reaction was not achieved successfully. Two phosphonium

<sup>240</sup> a) V. Terrasson, A. Lee, R. M. de Figueiredo, J. M. Campagne, *Chem. Eur. J.* **2010**, *16*, 7875 – 7880; b) A. Russo, S. Meninno, C. Tedesco, A. Lattanzi, *Eur. J. Org. Chem.* **2011**, 5096–5103.

species ( $\text{Ph}_3\text{PCH}_3\text{Br}$  and  $\text{Ph}_3\text{PCH}_2\text{OCH}_3\text{Cl}$ ) and various bases to deprotonate them (like  $n\text{BuLi}$ ,  $\text{LiHMDS}$ ,  $\text{LDA}$ ,  $t\text{BuOK}$ ,  $\text{NaH}$ ) were tested, but only degradation was observed in all conditions.

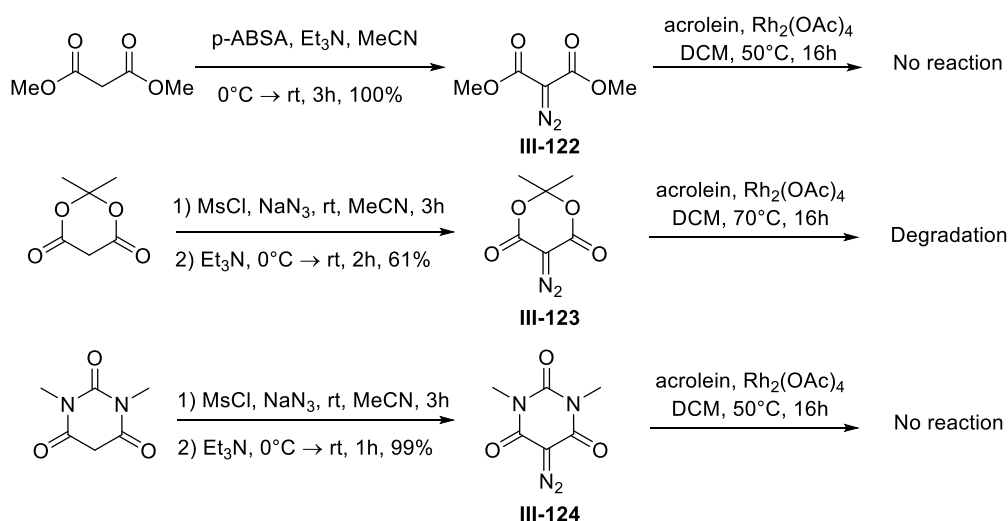
## 2.2.2. Cyclopropanation by using diazo-derived carbenoids

The metal-catalyzed cyclopropanations of olefins with carbenoids have largely been studied. Mild conditions are often considered advantageous over other diazo-derived cyclopropanations. (Scheme III-27)



Scheme III-27 Strategy involving cyclopropanation with diazo-derived carbenoids

The diazotation of 1,3-dicarbonyl compounds successfully resulted in their corresponding diazo derivatives **III-122**, **III-123** and **III-124** by using *p*-acetamidobenzenesulfonyl azide or mesyl azide as diazo transfer agents (Scheme III-28).



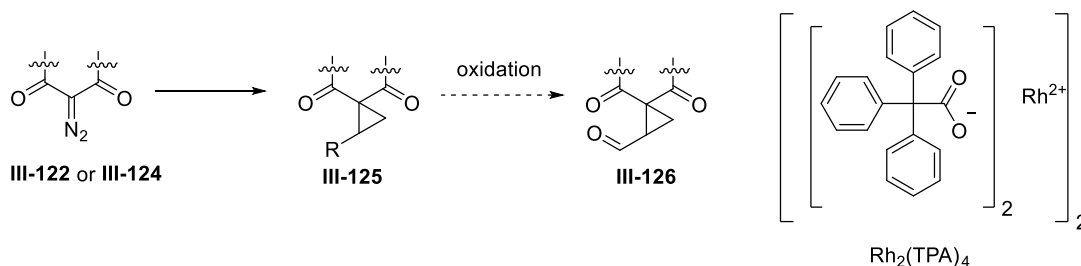
Scheme III-28 Preparation of diazo-derived carbenoids

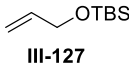
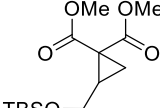

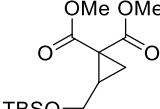
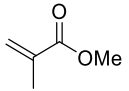
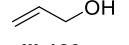
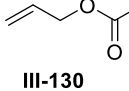
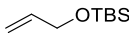
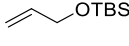
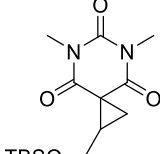
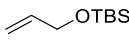
These three diazo intermediates were engaged in acrolein cyclopropanation by catalyzed by rhodium(II) acetate,<sup>241</sup> but no successful result was obtained. Thus, a brief screening of Rh(II) catalysts and olefin partners were performed. In the case of dimethyl diazomalonate, the

<sup>241</sup> a) D. A. Dias, M. A. Kerr, *Org. Lett.* **2009**, *11*, 3694–3697; b) F. González - Bobes, M. D. B. Fenster, S. Kiau, L. Kolla, S. Kolotuchin, M. Soumeillant, *Adv. Synth. Catal.* **2008**, *350*, 813 – 816.

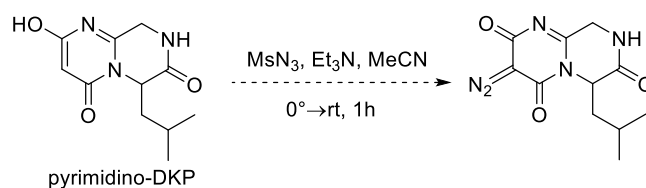
cyclopropanation took place only with allyl TBS ether, when catalyzed by  $\text{Rh}_2(\text{OAc})_4$  or  $\text{Rh}_2(\text{TPA})_4$  and gave a cyclopropane in 40% yield. The same screenings with diazo barbituric acid was performed as follows (Table III-3). The cyclopropyl compound **III-125b** was only observed in the reaction with allyl TBS ether when catalyzed by  $\text{Rh}_2(\text{TPA})$ .

Table III-3 Results of cyclopropanation by using diazo-derived carbenoids



Entry	Substrats	Catalyst	Conditions	Reagent	Results (yield)
1	<b>III-122</b>	$\text{Rh}_2(\text{OAc})_4$	$\text{CDCl}_3$ , 50°C, 16h	 <b>III-127</b>	 <b>III-125a</b> (43%)
2	<b>III-122</b>	$\text{Rh}_2(\text{TPA})_4$	$\text{CDCl}_3$ , 50°C, 16h		 <b>III-125a</b> (41%)
3	<b>III-124</b>	$\text{Rh}_2(\text{OAc})_4$	DCM, 80°C, 18h	 <b>III-128</b>	NR
4	<b>III-124</b>	$\text{Rh}_2(\text{OAc})_4$	DCM, 80°C, 18h	 <b>III-129</b>	NR
5	<b>III-124</b>	$\text{Rh}_2(\text{OAc})_4$	DCM, 80°C, 18h	 <b>III-130</b>	Trace
6	<b>III-124</b>	$\text{Rh}_2(\text{OAc})_4$	$\text{CDCl}_3$ , 50°C, 16h		NR
7	<b>III-124</b>	$\text{Rh}_2(\text{TPA})_4$	$\text{CDCl}_3$ , 50°C, 16h		 <b>III-125b</b> (15%)
8	<b>III-124</b>	$[(\text{CF}_3\text{COO})_2\text{Rh}]_2$	$\text{CDCl}_3$ , 50°C, 16h		complex mixture

Meanwhile we also attempted the diazotation of pyrimidino-DKP, which only led complex mixtures (Scheme III-29). Its detail will be discussed in Chapter IV. This result in consequence precluded the use of this diazo strategy in our total synthesis.



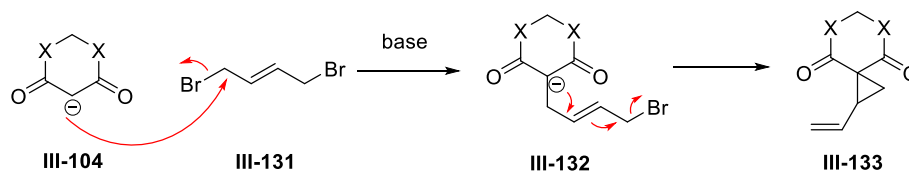
Scheme III-29 Application of diazo strategy in total synthesis of janoxepin

These unsatisfied results in the cyclopropanation arouse our reflection on the reactivity of starting materials and the stability of intermediates. Being electron deficient, these carbenes act usually as electrophiles, suggesting that their reaction with electrons-deficient olefins is more difficult if the metal carbene intermediates are also electron-deficient.<sup>242</sup> Thus, we concluded that the above strategies were not adapted to get the oxa-Cope rearrangement precursors.

### 2.3. Tandem cyclopropanation/oxa-Cope rearrangement by using 1,4-dibromobut-2-ene substrate as a conjunctive reagent

#### 2.3.1. First encouraging results

Since 1884, when W. H. Perkin reported a nucleophilic cyclopropanation<sup>243</sup> by using diethyl malonate and 1,2-dibromoethane in the presence of NaOEt, numerous studies have been carried out to perform cyclopropanes by conjunctive alkylation reagent. Inspired by this simple reaction, *trans*-1,4-dibromobutene was envisaged to directly synthesize 1,1-dicarbonyl-2-vinylcyclopropanes (Scheme III-30). Thanks to its double electrophilic character, this dibromobutene can be engaged in a tandem S<sub>N</sub>2-S<sub>N</sub>2' reaction, affording the vinylcyclopropane **III-133** when reacting with a doubly nucleophilic species like 1,3-dicarbonyl substrates **III-104**.

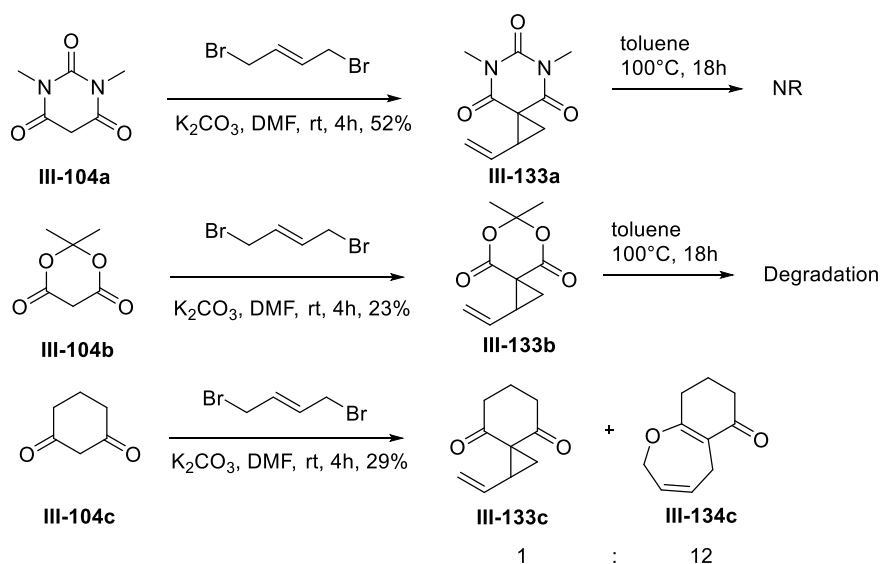


Scheme III-30 Mechanism of nucleophilic cyclopropanation by using dibromobutene

<sup>242</sup> M. Brookhart, W. B. Studabaker, *Chem. Rev.* **1987**, 87, 411–432.

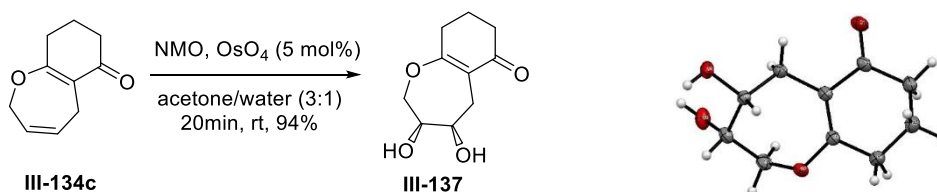
<sup>243</sup> W. H. Perkin, *Ber. dtsh. Chem. Ges.* **1884**, 17, 54–59.

1,3-Cyclohexanediones, Meldrum's acid and dimethyl barbituric acid were tested at first under typical basic reaction condition (Scheme III-31). Surprisingly, all the cyclopropane derivatives **III-113a**, **III-133b** and **III-133c** were formed, together with a cyclic product **III-134c** isolated in 29% yield, which was quickly suspected to be the expected 2,5-dihydrooxepine when the reaction was performed on 1,3-cyclohexanedione. According to  $^1\text{H-NMR}$  spectrum, the following signals appeared: a doublet of triplet at 6.26 ppm ( $J = 9.7, 6.2$  Hz) which coupled with a doublet of triplet of triplet at 6 ppm ( $J = 9.7, 6.6, 1.2$  Hz), suggesting that a low-field shifted and non-conjugated olefin was generated. Their corresponding coupling signals at 3.27 ppm (dd,  $J = 6.2, 1.1$  Hz) and at 4.69 ppm (d,  $J = 6.6$  Hz) revealed the presence of two neighbor  $\text{CH}_2$  to this double bond. This  $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-$  system led us to propose the structure of 2,5-dihydrooxepine **III-134c**.



Scheme III-31 Tandem cyclopropanation/oxa-Cope rearrangement by using 1,4-dibromo-2-butane

To confirm the structure of product **III-134c**, a dihydroxylation with  $\text{OsO}_4$  and NMO was performed. The resulted dihydroxylated solid product **III-137** was crystalized and revealed right structure by X-ray crystallographic analysis. (Scheme III-32)



Scheme III-32 Structural confirmation of 2,5-dihydrooxepine



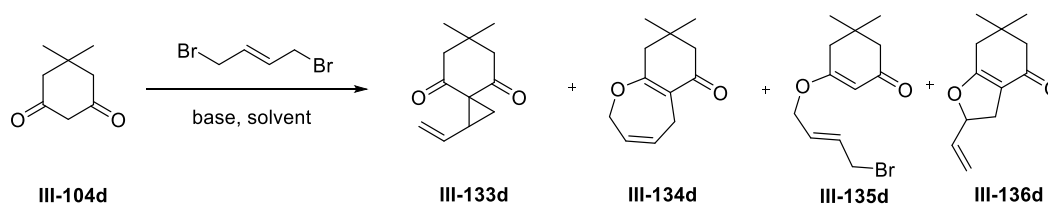
Unfortunately, heating of the other two cyclopropane derivatives **III-133a** and **III-133b** delivered no desired thermal [3,3] sigmatropic rearrangement products. The barbituric acid derivative remained unreactive while the Meldrum's acid derivatives decomposed.

These encouraging preliminary results led us to envisage further application of this tandem cyclopropanation/oxa-Cope rearrangement to synthesize diverse seven-membered oxacycles before its attempt toward natural product synthesis. In addition, the double elimination of hydroxyl groups (through mesylates) may furnish an entry to oxepines in our total synthesis of cinereain or janoxepin.

### 2.3.2. Optimization of reaction conditions by NMR studies

#### 2.3.2.3. Screening of solvents and bases

During this tandem cyclopropanation/oxa-Cope rearrangement, besides cyclopropane **III-133d** and dihydrooxepine **III-134d**, two other different compounds are also isolated: *O*-allylation product **III-135d** and dihydrofuran **III-136d** (Scheme III-33). In favor of the optimization of dihydrooxepines, different bases and solvents were screened. All results are presented in <sup>1</sup>H-NMR yields.



*Scheme III-33 Possible products of tandem cyclopropanation/oxa-Cope rearrangement*

The enolates of 1,3-dicarbonyl compounds are ambident anions. They have usually two reactive centers, which are capable of giving two types of products in nucleophilic substitution reactions.<sup>244</sup> In our case, the C-alkylation competed with *O*-alkylation. The major influencing factors of the ambident anion's reactivities include solvents, counterions, temperatures, concentrations and structures of the alkylating agent and leaving groups.<sup>245</sup> Here, we focused primarily on the hardness-softness character of ions and solvation effects.

As the dissociation constant between enolate and different cations may favor one product over the other. The first optimization was carried out between three different carbonate bases

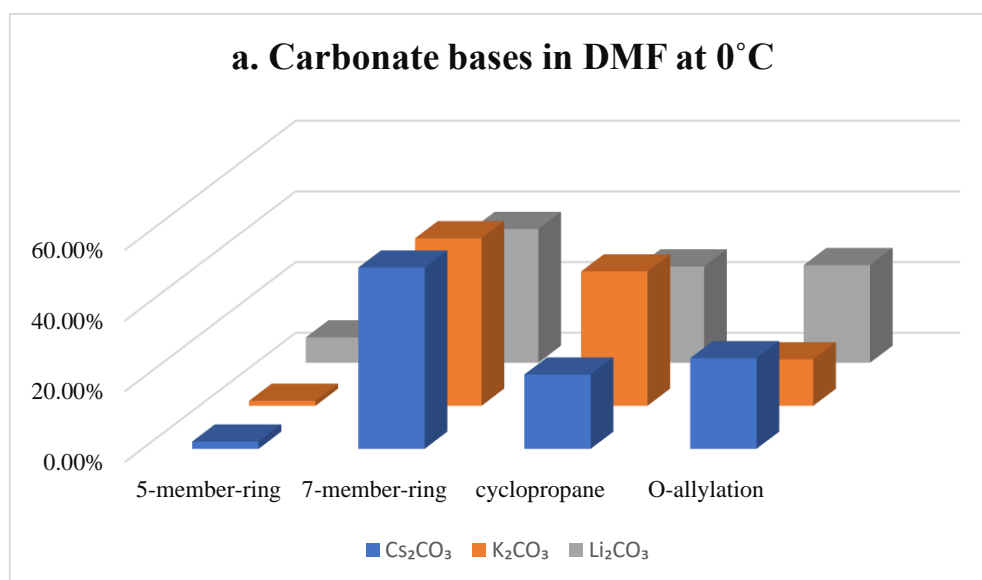
<sup>244</sup> H. Mayr, M. Breugst, A. R. Ofial, *Angew. Chem. Int. Ed.* **2011**, *50*, 6470-6505.

<sup>245</sup> S. A. Shevelev, *Russian Chemical Reviews* **1970**, *39*, 844-858.

( $\text{K}_2\text{CO}_3$ ,  $\text{Li}_2\text{CO}_3$  and  $\text{Cs}_2\text{CO}_3$ ) to investigate the counterion effect on this tandem reaction. In DMF,  $\text{K}_2\text{CO}_3$  led to less *O*-allylated product (12%) at 0 °C (Chart III-1a). Dramatically, the *O*-allylation was minimized in DMSO with any base at room temperature. The reaction with  $\text{Cs}_2\text{CO}_3$  in DMSO gave the least *O*-allylation product (5%) (Chart III-1b). The C/*O* alkylation ratio did not change a lot with the various counterions in both DMSO and DMF, highlighting the reactivity of the free carbanion.<sup>60</sup> However, DMSO showed higher C/*O* alkylation ratio for the three counterions than that in DMF, which could be rationalized by the fact that less coordinating solvents (here, DMSO)<sup>246</sup> led to higher aggregates between cation and enolate ions, therefore lowering *O*-alkylated products. In all cases, 2,5-dihydrooxepine **III-134d** was the major product, especially when  $\text{Cs}_2\text{CO}_3$  was used. NMR yields were always found superior to 60%.

Except carbonate bases, *t*BuOK and DIPEA were also investigated (Chart III-1c). Strongly basic conditions promoted *O*-allylation to the same ratio as dihydrooxepine formation, while amine base DIPEA largely increased dihydrofuran **III-136d** formation, which is also a non-desired side reaction.

In addition, cesium salts are well-known for their good solubility in dipolar aprotic solvents, like DMF and DMSO,<sup>247</sup> 20 times more soluble than their potassium counterparts.<sup>248</sup> The use of  $\text{Cs}_2\text{CO}_3$  as a base would thus also help to speed up the reaction.



<sup>246</sup> A. Bagno, G. Scorrano, *J. Am. Chem. Soc.* **1988**, *110*, 4577-4582.

<sup>247</sup> R. Rabie, M. M. Hammouda, K. M. Elattar, *Research on Chemical Intermediates* **2017**, *43*, 1979-2015.

<sup>248</sup> R. M. Kellogg, G. Dijkstra, W. H. Kruizinga, *J. Org. Chem.* **1987**, *52*, 4230-4234.

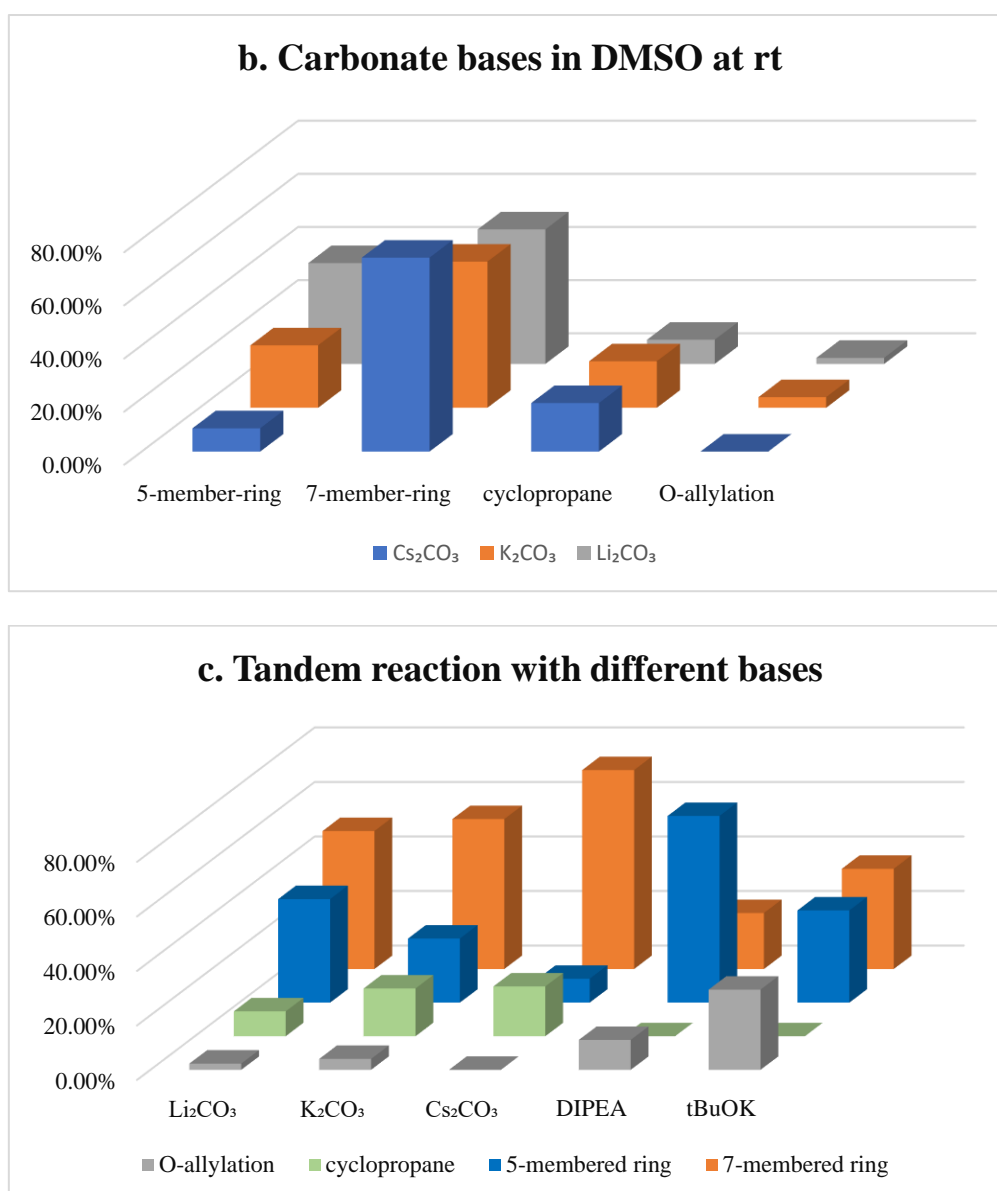


Chart III-1: Comparison of NMR yields between different bases: a) screening reaction of carbonate bases in DMF at 0°C; b) Screening reaction of carbonate bases in DMSO at room temperature; c) Screening reaction of 5 different bases in DMSO at room temperature

In the screening of solvents, polar systems were mainly analyzed because of the poor solubility of 5,5-dimethyl-1,3-cyclohexadione. According to resumed histogram (Chart III-2), polar aprotic solvents considerably favored seven-membered ring formation, such as DMF, DMSO, ether solvents and acetone. The larger dipole moment the solvent has, the better the solvent could be. In this case, DMSO gave the best result. Besides, THF, dioxane and Et<sub>2</sub>O completely suppressed five-membered ring formation, while increasing O-alkylation at the same time, thus excluding them from our study. Solvent mixtures were also tested (e.g.

DMSO/butanone) without success. Finally, the use of a phase transfer catalyst, tetrabutylammonium iodide, in acetone gave comparable results as DMSO alone.

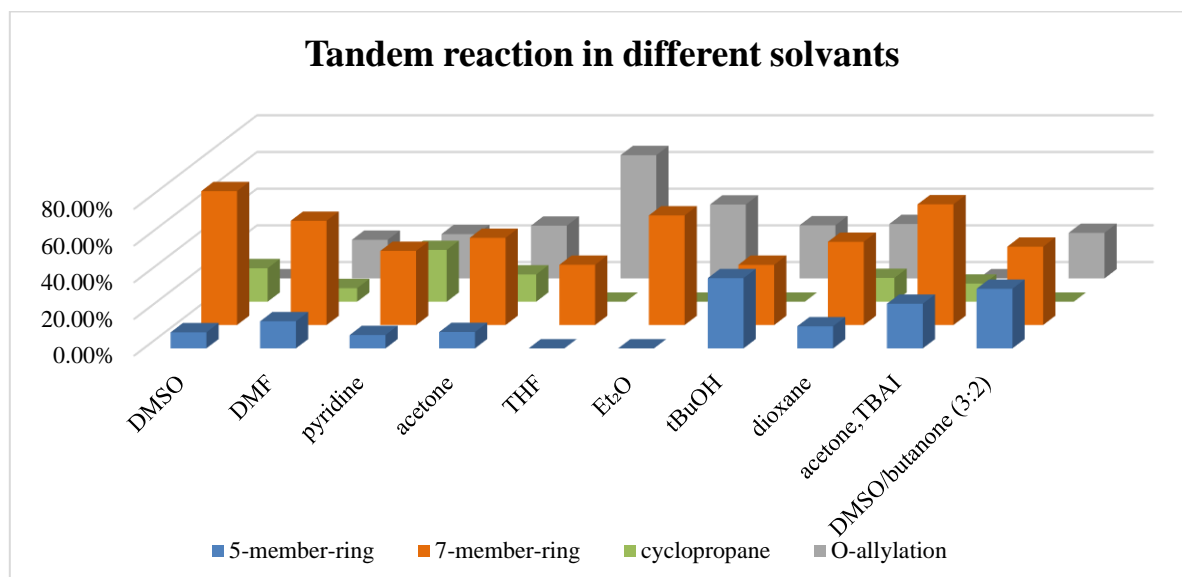


Chart III-2: Comparison of NMR yields in different solvent systems

To sum up, the combination of DMSO and  $\text{Cs}_2\text{CO}_3$  provided the best C-allylation ratio and maximized the formation of 2,5-dihydrooxepine.

#### 2.3.2.4. NMR kinetic studies

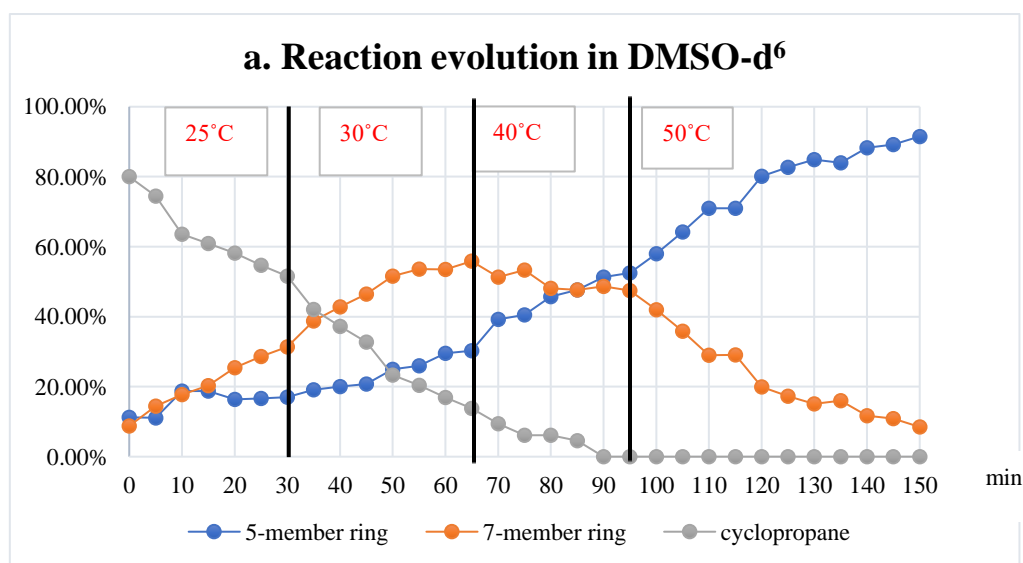
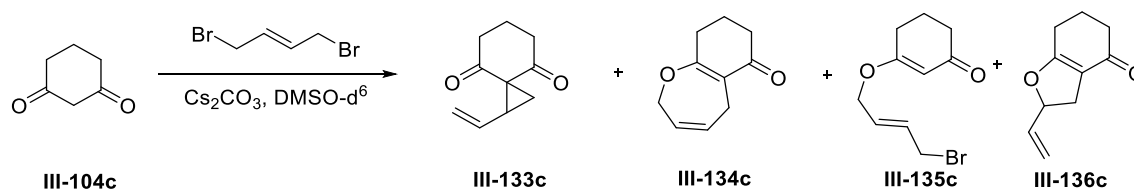
The sigmatropic rearrangements are usually considered as thermal reactions.<sup>249</sup> To better understand the mechanism of our tandem cyclopropanation/oxa-Cope rearrangement, kinetic studies on the equilibration between the 1-acyl-2-vinylcyclopropane intermediate and 2,5-dihydrooxepine were investigated through temperature-dependant NMR studies. All reactions were carried out directly in NMR tubes with a recording interval of 5 minutes, 15 minutes or 1 hour. The proton integration value of each compound from all spectra was mapped out as a line chart. O-alkylation products were formed in each case with an approximate 20% yield, demonstrating their rapid formation and low reactivity. As no evolution of these species was observed during the experiment, they are not involved in the following discussions.

The first kinetic experience was performed with a range of temperature from 25 °C to 50 °C. The reaction was kept at each temperature for 30 min. The line plot below (Chart III-3a) indicates that the cyclopropanation step rapidly ended. The 1,1-dicarbonyl-2-

<sup>249</sup> J. E. Baldwin, *Chem. Rev.* **2003**, *103*, 1197–1212.

vinylcyclopropane has already rearranged into 10% of 7-membered ring form and 10% five-membered ring at  $t_0$  of the NMR experiment, 5 minutes after the addition of 1,4-dibromobutene. From 25 °C to 30 °C, the equilibrium shifted principally to the seven-membered-ring form, while the 5-membered ring progressively formed along with the temperature increasing. At 40 °C, the dihydrooxepine began to decline, and the dihydrofuran was formed with a higher speed rate. At 50 °C, the dihydrooxepine decomposed completely after one hour. These results illustrate that the formation and degradation of 2,5-dihydrooxepine are temperature-dependant. Delicate reaction and work-up conditions should thus be employed, carefully avoiding warm temperatures.

Then, a long time-range kinetic study at 25 °C was carried out to well understand the equilibrium under isotherm condition and acquire more information about the stability of each product at 25 °C (Chart III-3b). The vinylcyclopropane completely disappeared in 2 hours. The highest yield of dihydrooxepine (40%) was attained at 1h, then remained nearly stable for 5h. Its disappearance mildly took place within 24 h. As for dihydrofuran **III-136c**, a steady increase occurred up to 3h. Then its formation slowly raised, which corresponded precisely to the decline of the dihydrooxepine form. These results outline that the dihydrooxepine is not stable even at 25 °C. This seven-membered ring may be converted to the five-membered ring with the time.



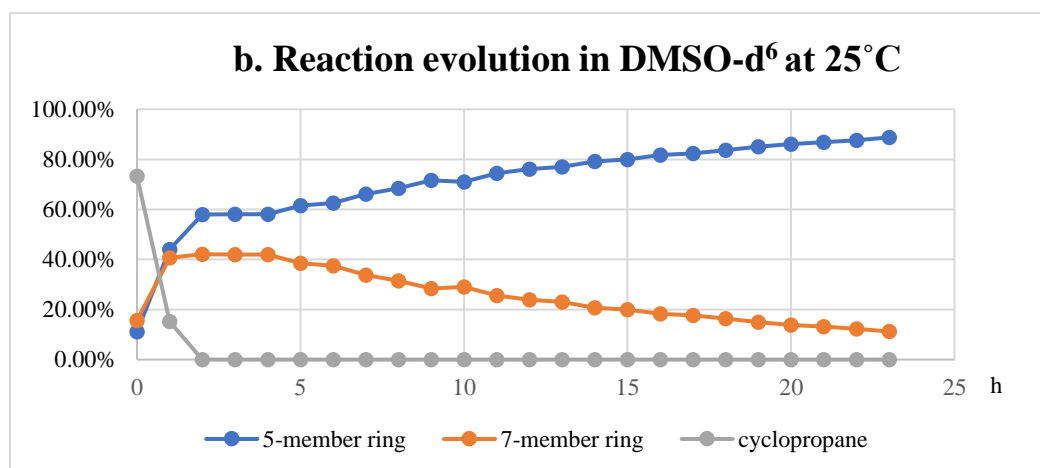


Chart III-3: NMR yield evolutions of 3 products (**III-133c**, **III-134c** and **III-136c**) in DMSO: a) NMR yield evolutions range from 25 °C to 50 °C; b) NMR yield evolutions at 25 °C for 24h

The kinetic NMR study was also accomplished with 5,5-dimethyl-1,3-cyclohexadione to ensure that the previous study was not unique. At 25 °C, dihydrooxepine **III-134d** attained a maximum yield of 60% after 2 h, and then dropped considerably without any stabilization stage (Chart III-4a). However, dihydrofuran **III-136d** formed more slowly than dihydrofuran **III-136c** (Chart III-3) of the previous case during the first 2 hours, and then increased with the same formation rate as the dihydrooxepine degradation rate during 24h. These observations might be related to the fact that the dimethyl substitution increases the activation energy between cyclopropanes and seven-membered or five-membered ring products. At 25 °C, the provided energy is strong enough to convert the cyclopropane to the dihydrooxepine; whereas, the conversion to dihydrofuran occurs along with continuous heat supply.

Since DMSO has a higher melting point (19 °C) compared to other solvents, lower reaction temperature is limited to 19°-20 °C. A kinetic study was performed in DMF at 20 °C, to avoid solvent freeze during the study. As shown in the line graph (Chart III-4b), the vinylcyclopropane was converted into dihydrooxepine in 10 hours with nearly 70% yield. Surprisingly, the yield did not drop during 24 hours, with no more dihydrofuran formed as well. This gratifying result indicated that the equilibrium ratio between the vinylcyclopropane and the 2,5-dihydrooxepine is approximately 7:2 at 20 °C in DMF. However, this reaction is exceedingly dependant on the temperature, as previously discussed, and it becomes obvious that the temperature window for the formation of 2,5-dihydrooxepines **III-134d** in DMSO will be very narrow.

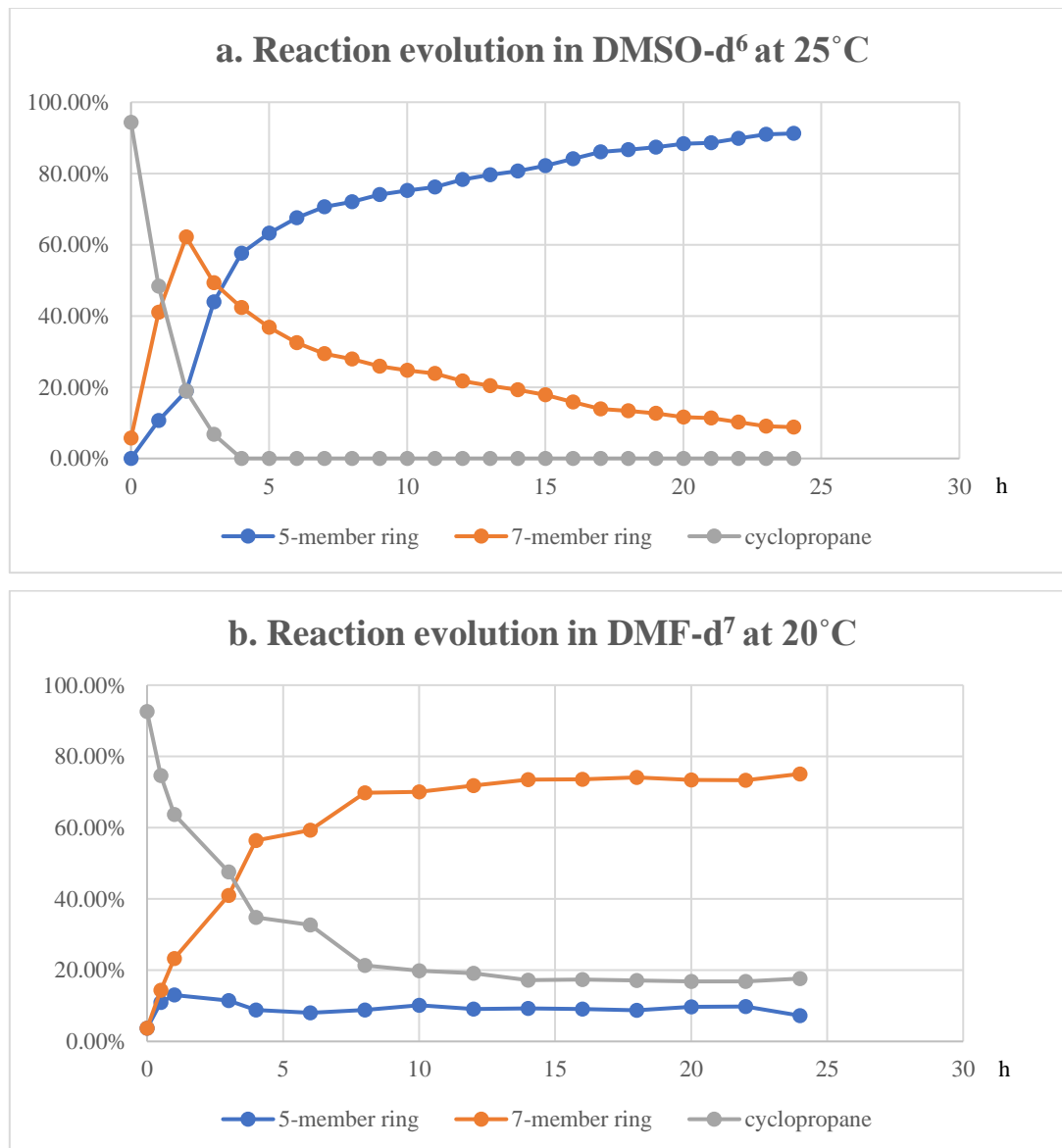
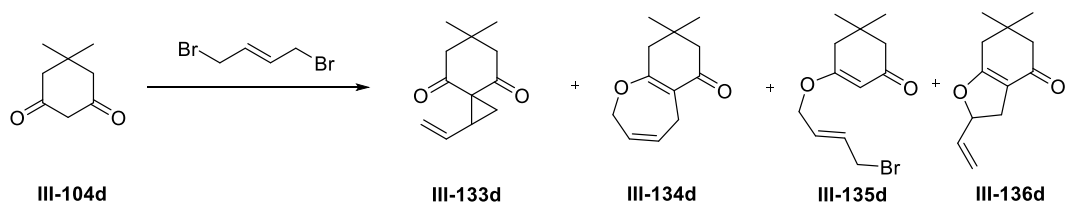


Chart III-4: Evolutions of NMR yields for 3 products (**III-133d**, **III-134d** and **III-136d**): a) NMR yield evolutions at 25 °C in DMSO; b) NMR yield evolutions at 20 °C in DMF

### 2.3.3. Reaction attempts with cyclic substrates

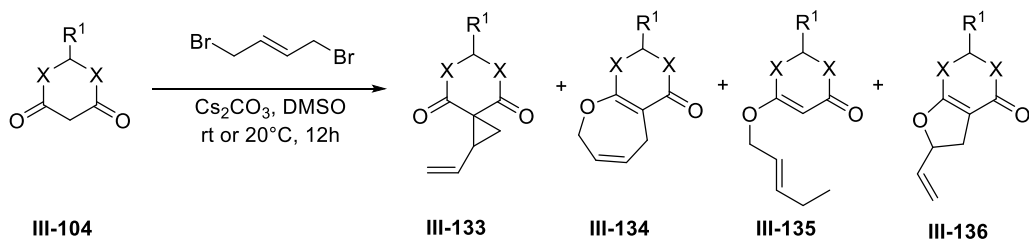
From previous optimization and NMR temperature-dependant studies, the best reaction conditions found employed Cs<sub>2</sub>CO<sub>3</sub> in DMSO at 20 °C. These specific tandem reaction conditions were afterwards applied in a reaction scope study of cyclic substrates.

Depending on the substitution pattern, products of [3,3] sigmatropic rearrangement of 2-vinylcyclopropyl diketones may change in thermodynamic stability (Scheme III-34). Cyclohexadione and its derivatives are good reaction substrates to favor 2,5-dihydrooxepines formation. The substituted carbonyl group on C6 in **III-134c** might stabilize the seven-membered ring products, so that no cyclopropane product was isolated alone and isomerized spontaneously to the ring compounds. Occasionally, the cyclopropane product could be found as a minor component of the dihydrooxepine. The reactivity of 1,3-pentanedione dropped, giving lower yields of **III-134h** (23%). A large substitution group like a phenyl seems to stabilize relatively the seven-membered product **III-134f** upon isolation. In the case of a non-symmetrical cyclohexadione (*e.g.* **III-134e**), the most electron-rich carbonyl group (also the most hindered in the case of **III-134e**) reacted preferably. This observation may predict that such ketone can facilitate the Cope-rearrangement. Subsequently, some other heterocyclic dicarbonyl substrates were tested. Without surprise, selective reactivity was observed on the ketone group over the ester or amide group (see **III-134i-m**).

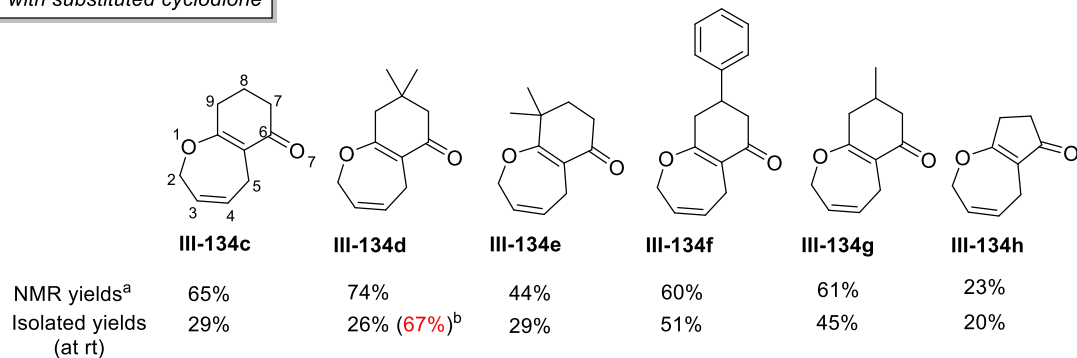
As the first cyclopropanation step is not stereoselective (affording *cis:trans* = 1:1, only the *cis* isomer could undertake [3,3]-sigmatropic rearrangement), the maximum yield for these asymmetric compounds is 50% (Scheme III-35). Substrates containing aromatic or conjugated systems stabilize moderately the starting materials, which largely inhibit the reaction. Better yields are obtained for  $\beta$ -keto lactone and lactam derivatives, affording for example dihydrooxepines **III-134i** (78%), **III-134l** (80%) and **III-134m** (100%) respectively (yields based on the reacting *cis*-vinylcyclopropane). All these promising results augur well for synthetic applications on oxepin-based natural products.

Nevertheless, the isolated yields dropped substantially for all substrates. Neutral alumina, basic alumina, florisil and silica gel were tested to increase the yield of the purification step, none of them improved the result. Gratifyingly, the purification with a column refrigerated at 5-10°C exclusively increased the yield to 67% for compound **III-134d** instead of 26%, which was comparable to the NMR yield (74%) and coherent with the NMR stability studies. Practically, we show again that the control of the temperature is determinant for 2,5-dihydrooxepin synthesis from the synthetic to the purification and thus storage processes.

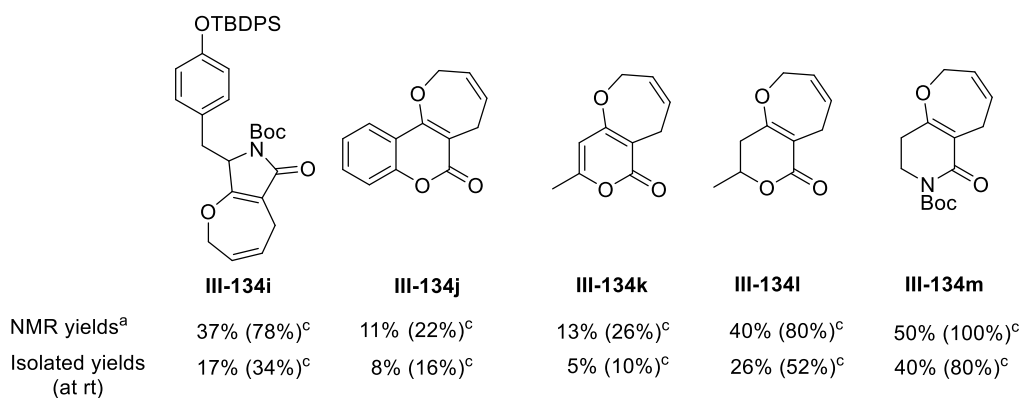




with substituted cyclopropane



with other cyclic dicarbonyl compounds

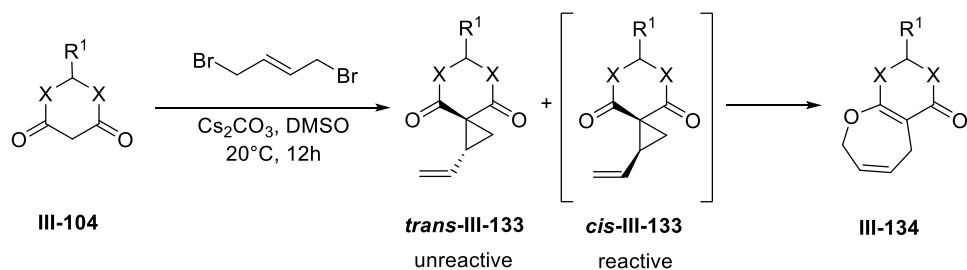


<sup>a</sup> NMR yields are calculated for reactions at 20°C

<sup>b</sup> Isolated yield at 5-10°C

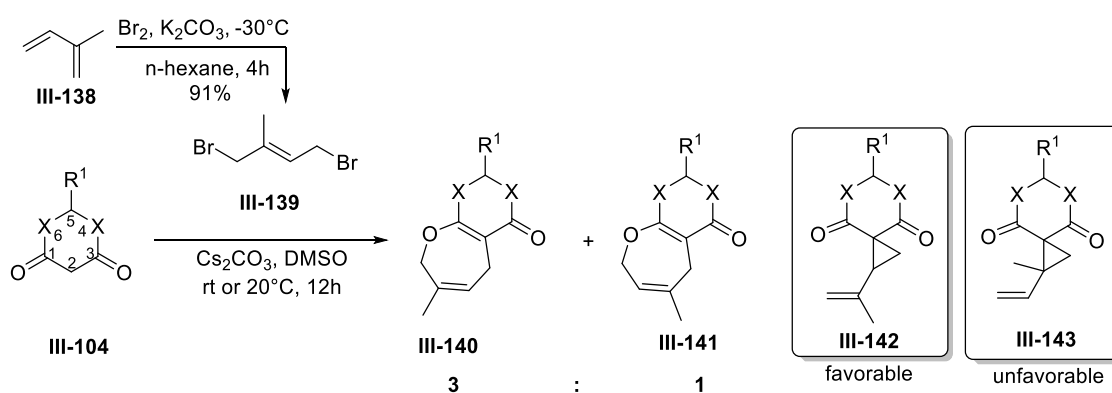
<sup>c</sup> Based on the maximum 50% yield which can be obtained with these substrates due to the formation of a non-reactive trans vinylcyclopropane isomer

*Scheme III-34 Results for cyclic substrates III-104c-m*



*Scheme III-35 Cis-vinylcyclopropyl ketones affording the dihydrooxepines*

For reactions involving monosubstituted *trans*-1,4-dibromo-2-methyl-2-butene **III-139** (synthesized from isoprene),<sup>250</sup> the tandem reaction took place in all cases and yielded two regioisomers **III-140** and **III-141** with a ratio of 3:1. (Scheme III-36) This selectivity is explained by the fact that the formation of less sterically strained cyclopropane **III-142** is kinetically favored over **III-143** at the very first S<sub>N</sub>2 allylation. Consequently, the substitutions on cyclohexadiones did not affect the ratio of the two final regioisomeric products. In addition, it was observed that an ester substitution on position 4 of the cyclohexadione did not differentiate ketones since compounds **III-140e** and **III-140f** were formed equally. This interesting result will be further employed in total synthesis of radulanin H and E.



	<b>III-140a</b>	<b>III-140b</b>	<b>III-140c</b>	<b>III-140d</b>	<b>III-140e</b>	<b>III-140f</b>
NMR yields	65%	62%	61%	49%	23%	23%
Isolated yields (at rt)	31%	26%	31%	40%	16%	16%

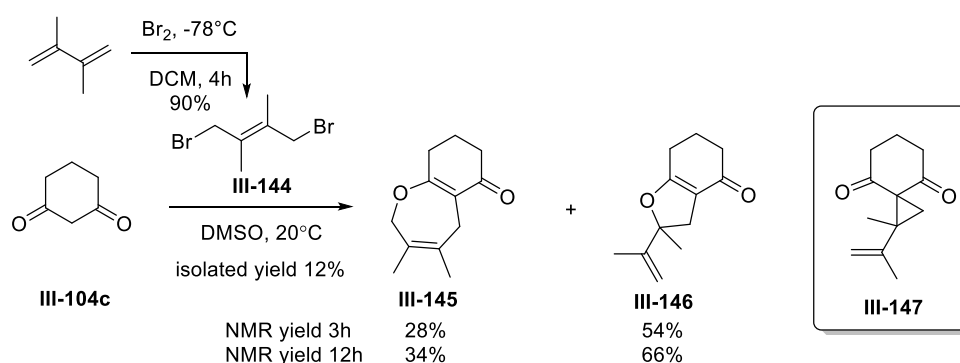
\* Isolated from the same reaction

*Scheme III-36 Reaction results with *trans*-1,4-dibromo-2-methyl-2-butene **III-139***

Cyclohexanedione reacted as well with dimethyl substituted dibromobutane **III-144**

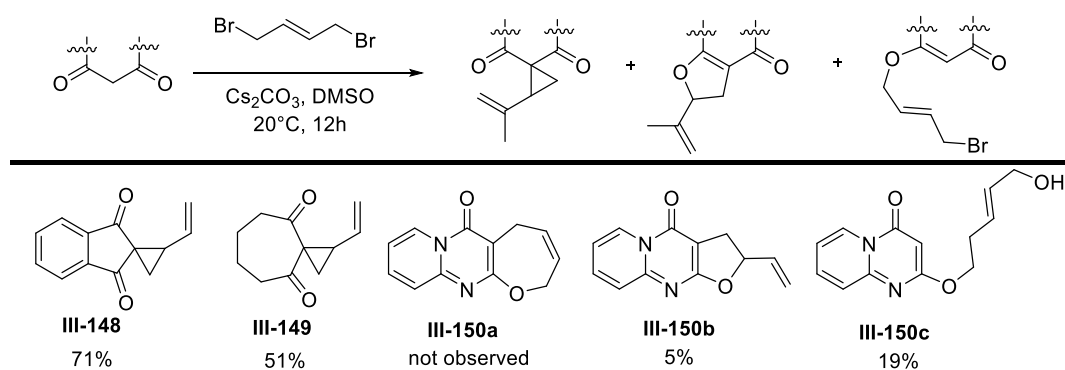
<sup>250</sup> C. A. Falcicola, K. Tissot-Crosset, H. Reyneri, A. Alexakis, *Adv. Synth. Catal.* **2008**, 350, 1090–1100.

(synthesized from 2,3-dimethyl butadiene).<sup>251</sup> The corresponding seven-membered product **III-145** was successfully formed under the same conditions, despite a lower yield. The major product herein was dihydrofuran **III-146**, even at shorter reaction times, which was formed abundantly. This result suggests that the highly substituted vinylcyclopropyl ketone **III-147** might prefer [1,3]- to [3,3]-sigmatropic rearrangement at 20°C. However, it is still unclear whether this reactivity is due to the reaction temperature or to the steric hindrance of the vinylcyclopropyl intermediate (Scheme III-37). However, the high donor-acceptor character of this intermediate may at least partially account for this result.<sup>252</sup>



Scheme III-37 Cyclohexanedione reacted with dimethyl substituted bromobutane 3.095

The scope was finally extended to other substrates. 1,3-Heptadione and indane-1,3-dione gave only stable vinylcyclopropane products **III-148** and **III-149** (Scheme III-38). Considering the structural similarity between **III-158a** and cinereain, the absence of oxa-Cope product **III-158a** caused our concern about the application of the method to synthesis of cinereain. All the vinylcyclopropanes were brought to heating conditions until 100°C, but no desired seven-membered product was obtained, highlighting some limits to this tandem methodology.

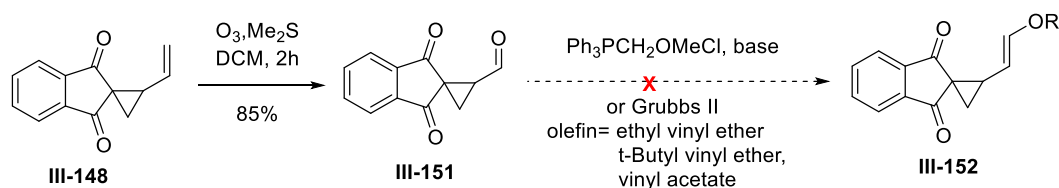


Scheme III-38 Screening results of other compounds (shown in isolated yields)

<sup>251</sup> A. M. Camelio, T. C. Johnson, D. Siegel, *J. Am. Chem. Soc.* **2015**, *137*, 11864–11867.

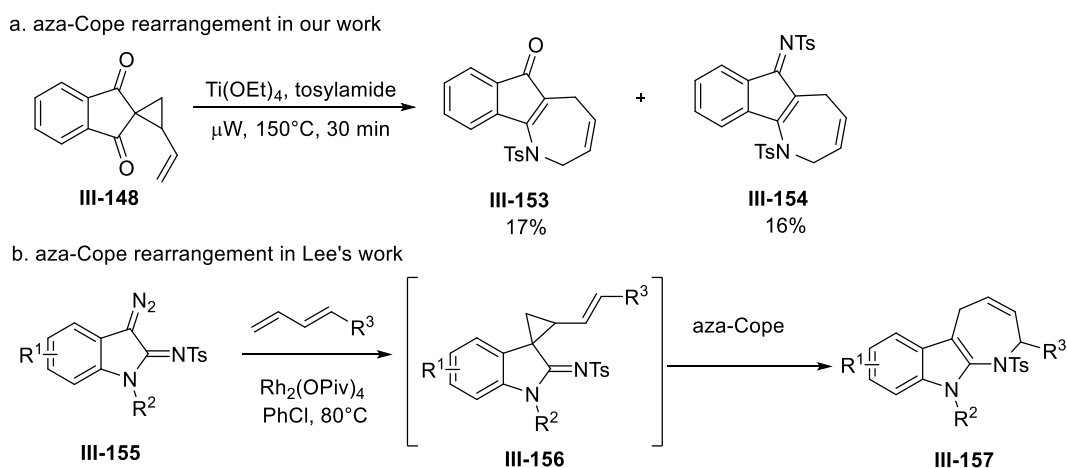
<sup>252</sup> T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 2–22.

Some structural post-modifications were attempted to either activate the vinyl or carbonyl function of these vinylcyclopropanes. Ozonolysis of **III-148** was performed at first to give the aldehyde partner **III-151** of a Wittig reaction. Unfortunately, the ylide generated from methoxymethyltriphenyltriphenylphosphonium chloride did not allow the olefination of the aldehyde. Besides, cross metathesis with vinyl acetate and vinyl ethers were also envisaged, but with no encouraging results obtained. Thus, the feasibility of the oxa-Cope rearrangement from vinylcyclopropyl intermediate **III-152** could not be studied (Scheme III-39).



Scheme III-39 Substituent effects for oxa-Cope rearrangement

However, the imine formation of product **III-148** enabled an azepines **III-153** and **III-154** to be obtained through an aza-Cope reaction (Scheme III-40a).<sup>253</sup> This transformation is reminiscent of a literature work describing the sequential Rh-catalyzed cyclopropanation/1-aza-Cope rearrangement to synthesize azepinoindoles (Scheme III-40b)<sup>254</sup>. These aza-type rearrangements also took advantages of combined effects of the release of the ring strain and the  $\pi$ -resonance stabilization. However, why aza-Cope rearrangement is more favored than oxa-Cope in this case is worth to be further investigated.



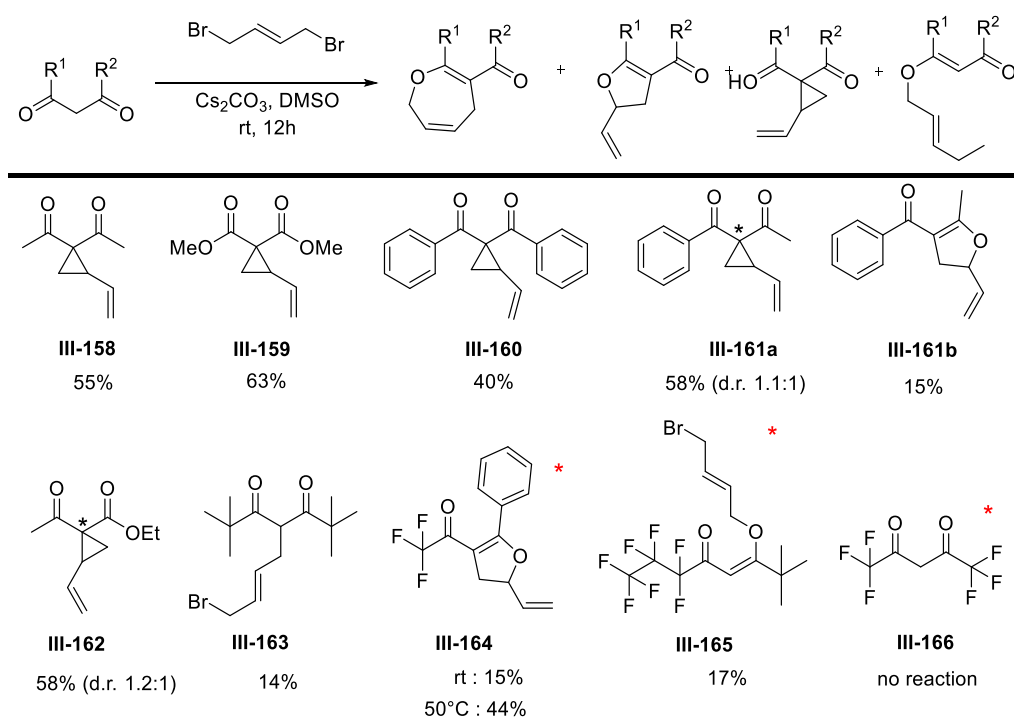
Scheme III-40 Aza-Cope rearrangement of cyclic substrate III-156 and comparison with literature

<sup>253</sup> P. Ortiz, J. F. Collados, S. R. Harutyunyan, *Eur. J. Org. Chem.* **2016**, 1247–1250.

<sup>254</sup> P. H. Lee, S. Kim, H. Kim, K. Um, *J. Org. Chem.* **2017**, *82*, 9808–9815.

### 2.3.4. Reaction attempts with linear substrates

Linear substrates were also explored for this tandem cyclopropanation/oxa-Cope rearrangement. As listed in Scheme III-41, no 2,5-dihydrooxepine was detected. The isolated products were only cyclopropane and dihydrofuran derivatives. The vinylcyclopropane products were favored with acyclic substrates, such as **III-158**, **III-159** and **III-160**. For unsymmetrical reagents, mixtures of diastereomeric vinylcyclopropane products were obtained like **III-161a** and **III-162**, due to the non-stereoselective cyclopropanation step. For sterically hindered dione precursors, only simple *C*-alkylation or *O*-alkylation products were observed such as **III-163** and **III-165**, yet in low yields (14% and 17%, respectively). The reactivity of fluorinated substrates decreased significantly. However, dihydrofuran **III-164** was isolated, but in no more than 40%, even under long-time heating condition.<sup>255</sup> As no cyclopropane product was detected, it is supposed that these intermediates were either not stable, or that the formation of dihydrofuran **III-164** does not proceed through [1,3]-sigmatropic rearrangement.<sup>256</sup>

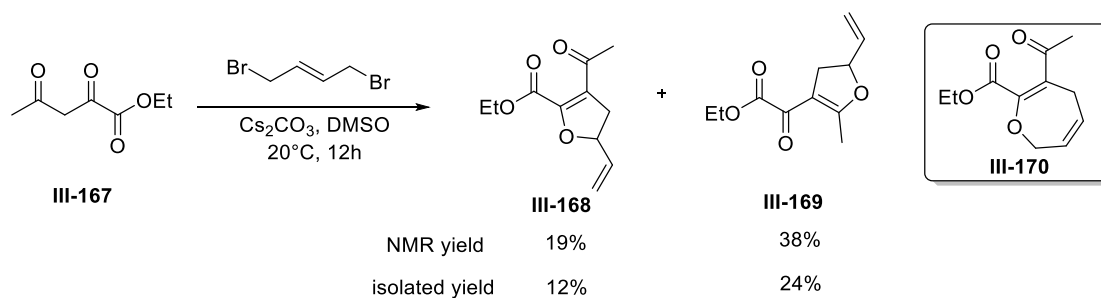


Scheme III-41 Results of acyclic substrates (shown in isolated yields)

<sup>255</sup> a) C. Aubert, J. P. Begue, M. Charpentier-Morize, G. Nee, B. Langlois, *Journal of Fluorine Chemistry* **1989**, *44*, 361-376; b) J. P. Begue, M. Charpentier-Morize, G. Nee, *J. Chem. Soc. Chem. Commun.* **1989**, 83-34.

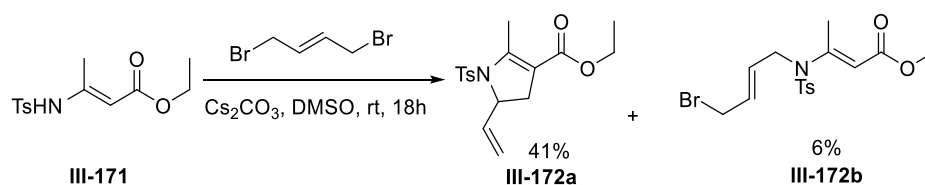
<sup>256</sup> J. O. Smith, B. K. Mandal, R. Filler, J. W. Beery, *Journal of Fluorine Chemistry* **1997**, *81*, 123-128.

Exceptionally, ethoxalylacetone **III-167** afforded two dihydrofuran regio-isomers under our normal reaction condition after 12 hours, while 23% of 2,5-dihydroxepin **III-170** was observed by NMR after 3 hours (Scheme III-42). At this point, it was considered that the oxa-Cope rearrangement could occur to produce dihydrooxepines from such linear substrates, but their instability may complicate their isolation.



Scheme III-42 Oxa-Cope rearrangement for ethoxalylacetone

The similar aza-Cope rearrangement was contemplated for one of the acyclic substrates (Scheme III-43). However, the [1,3]-rearrangement occurred instead of the [3,3]-rearrangement to afford 2,3-dihydropyrrole **III-172a**.<sup>257</sup> It seemed that the aza-Cope rearrangement remains difficult for linear substrates and we did not investigate further this reaction.



Scheme III-43 Aza-Cope rearrangement for acyclic compounds

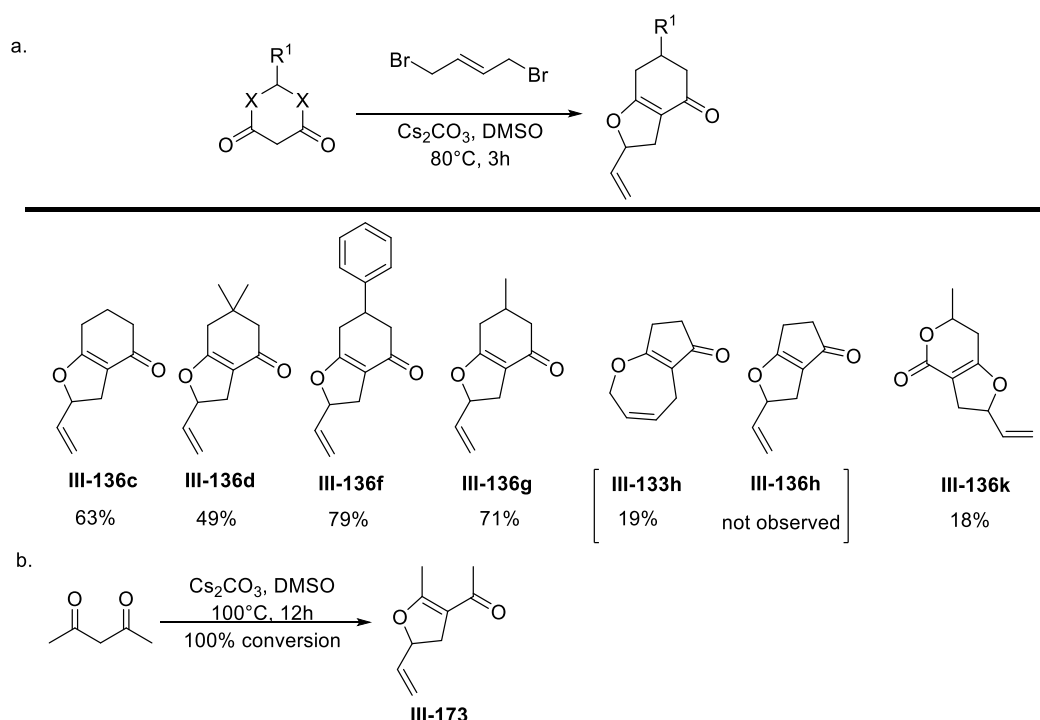
### 2.3.5. Comments on the associated Cloke-Wilson rearrangement during these experiments

The Cloke-Wilson rearrangement is an important reaction occurring when the vinylcyclopropyl group is present. As mentioned in the previous introduction, heating conditions might only yield dihydrofurans or increase the yield of dihydrofurans.

Some substrates involved in the Cope-type reaction were reused to react with 1,4-dibromobutene and  $\text{Cs}_2\text{CO}_3$  in DMSO at 80 °C for 3 h (Scheme III-44a). For cyclohexadione

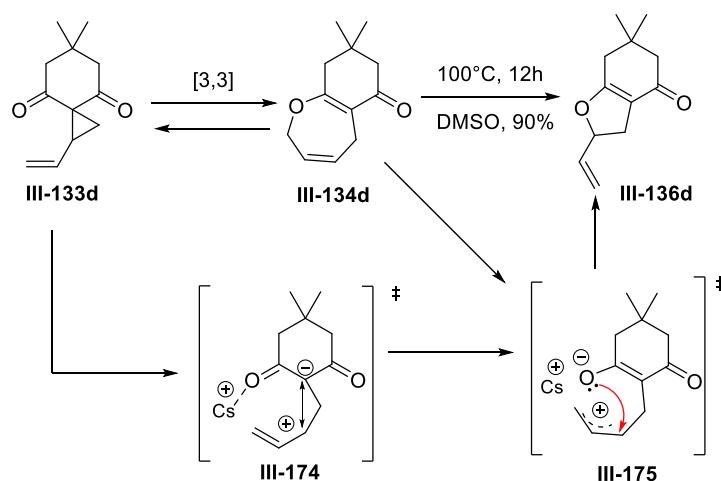
<sup>257</sup> D. Jacoby, J. P. Celerier, G. Haviari, H. Petit, G. Lhommet, *Synthesis* **1992**, 9, 884 -887.

derivatives, no dihydrooxepine was observed, only dihydrofurans were isolated with good yields, which strongly indicated that the [1,3] rearrangement can compete with [3,3] rearrangement if the reaction temperature is not under control. For acyclic substrate acetylacetone, 100% conversion to dihydrofuran **III-173** was achieved and quantified by  $^1\text{H-NMR}$  (Scheme III-44b). In the case of 1,3-cyclopentadione, only the seven-membered product **III-140d** was obtained in 19% yields (Scheme III-44a). Indeed, the corresponding dihydrofuran fused to a cyclopentanone **III-141d** would be particularly strained and thus disfavored.



Scheme III-44 Cloke-Wilson rearrangements

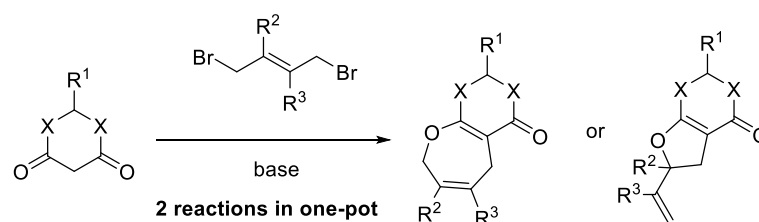
Besides, vinyl-dihydrofurans could also be obtained from the rearrangement of dihydrooxepines (Scheme III-45). The yield shown here is coherent with previous NMR studies: the dihydrooxepine yield decreases in the same manner as the dihydrofuran yield increases. Interestingly, the rearrangement rate in DMSO (90% yield after 12 hours) was higher than that in DCE (60% conversion after 12 hours), indicating that a dipolar transition state could be envisaged in this [1,3] rearrangement. A zwitterion pair of allyl cation and enolate might be generated and react intramolecularly (**III-181**) to give a five-membered ring product. Cs<sup>+</sup> cations could play at the same time the role of a Lewis acid catalyst, chelated to the carbonyl groups and weakening the cyclopropane bond (**III-180**) (Scheme III-45).



Scheme III-45 Possible mechanism involved in the formation of dihydrooxepines and dihydrofurans

## 2.4. Conclusions

The one-pot cyclopropanation/oxa-Cope rearrangement of vinylcyclopropanated 1,3-dicarbonyl compounds, formed by their reaction with 1,4-dibromo-2-butene, has been successfully developed to synthesize 2,5-dihydrooxepines and studied in detail (Scheme III-46). The [1,3]-transposition concurrently afforded an entry to dihydrofurans. Kinetic NMR investigations preponderantly contributed to optimize the desired reaction conditions, to understand the progress of this tandem reaction, and to monitor the stability of seven-membered products. The [3,3]-rearrangement and [1,3]-rearrangement are delicately controlled by temperature. Depending on the substitution pattern, the stability of obtained compounds changes. Appropriate reaction conditions could thus influence the formation of 5 or 7-membered ring. Besides, all the results proved that these rearrangements could be achieved without any metal catalysis. Thus, this metal free method could also bring a significant advance in both cost and toxicity issues, providing an alternative route toward the synthesis of highly functionalized dihydrooxepines and dihydrofurans.



Scheme III-46 General resume of new methodology

Meanwhile, there are still some limitations and obscurities for this cascade reaction. For



example, the cyclopropanation step is not selective, limiting the yield of unsymmetrical products. No 2,5-dihydrooxepine could be isolated for acyclic substrates, while reasonable explanations remain unclear. Some further computational studies were thus necessary to uncover the reactivity of vinylcyclopropane ketones, in complement to those existing in the literature for vinylcyclopropanecarboxaldehyde.<sup>211</sup>

### 3. DFT calculations on the transformations of acylvinylcyclopropanes to dihydroxepines and dihydroxyfurans

#### 3.1. General background introduction

Due to the development of many new methods, algorithms and more and more powerful computers, quantum mechanical calculations are assuming an increasing role in synthesis and applied frequently to study some important and fundamental reactions such as substitutions, eliminations and pericyclic reactions.<sup>258</sup> Right now, computational organic chemistry becomes a useful tool to know why and how the reaction occurs and to understand factors affecting the reaction's performance. With this help, yields or stereoselectivity could be also optimized and a reasonable mechanism could be mapped out.<sup>259</sup>

In this thesis work, we were interested in 1,1-diacyl-2-vinylcyclopropane rearrangements. Part of our computational calculation work<sup>260</sup> will be described herein, mainly to answer several unsolved questions in the previous experimental part:

- What is the relationship between 1-acyl-2-vinylcyclopropane, 2,5-dihydrooxepine and 2-vinyl-2,3-dihydrofurans?
- Could the 2,5-dihydrooxepine be transformed directly to the 2,3-dihydrofuran without the 2-vinyl cyclopropane as an intermediate?
- Why cyclic and acyclic substrates behave differently?

#### 3.1.1. Computational chemistry and associated methods

*Ab initio* means “from the beginning” or “from first principles”. *Ab initio* quantum chemistry distinguishes itself from other computational methods in that it is only based on established

---

<sup>258</sup> S. M. Bachrach, *Computational Organic Chemistry*, Wiley-VCH, Hoboken, **2006**, 1-278.

<sup>259</sup> Z. Yu, Y. Liang, *Organic Chemistry-breakthrough and perspectives*, Wiley-VCH, Weinheim, **2012**, 561-600.

<sup>260</sup> This work was undertaken under the guidance of Dr. Gilles Frison, CNRS researcher at LCM of Ecole Polytechnique.

laws of nature: quantum mechanics.<sup>261</sup> Ab initio calculations can be performed on any system with moderate to high accuracy but consume for some methods a considerable computational cost. Hartree-Fock theory is the simplest wavefunction-based method which contributed to develop electronic structure method calculations. However, the correlation (*e.g.* the correlated electron-electron) is not specifically modeled in this single-determinant wavefunction approach; only its average effect is included. To compute the correlation energy, a plethora of methods, called post-HF methods, are developed:<sup>262</sup>

- Configuration interaction (CISD, CISD(T))
- Møller-Plesset perturbation theory (MP2, MP3...)
- Quadratic configuration interaction (QCISD)
- Coupled-cluster theory (CCD, CCSD, CCSD(T))
- Multi-configuration self-consistent field theory (MCSCF)

Each of these methods gives a hierarchy to exactitude. These post-Hartree-Fock methods give much more accurate energies of small systems but are limited by computational restrictions. Among them, coupled-cluster methods are currently the most accurate generally applicable methods in quantum chemistry. Thus CCSD(T) has been qualified as “gold standard” to yield the chemical calculation accuracy.

Density functional theory (DFT) is another class of computational quantum chemistry methods, which helps to simulate molecular structural features and calculate molecular properties. Compared to Hartree-Fock theory which calculates the full N-electron wavefunction, DFT methods only attempt to calculate the total electronic energy and the overall electronic density distribution. As wavefunction-based methods cost a lot of time and memory to get the correlation energy, DFT techniques provide solutions with lower time- and memory-consuming. By far, DFT is well-reputed as the most popular quantum chemistry method to predict efficiently accurate energies and geometries, meanwhile elucidating electronic rearrangement mechanisms.<sup>263</sup> The restricted DFT wavefunctions applied to chemical reactions are limited by their closed-shell nature, thus employed to describe heterolytic mechanisms. The unrestricted open-shell (U) DFT is allowed to study biradicaloid

---

<sup>261</sup> a) D. C. Young, *Computational Chemistry*, Wiley-VCH, New York, **2001**, 19-27; b) C. J Cramer, *Computational Chemistry-Theories and Models*, Wiley-VCH, Weinheim, **2004**, 165-201.

<sup>262</sup> F. Jensen, *Introduction to Computational Chemistry*, Wiley-VCH, Weinheim, **2007**, 80-189.

<sup>263</sup> W. Kohn, M.C. Holthausen, *A Chemist's Guide to Density Functional Theory*, Wiley-VCH, Weinheim, **2000**.

singlet transition states.

The total energy within DFT approach is given by an approximated functional of the electronic density, as an exact evaluation is not feasible. Therefore, there are several categories of functionals. The most popular is hybrid methods which attempt to incorporate some of the more useful features from *ab initio* methods (specifically Hartree-Fock exchange) with the DFT framework. For example, Becke's three-parameter exchange functional in conjunction with the Lee-Yang-Parr correlation functional (B3LYP) was the most commonly used hybrid methods, introduced in 1994 by Stephens, Devlin, Chabalowski and Frisch.<sup>264</sup> It is a hybrid generalized gradient approximation (HGGA) functional, which could yield usually very good structural and thermochemical properties. Zhao and Truhlar have more recently developed the hybrid M06 meta-GGA functionals<sup>265</sup> that show promising performance for noncovalent interactions and do a good job in reproducing the relative energetics of small clusters. This new functional has 27% of Hartree-Fock exchange, whereas B3LYP has only 20%. Its performance is on average as good as the popular B3LYP functional or even better for ground-electronic-state energetics. It is known also to perform well for main group and organometallic compounds.

Besides, the accuracy of the computed properties is also sensitive to the quality of the basis set.<sup>81-83</sup> A 'basis set' is a group of basis functions, which was used to describe the atomic orbitals. Larger basis sets give a better approximation but involved a higher computational cost. Split valence functions (like 6-31G and 6-311G), polarization functions ("d" and "p" in 6-31G(d), 6-31G(d,p)), diffuse functions ("+" in 6-31+G or 6-31++G) have been developed for different required calculations. The size and quality of the basis used in calculations may drastically affect the results. It is now recognized that triple zeta split valence basis sets including polarization and diffuse functions give good geometries and energetics.

The theoretical studies of chemical reactions, by using a combination of adapted computational method and basis set, give information on the optimized geometry of the stationary states (minima, transition states on the potential energy surfaces). Vibrational frequencies are computed to deliver enthalpy, entropy, free energy, and to check the nature of the stationary states. Transition structures could also be confirmed by calculating the

---

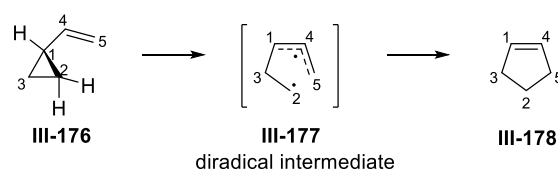
<sup>264</sup> P. J Stephens, P. N. Schatz, A. B. Ritchie, A.J. McCaffery, *J. Chem. Phys.* **1994**, *98*, 11623-11627.

<sup>265</sup> Y. Zhao, D. G. Truhlar, *J. Chem. Phys.* **2006**, *110*, 13120-13130.

minimum-energy path (MEP), also known as intrinsic reaction coordinate (IRC), connecting reactants, transition structure (TS) and product. All data produced from these calculations allow understanding the required reaction mechanism and impacted parameters.

### 3.1.2. Literature review on [1,3] and [3,3] rearrangement calculations for 2-vinylcyclopropyl aldehyde

In the 1960s, the thermal isomerization of vinylcyclopropane to cyclopentene was discovered, exhibiting characteristics of both stepwise and concerted mechanisms. This simplest [1,3] sigmatropic shift model was further studied kinetically and theoretically by Baldwin and Doering.<sup>266</sup> This Cope rearrangement, whether it is concerted or stepwise with transient formation of a diradical intermediate, has been hotly debated.<sup>267</sup> Almost at the same time, Houk et al. used the computationally less demanding spin-unrestricted version of (U)DFT (UB3LYP/6-31G\*), compared with CASSCF multiconfigurational method, to rationalize that this rearrangement involves a biradicaloid transition structure possessing also characteristics of concerted reactions (Scheme III-47).<sup>268</sup>



*Scheme III-47 The vinylcyclopropane-cyclopentene rearrangement*

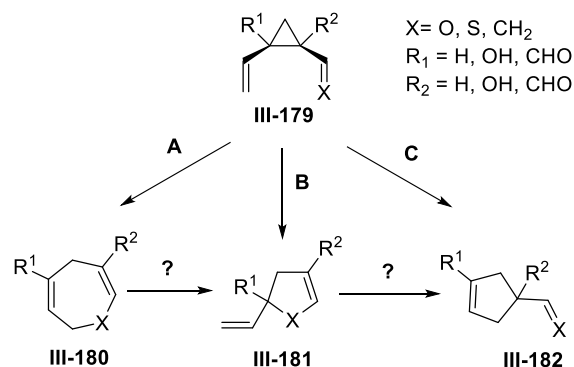
The *cis*-divinylcyclopropane rearrangement has as well as attracted theoretical interest in recent years. Experimental studies resumed in the first part of this chapter have shown that *cis*-divinylcyclopropane derivatives **III-179** (X=CH<sub>2</sub>) may undergo either [3,3]-sigmatropic rearrangement (Cope reaction) resulting to 1,4-cycloheptadienes **III-180** (pathway **A**), or [1,3]-sigmatropic rearrangements affording vinyl-substituted cyclopentenes **III-181** (pathway **B**) (Scheme III-48). Under pyrolytic conditions, another [1,3]-sigmatropic rearrangement was also involved to furnish cyclopentene **III-182** when X=CH<sub>2</sub> (pathway **C**). The relationship

<sup>266</sup> a) J. E. Baldwin, K. A. Villarica, D. I. Freedberg, F. A. L. Anet., *J. Am. Chem. Soc.* **1994**, *116*, 10845-10846; b) W. V. E. Doering, Y. Wang, *J. Am. Chem. Soc.* **1999**, *121*, 10112-10118.

<sup>267</sup> a) J. E. Baldwin, *Journal of Computational Chemistry*, **1998**, *19*, 222-231; b) W. T. Borden, *Theory and Applications of Computational Chemistry* **2005**, 859-873.

<sup>268</sup> K.N. Houk, M. Nendel, O. Wiest, J. W. Storer, *J. Am. Chem. Soc.* **1997**, *119*, 10545-10546.

between these three rearrangements was first studied by Fabian and his coworkers.<sup>269</sup> By analogy to Houk's work, the [1,3]-sigmatropic rearrangement was studied by using unrestricted UDFT, whereas the [3,3]-sigmatropic rearrangement was investigated by restricted B3LYP/6-31G\* density functional and MP2/6-31G\* *ab initio* quantum theoretical calculations.



*Scheme III-48 [3,3]-Sigmatropic rearrangement (A) and [1,3]-sigmatropic rearrangement (B, C) of divinylcyclopropane derivatives and hetero (X=O,S) analogs in Fabian's work*

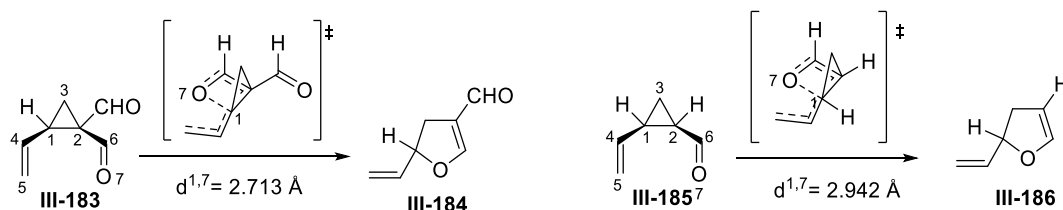
On the basis of these calculations, the formation of 2,5-dihydrooxepines **III-180** (X=O), the products of the [3,3] rearrangement, is kinetically favored compared to the [1,3] rearrangements. Between the two [1,3] rearrangements, the reaction from vinylcyclopropanecarbaldehydes **III-179** (X=O) to 2,3-dihydrofurans **III-181** is kinetically favored over the conversion to cyclopentenes **III-182**, which should be the thermodynamically stable product.

The substituent effects were also investigated by calculations. In the case of Cope-type reaction (pathway **A**), the calculated activation barrier is 19 kcal/mol for the 2-vinylcyclopropanecarbaldehyde to 2,5-dihydrooxepine rearrangement (X=O), whereas the DFT activation energy of the 1,2-divinylcyclopropane to 1,4-cycloheptadiene (when X=CH<sub>2</sub>) is 24 kcal/mol.<sup>211</sup> As the latter reaction occurs at low temperature experimentally, the hetero-Cope reaction might not either need a high temperature to proceed. In addition, CHO substitution as R<sub>2</sub> lowers the activation energy, which predicts the reaction could occur more easily if there are two carbonyls substituting the vinylcyclopropane.

As for [1,3]-sigmatropic shifts (pathway **B**), the different substitutions of R<sub>1</sub> and R<sub>2</sub> change the biradicaloid characters (Scheme III-49). The transition state from **III-185** owns a longer

<sup>269</sup> J. Fabian, D. Sperling, H. U. Reißig, *Eur. J. Org. Chem.* **1999**, 1107-1114.

distance between atom C1 and O7 than that from **III-183**. This observed smaller-space interaction for **III-183** may be caused by the increased delocalization of electrons, thus decreasing the biradicaloid character. Meanwhile, OH or CHO substitutions at C1 led to a strong decrease of the activation enthalpy, but the OH or CHO substitutions at C2 gave only negligible effects.



Scheme III-49 Substituent effects of [1,3]-sigmatropic rearrangement (reaction B)

In their work, the stereoisomerizations and rearrangements of *trans*-2-vinylcyclopropanecarbaldehydes were also investigated. Cope-type [3,3]-rearrangements only take place in the case of *cis*-2-vinylcyclopropanecarbaldehydes. However, the activation energy differences for [1,3]-rearrangements between the two isomers are relatively small, which suggested that the stereoisomerization and the [1,3]-sigmatropic rearrangement of 2-vinylcyclopropanecarbaldehydes may take place simultaneously.

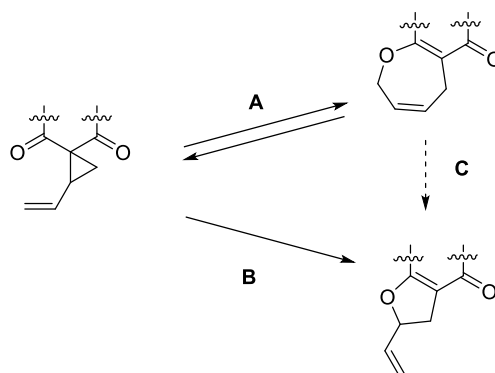
### 3.2. Modelisation results of [1,3] and [3,3] rearrangements for cyclohexadione and acetylacetone vinylcyclopropane derivatives

All calculations were performed with the Gaussian 09 package. To maximize the trade-off between computational cost and accuracy, it is common to optimize the geometry at a given theory, and then to compute the energy at a higher level of theory. Thus, the geometrical parameters of reactants, products and transition states were optimized by using the M06 DFT functional with the 6-311G(d,p) basis set. In order to check the biradicaloid character of the TS, all geometry optimization of TS have been performed both at the restricted and unrestricted-M06. DFT methods are generally good for geometries, but sometimes not as good for energies.<sup>270</sup> Therefore, final energy calculations were determined using the M06/6-311++G(2d,2p) level of theory at the M06/6-311G(d,p) geometries, but also at the B3LYP/6-311++G(2d,2p) level to compare the results. Last, CCSD(T)/6-311++G(2d,2p) calculations were also executed to serve as a reference and confirm the accuracy of all results. All thermal

<sup>270</sup> R.A. Friesner, *PNAS* **2005**, *102*, 6648-6653.

and entropy corrections have been obtained from gas phase M06/6-311G(d,p) calculations. Organic reactions are however carried out in solution. Therefore, self-consistent reaction field (SCRF) was employed with the IEFPCM formalism to model solvent effects (here DMSO) at the final energy calculation step.

Cyclohexadione and acetylacetone are here taken as study models to estimate the energy differences between cyclic and acyclic substrates. The acylvinylcyclopropane rearrangements through pathway A and pathway B were calculated. The transition state from 2,5-dihydrooxepine to 2,3-dihydrofuran was also investigated (Scheme III-50, pathway c).



Scheme III-50 [3,3]-sigmatropic rearrangement (A) and [1,3]-sigmatropic rearrangement (B) of 1,1-diacyl-2-vinylcyclopropane in this thesis work

Detailed theoretical results and discussions about activation barriers, steric effects and the behavior in solution of our acylvinylcyclopropane rearrangements are presented as follow.

### 3.2.1. Calculations results for cyclohexadione derivative III-133c

The results of calculation show that cyclopropane **III-133c** and 2,5-dihydrooxepine product **III-134c** are nearly isoenergetic (Figure III-2) and are connected by a relatively low TS (pathway A), which demonstrates that the oxa-Cope reaction envisaged here is a reversible process. The transition state of this Cope rearrangement is a ‘delocalized’ (aromatic) intermediate, exhibiting a boat-like conformation. In addition, this reaction behaves as a concerted pericyclic rearrangement, no biradicaloid was found during this calculation.

For pathway B, dihydrofuran **III-136c** shows better stability than reactant **III-133c**, and its activation energy is higher than that of the seven-membered ring counterpart which suggest a more difficult irreversible reaction feature. This outcome indicates the possible competition of [1,3]- and [3,3]-rearrangements depending on the temperature reaction condition, which correlates our previous experimental result differences observed at 20°C and 25°C. Different

from Fabian's results on the 2-vinylcyclopropyl aldehyde rearrangements, transition state **III-188** shows no biradical character, therefore all data shown correspond to restricted calculations. It could be explained by the increased delocalization of electrons on this constrained biacyl intermediate transition structure.

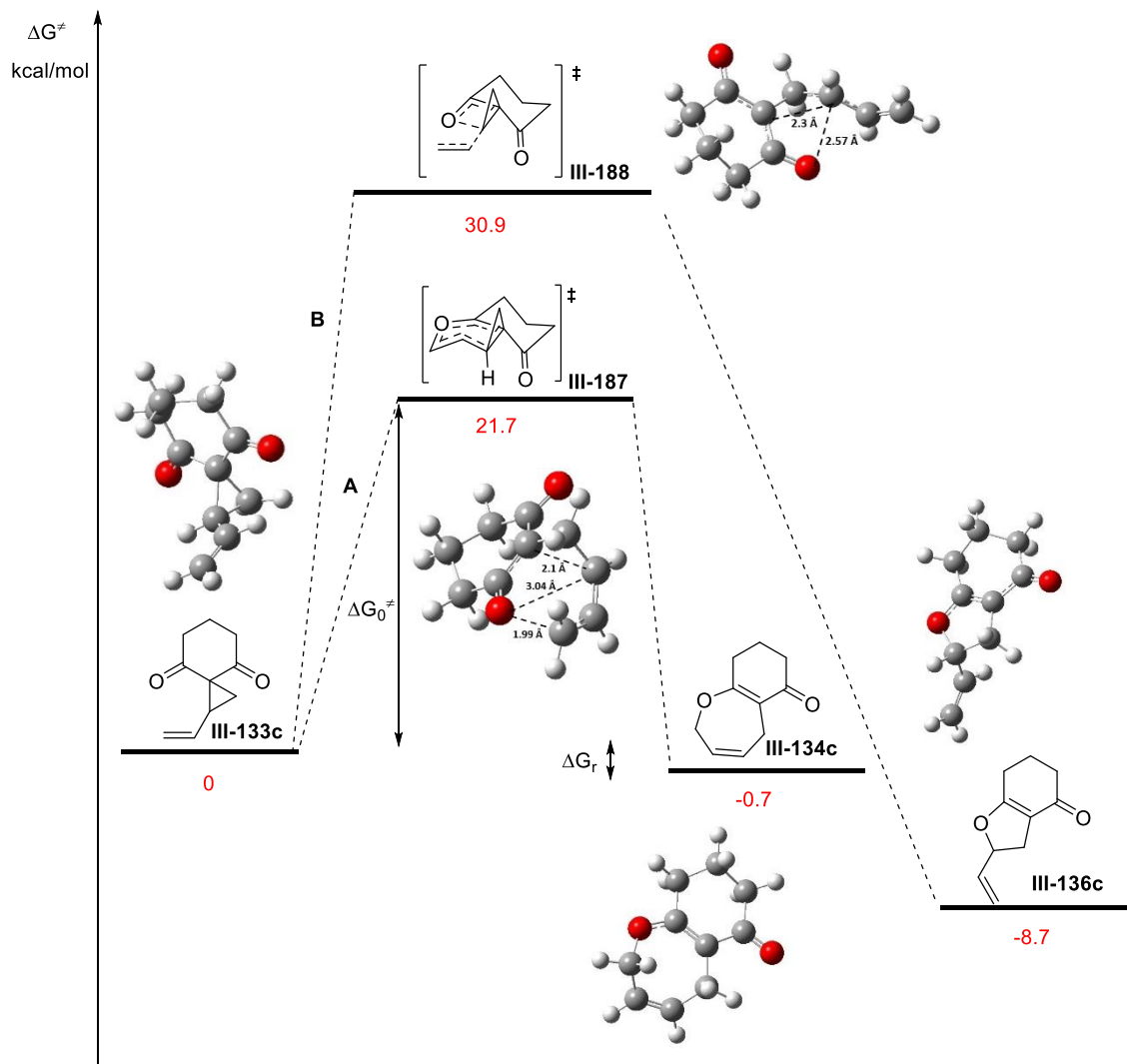


Figure III-2 Computed Gibbs free energies rearrangements from acylvinylcyclopropane **III-133c** for the two pathways (A and B) at the CCSD(T)/6-311++G (2d, 2p)//M06/6-311G(d,p) level in DMSO.

Besides, Table III-4 provides a comparison of activation barriers in gas phase and in DMSO for [1,3]- and [3,3]-rearrangements. The energetic reaction profile to form the 2,5-dihydrooxepine is similar in both cases, whereas a slight difference was identified (3 kcal/mol) for the dihydrofuran formation. The high dipolar property of DMSO might stabilize the transition state of this [1,3]-sigmatropic rearrangement, which is coherent with our experimental data. This observation may suggest a zwitterionic transition state engaged



during this reaction or a polarized transition state with a high zwitterionic character, and may also rule out the biradicaloid hypothesis.

Table III-4 Comparison of computed activation energies of reaction A and B at the three calculation levels in vacuo and DMSO (in kcal/mol).

Method	Reaction A	Reaction A	Reaction B	Reaction B
	$\Delta G_0^\ddagger(\text{vacuo})$	$\Delta G_0^\ddagger(\text{DMSO})$	$\Delta G_0^\ddagger(\text{vacuo})$	$\Delta G_0^\ddagger(\text{DMSO})$
M06/6-311++G (2d, 2p)	23.8	23.8	31.9	28.2
CCSD(T)/6-311++G (2d,2p)	21.7	21.7*	34.6	30.9*
B3LYP/6-311++G (2d,2p)	18.4	18.6	24.7	21.6

\*Solvation Gibbs free energies computed at the M06 level.

Because of the difference of activation energy barrier (9.2 kcal/mol) between pathways A and B, the [1,3]-sigmatropic rearrangements compete with the [3,3]-sigmatropic rearrangements in particular at higher temperature. A search for transition structures of the isomerization of 2,5-dihydrooxepines to 2,3-dihydrofurans was explored, but no plausible direct intermediate was found. As a consequence, the thermal conversion of dihydroxepines into dihydrofuran may involve vinylcyclopropane **III-133c**, which is reversibly formed from 2,5-dihydrooxepines (Scheme III-50).

### 3.2.2. Calculation results for acetylacetone vinylcyclopropane **II-164**

The similar energetic reaction profiles were obtained when using acetylacetone 2-vinylcyclopropane **III-158** as an acyclic substrate (Figure III-3). The solvent DMSO displayed the same energetic effects for these two ring product formations. The only remarkable difference in this case compared to cyclohexadione is that cyclopropane **III-158** possesses a higher thermodynamic stability than 2,5-dihydrooxepine product **III-197**, which suggests that the equilibrium between **III-158** and **III-191** is strongly displaced in favor of the former. This calculated result is in close agreement with the experimental data, where no seven-membered ring products were isolated.

Comparison between the relative Gibbs free energy of transition states **III-187** in the cyclic case (Table III-4) and **III-189** in the acyclic case indicates an averagely higher value for the latter (Table III-5). This small variation is probably due to the difference of conformational constraints in cyclic and acyclic substrates. To get a more reasonable explanation, electronic

and steric effects were further elucidated.

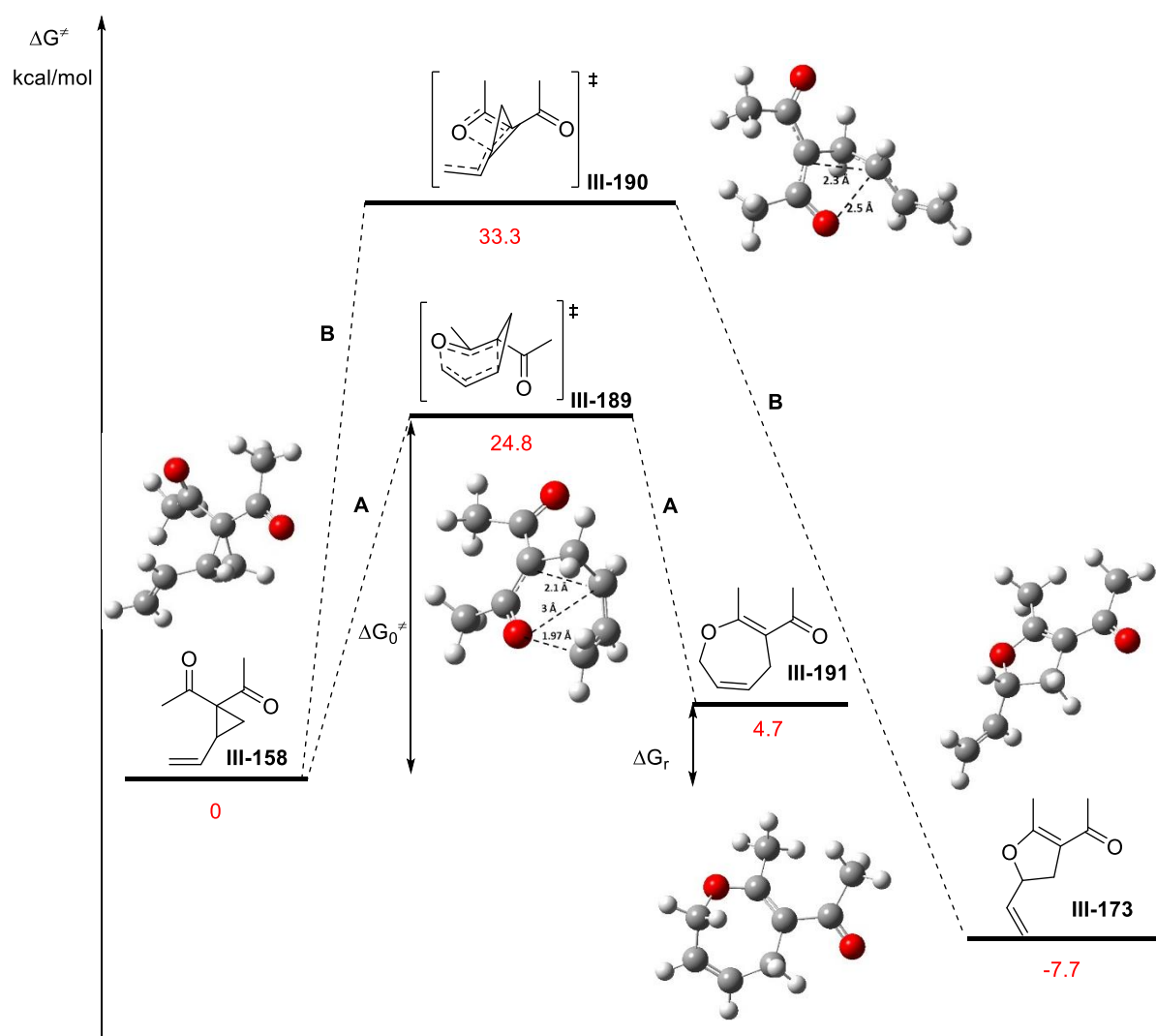


Figure III-3 Computed Gibbs free energies from acyl-vinylcyclopropane **III-158** for the two rearrangements *A* and *B* at the CCSD(T)/6-311++G(2d, 2p)//M06/6-311G(d,p) level in DMSO.

Table III-5 Comparison of computed activation energies of reaction *A* and *B* at the three calculation levels in vacuo and DMSO (in kcal/mol).

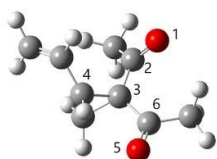
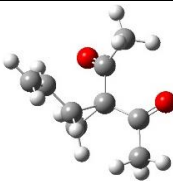
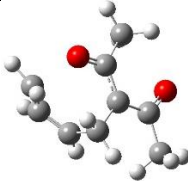
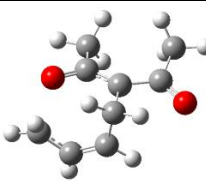
Method	Reaction A	Reaction A	Reaction B	Reaction B
	$\Delta G_0^\ddagger(\text{vacuo})$	$\Delta G_0^\ddagger(\text{DMSO})$	$\Delta G_0^\ddagger(\text{vacuo})$	$\Delta G_0^\ddagger(\text{DMSO})$
M06/6-311++G (2d, 2p)	26.6	26.9	33.4	30.4
CCSD(T)/6-311++G (2d,2p)	24.8	24.6*	36.3	33.3*
B3LYP/6-311++G (2d,2p)	20.7	20.3	28.0	24.2

\*The solvation Gibbs free energies computed at the M06 level.

### 3.2.3. Electronic and steric effects for acyclic substrate

Regarding the acyclic substrate, there are several possible conformers because of the high flexibility of one vinyl group and two carbonyl groups bound to the cyclopropane. The question was to understand why 2-vinylcyclopropyl carbaldehyde<sup>211</sup> and cyclic ketone do cyclize while those from linear ketones do not. Some conformers of the 2-vinylcyclopropyl ketones **III-158** and their transition states are illustrated in Figure III-4. The most stable form is **III-158a**, when the vinyl substituent is at opposite position to both carbonyl groups (*trans*-isomers), which minimizes the electronic repulsions. The energy difference between each conformer is very small, which indicates that they are in equilibrium at room temperature. Besides, there were no energy difference between their corresponding *trans*- and *cis*-transition states **III-192a** and **III-192b**. Although the *cis*-conformation of vinyl and carbonyl substituents is not a favored geometry, the calculation results demonstrated that the flexibility could not be a reason for the non-formation of 2,5-dihydrooxepine rings for acyclic substrates.

Figure III-4 Selected vinylcyclopropanecarbaldehyde conformers and transition structures of Cope-type rearrangements for acyclic substrate.

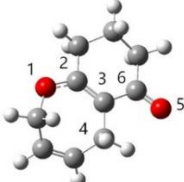
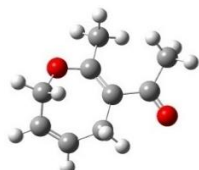
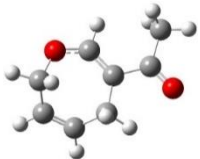
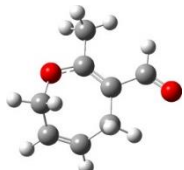
				
	<b>III-158a</b>	<b>III-158b</b>	<b>III-192a</b>	<b>III-192b</b>
Relative energy* (kcal/mol)	trans (0)	cis (0.3)	trans (24.7)	cis (24.8)
Dihedral angle (°) 1-2-3-4/5-6-3-4	99/28	-79/-137	47/128	48/-35

\* Computed Gibbs free energies for vinylcyclopropyl ketone 3.077 and their transition states at the CCSD(T)/6-311++G(2d, 2p)//M06/6-311G(d,p) level in DMSO.

Comparison between the 2,5-dihydrooxepine products **III-134c** and **III-191** indicates that the two C-O bonds of compound **III-134c** are nearly in the same plane but are slightly staggered for compound **III-191**, revealing that weaker conjugation might lead to a slightly higher relative energy. (Figure III-5) This difference may probably be produced by the steric interaction of the two methyl groups of **III-191**. To prove this hypothesis, one of the methyl groups was replaced by a hydrogen, shown as **III-193** and **III-194**. Due to this suppression of

steric effects, their planarity and therefore their relative thermodynamic stabilities have been restored, leading to a situation close to the one observed for compound **III-134c**.

Figure III-5 Comparison of the relative energies (compared to the reactant) and dihedral angles for different substituted 2,5-dihydrooxepine structures from cyclic and acyclic diketone substrates.

				
	<b>III-134c</b>	<b>III-191</b>	<b>III-193</b>	<b>III-194</b>
$\Delta G_r^\ddagger(\text{DMSO})^*$ (kcal/mol)	-0.7	4.7	-3	-0.9
Dihedral angle (°) 1-2-3-4/5-6-3-4	2.3/-2.4	-12/-19	5/-1	6/0

\* Computed Gibbs free energies for different dihydrooxepines at the CCSD(T)/6-311++G(2d,2p)//M06/6-311G(d,p) level in DMSO.

### 3.3. Conclusions

We presented a systematic investigation by means of M06 and CCSD(T) methods for [1,3]- and [3,3]-sigmatropic rearrangements to afford 2,5-dihydrooxepines and dihydrofurans. The relative stabilities between the 1,1-diacyl-2-vinylcyclopropane, the seven-membered ring and the five-membered ring products have been mapped out, which theoretically illustrated that 2,5-dihydrooxepines are kinetic products but metastable molecular states for acyclic ketone substrates; while 2,3-dihydrofurans are thermodynamic products in both cyclic and acyclic ketone cases. The reversibility between the 2-vinylcyclopropanes and the 2,5-dihydrooxepines forms and the irreversibility of the 2-vinylcyclopropane transformations to the 2,3-dihydrofurans, might be the two main reasons for the metastability of 2,5-dihydrooxepines in previous experimental results.

Electronic and steric effects were discussed to better understand reactivity differences of cyclic and acyclic diketone substrates. The constraint of cyclic substrates might preshape the molecular structure, close to the right transition state, which would facilitate the transformation. The calculated behavior in solution confirmed that DMSO envisaged for the methodology development could maintain a good energetic profile. The small energetic gap

decrease of the five-membered ring transition state suggests that the [1,3]-sigmatropic rearrangement could be influenced by solvent systems. An appropriate control of both temperature and solvent system may help tunnelling two reaction pathways.

In summary, the calculation results gave interesting explanation and reflection on the reaction mechanism and may help to further optimize and develop the appropriate synthetic method towards 2,5-dihydrooxepines. The high accuracy of calculations provided interesting results fully consistent with those from experiments. However, synthetic conditions cannot all be computed with high accuracy. For the design of new reactions, early-stage experimental discoveries are also important for computational organic chemistry in predicting the products and parameters involved. The experimental techniques could help to increase the credibility of calculations. Therefore, an appropriate combination of experimental and computational organic chemistry should lead to further success in organic chemistry at theory, mechanism, and synthesis levels. In our case, this goal has been achieved successfully during this study.

Having developed a strong methodological survey of the oxa-Cope rearrangement involving cyclic 1,3-dicarbonyl substrates, this methodology was applied to the total synthesis of oxepin-based natural products. Thereby, the total synthesis of natural benzoxepins, radulanins will be developed in Chapter IV and the studies on synthesis of oxepino-DKPs are still in progress.



**CHAPTER IV. TOTAL SYNTHESIS OF BENZOXEPINES  
AND OXEPINO-DIKETOPIPERAZINES BY USING  
OXA-COPE REARRANGEMENTS**

---

*“The more difficult something became, the more rewarding it was in the  
end.”*

*---Daniel Wallace*

---





## Chapter IV. Total Synthesis of Benzoxepines and Oxepino-Diketopiperazines by using Oxa-Cope Rearrangement

### 1. Total synthesis of radulanin natural products

Our previous study showed that the oxa-Cope rearrangement of acylvinylcyclopropane could get a fast entry to the synthesis of such oxacycles. This chapter will describe the extended application of our tandem cyclopropanation/oxa-Cope rearrangement method toward the total synthesis of natural products.

The first part of this chapter will detail the total synthesis of radulanins as a direct application of our methodologies, containing a 2,5-dihydrooxepines as structure pattern (Figure IV-1), and their related bioactivity tests results.

In the second part, we are going to apply our new approach on the total synthesis of janoxepin and cinereain, which led us to construct the oxepine core in oxepino-DKP system.

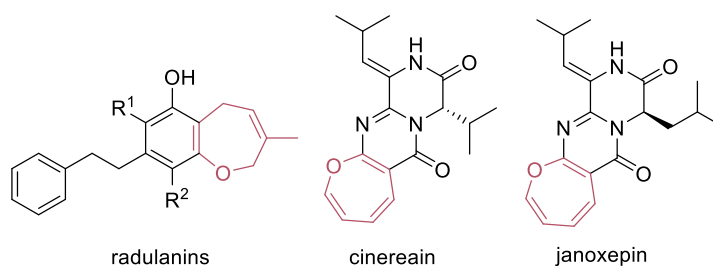


Figure IV-1 Target synthesis natural products in Chapter IV

#### 1.1. Introduction: isolation and biological activities of radulanins

The benzoxepine skeleton is present in some naturally occurring sesquiterpenes and lipophilic aromatic compounds.<sup>271</sup> The main framework in this family consists of a 7-membered oxacycle fused with benzene ring. The family of radulanin natural products belongs to 3-methyl-2,5-dihydro-1-benzoxepins, shown in Figure IV-1.<sup>272</sup>

Radulanins A (IV-1) and E (IV-4) were isolated from the epiphytic liverwort *Radula variabilis* by Asakawa et al. in 1978.<sup>273</sup> The same group reported the discovery of radulanin B

<sup>271</sup> Y. Asakawa, *Pure and Applied Chemistry* **2007**, *79*, 557-580.

<sup>272</sup> N. Kuntala, J. R. Telu, J. Anireddy, S. Pal, *Letters in Drug Design & Discovery* **2017**, *14*, 1086-1098.

<sup>273</sup> Y. Asakawa, M. Toyota, T. Takemoto, *Phytochemistry* **1978**, *17*, 2005-2010.

(methyl ether of radulanin A) from *Radula tokiensis* in 1981.<sup>274</sup> Radulanins H (**IV-3**) and radulanolide (**IV-5**) were isolated from *Radula complanate* in 1982.<sup>275</sup> *Radula* species of liverwort are rich sources of prenylbiphenyls,<sup>276</sup> from which radulanins might be biogenetically derived (Figure IV-2). Most liverworts produce biologically interesting properties, such as allergenic contact dermatitis, antifeedant, anticancer and plant growth regulatory activities.<sup>277</sup> *Radula* species also contain allergenic agents, and their crude extracts show antimicrobial activities at low concentration. However, the hapten responsible for allergenic contact dermatitis has not been identified.<sup>3</sup> Concerning pure compounds, it has been only reported that radulanin H shows significant 5-lipoxygenase, calmodulin inhibitory and antitrypanosomal activities,<sup>278</sup> while they have been suspected to have plant growth inhibition properties (never demonstrated yet) due to their structural analogy to lunularic acid.<sup>279</sup> Thus, this family still attracts the attention of natural product and synthetic chemists for their related or suspected bioactivities.

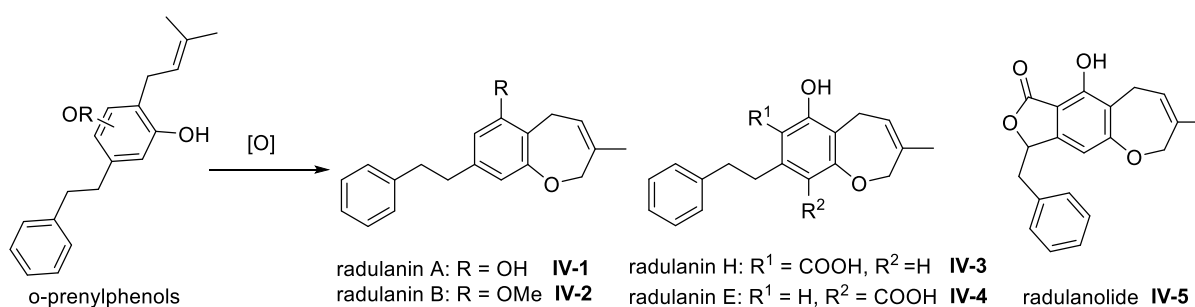


Figure IV-2 Natural products isolated from *radula* species

## 1.2. Literature reviews on radulanin synthesis

Up to the present, major synthetic methods reported for the synthesis of 2,5-dihydro-1-benzoxepines like radulanins most commonly rely on ring closing metathesis or intramolecular Mitsunobu cyclization of bifunctional precursors.

Snieckus published the first total synthesis of radulanin A in 1998 by using a combination of

<sup>274</sup> Y. Asakawa, R. Takeda, M. Toyota, T. Takemoto, *Phytochemistry* **1981**, *20*, 858-859.

<sup>275</sup> Y. Asakawa, R. Takeda, M. Toyota, T. Takemoto, *Phytochemistry* **1982**, *21*, 2481-2490.

<sup>276</sup> Y. Asakawa, T. Hashimoto, K. Takikawa, M. Tori, S. Ogawa, *Phytochemistry* **1991**, *20*, 235-251.

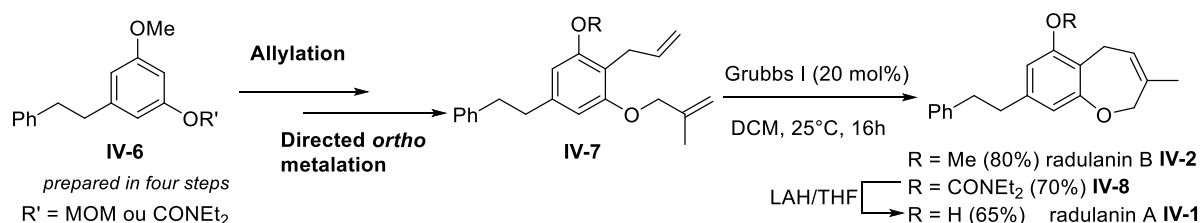
<sup>277</sup> Y. Asakawa, K. Takikawa, M. Toyota, T. Takemoto, *Phytochemistry* **1982**, *21*, 2481-2490.

<sup>278</sup> a) Y. Asakawa, *Pure and Applied Chemistry* **2007**, *79*, 557-580; b) C. Schwartner, W. Bors, C. Michel, U. Franck, B. Müller-Jakic, A. Nenninger, Y. Asakawa, H. Wagner, *Phytomedicine* **1995**, *2*, 113-117; c) H. Yamada, K. Otoguro, M. Iwatsuki, *J. Nat. Med.* **2012**, *66*, 377-382.

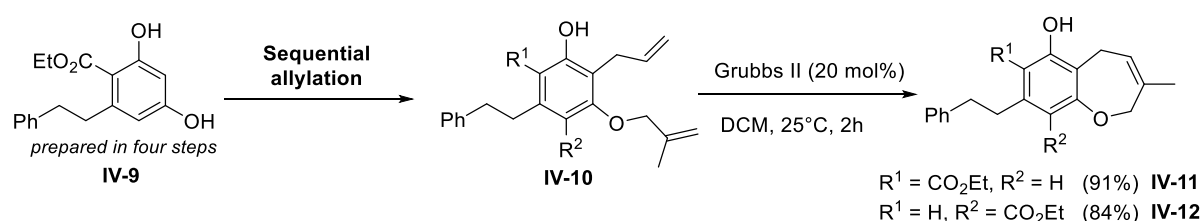
<sup>279</sup> R. J. Pryce, *Planta* **1971**, *97*, 354-357.

regiospecific directed ortho-metalation of a phenol ring and ring-closing olefin metathesis strategy (15 steps, 7%) (Scheme IV-1a).<sup>280</sup> In 2009, Yoshida *et al.* combined the ring-closing metathesis with a biomimetic intramolecular condensation and a sequential regioselective *C*- and *O*-allylation to achieve the total synthesis of radulanin H (8 steps, 11%) and E (11 steps, 7%) (Scheme IV-1b).<sup>281</sup>

a. Synthesis of radulanin A by Snieckus



b. Synthesis of radulanin H and E by Yoshida



Scheme IV-1 Total synthesis of radulanins A, B, E and H by using ring-closing metathesis as a key step to 2,5-dihydrooxepines

Yamaguchi and his coworkers described another synthetic strategy to make radulanins A, B and E by using the Mitsunobu cyclization. The synthesis began with a Stille coupling between a benzyl bromide IV-13 and a stannane IV-14 to make *Z*-methyl-oxidized *o*-prenylphenols IV-15 and IV-16. The generated diols were subjected to Mitsunobu cyclization, which gave radulanins A and B as the desired products (7 steps, 16% for radulanin A; 8 steps, 13% for radulanin B).<sup>282</sup> Later the same approach was combined to regioselective Vilsmeier formylation. After oxidation of the intermediate aldehyde IV-18 by Ag<sub>2</sub>O, radulanin E was successfully obtained (Scheme IV-2).<sup>283</sup>

Those synthetic methods still have disadvantages including tedious reaction conditions, lengthy synthetic sequences and low overall yields. Thus, alternative synthetic methods are

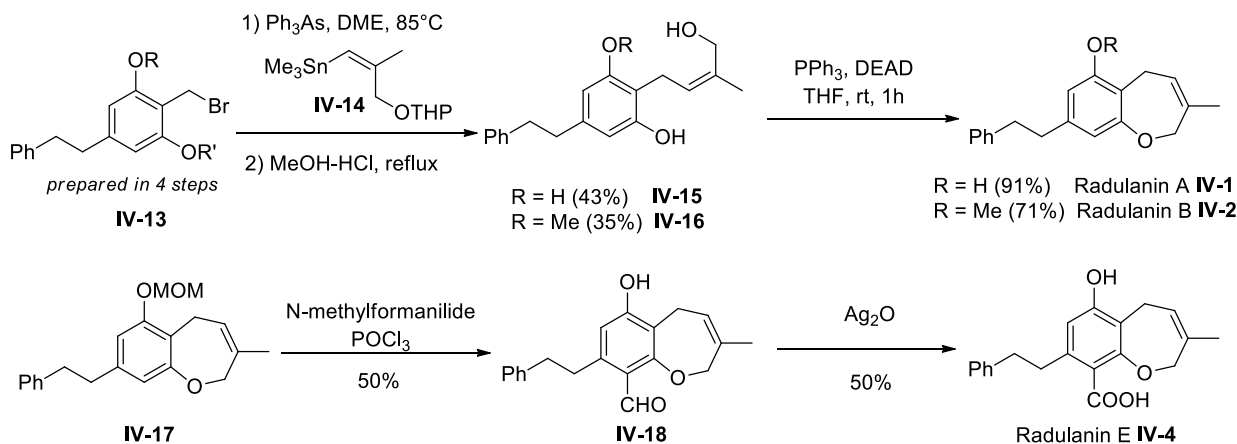
<sup>280</sup> M. Stefinovic, V. Snieckus, *J. Org. Chem.* **1998**, *63*, 2808-2809.

<sup>281</sup> M. Yoshida, K. Nakatani, K. Shishido, *Tetrahedron* **2009**, *65*, 5702-5708.

<sup>282</sup> S. Yamaguchi, K. Furihata, M. Miyazawa, H. Yokoyama, Y. Hirai., *Tetrahedron Letters* **2000**, *41*, 4787-4790.

<sup>283</sup> S. Yamaguchi, N. Tsuchida, M. Miyazawa, Y. Hirai., *J. Org. Chem.* **2005**, *70*, 7505-7511.

still required to get these compounds and we thought to apply our previously described oxa-Cope methodology to do so.

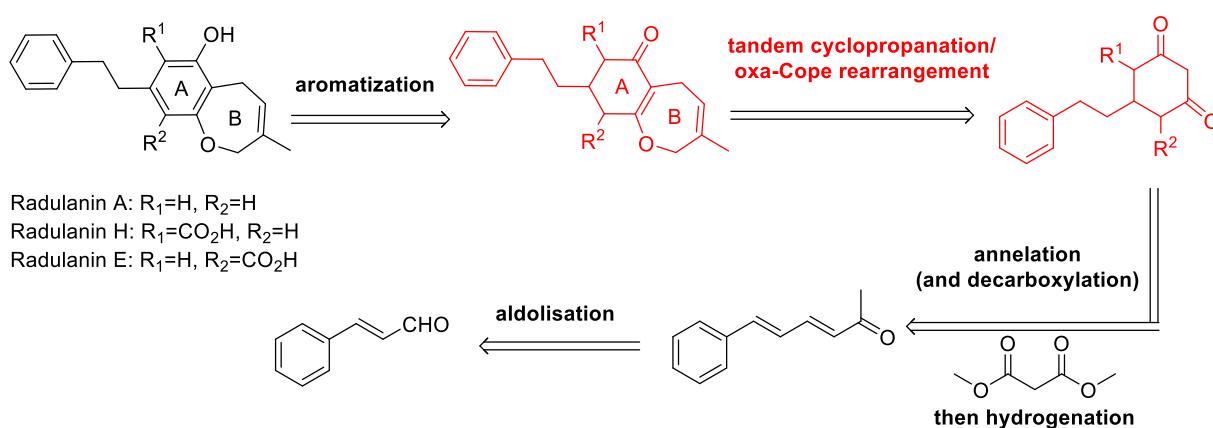


Scheme IV-2 Total synthesis of radulanins A, B and E by Yamaguchi, using a Mitsunobu cyclization

### 1.3. New synthetic strategy and results

#### 1.3.1. Retrosynthesis of radulanin A, H and E

A new retrosynthetic strategy is presented in Scheme IV-3. This strategy relied upon our previous study to construct the 2,5-dihydrooxepine ring, followed by a late stage aromatization of ring A. The intermediate dicarbonyl substrates could be synthesized according to literature<sup>284</sup> by using an annulation (with or without a decarboxylation) between cinnamylideneacetone and dimethylmalonate followed by hydrogenation of the residual double bond. An aldolisation between cinnamaldehyde and acetone could be simply used to generate cinnamylideneacetone.



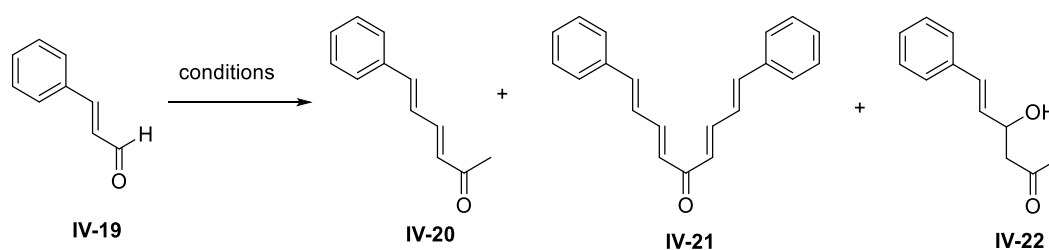
Scheme IV- 3 New retrosynthesis pathway by using cyclopropanation/oxa-Cope rearrangement

<sup>284</sup> M. F. Mechelke, A. A. Dumke, S. E. Wgwerth, *Journal of undergraduate chemistry research* **2013**, *12*, 47-50.

### 1.3.2. 2,5-Dihydrooxepine installations from a 1,3-cyclohexadione intermediate

The total synthesis began by making cinnamylideneacetone **IV-20** following some literature methods. The aldolisation with acetone<sup>285</sup> and the Wittig reaction<sup>286</sup> with triphenylphosphoranylidene acetone were compared at first, and both gave good results (Table IV-1). Considering that the first step of a total synthesis should produce multigram scale materials, the aldolisation was chosen as a cheaper and better choice.

Table IV-1 Optimization of aldolization step



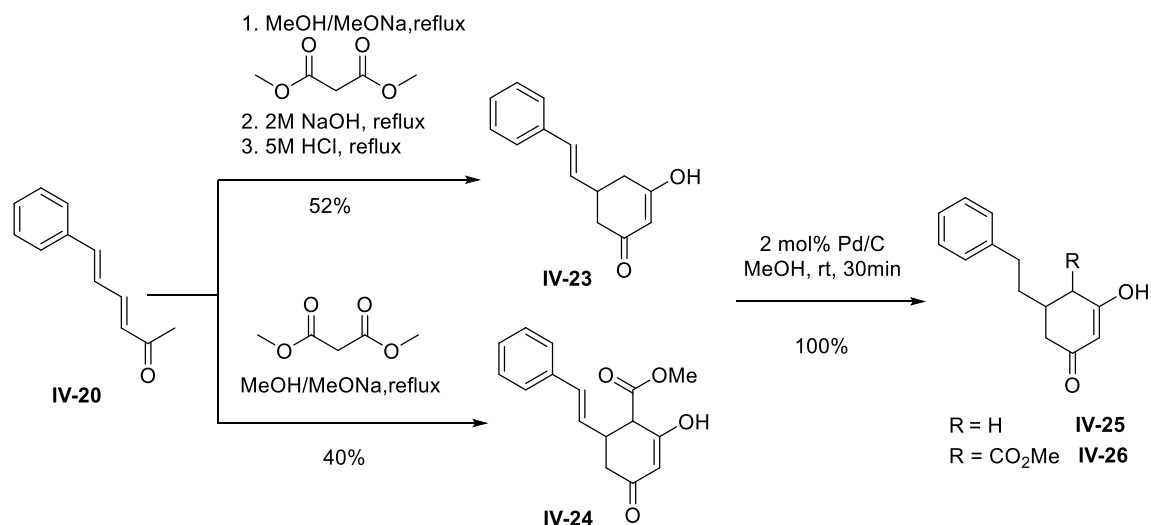
Entry	Conditions	Results
1	acetone (2 equiv.), NaOH (6 equiv.), ethanol, rt, 6h	<b>IV-21</b> (52%)
2	acetone (1equiv.), NaOH (1equiv.), ethanol/H <sub>2</sub> O (2:8), rt, 4h	<b>IV-20</b> (32%)
3	acetone (1equiv.), Ca(OH) <sub>2</sub> (1equiv.), ethanol/H <sub>2</sub> O (2:8), rt, 8h	<b>IV-20</b> (32%)
4	acetone (20 equiv.), NaOH (1equiv.), 0°C, 1h	<b>IV-20</b> (75%) <b>IV-22</b> (6%)
5	Triphenylphosphoranyli-dene-2-propanone (1.2 equiv.), DCM, reflux, 16h	<b>IV-20</b> (69%)

Then the 1,3-cyclohexadione compounds were prepared by annulation through the condensation of cinnamylideneacetone **IV-20** with commercially available dimethyl malonate in the presence of NaOMe, refluxing in MeOH. Combined or not with decarboxylation under acidic condition gave two different intermediate diketones **IV-23** and **IV-24**, which were purified as enol tautomer forms (Scheme IV-4). The keto-enol equilibrium might complicate purifications, resulting in moderate yields. The treatment with NaOH and HCl during the decarboxylation step seemed to eliminate some byproducts, so that compound **IV-23** was easier to be purified, affording a yield of 52%. However, the ester form **IV-24** was achieved in 40% yield. Then the purified ketones were then converted to the direct precursors **IV-25** and

<sup>285</sup> R. L. Nongkhilaw, R. Nongrum, B. Myrboh, *J. Chem. Soc., Perkin Trans.* **2001**, *1*, 1300–1303.

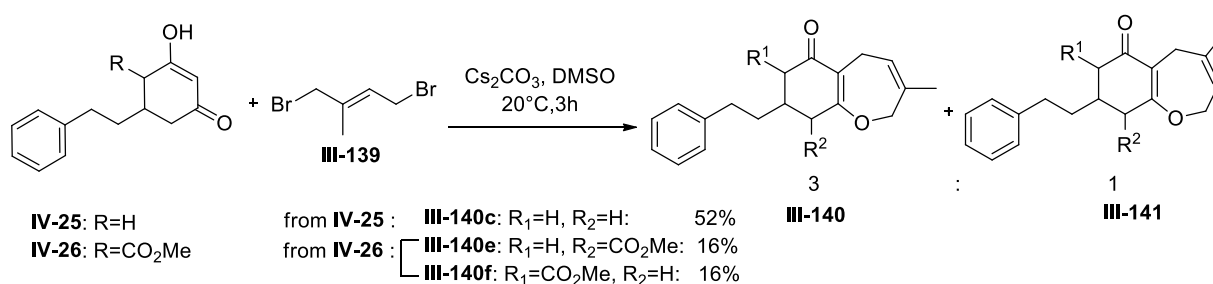
<sup>286</sup> A. A. Jafari, M. Ghadami, *Environmental Chemistry Letters* **2016**, *14*, 223–228.

**IV-26** for cascade cyclopropanation/Cope rearrangement by palladium-catalyzed hydrogenation in MeOH in quantitative yields.



*Scheme IV-4 Preparations of diketone intermediates.*

The key step of these synthesis was the tandem cyclopropanation/oxa-Cope rearrangement. After applying the optimal conditions found during the previous study (1,4-dibromo-2methyl-2-butene, Cs<sub>2</sub>CO<sub>3</sub> in DMSO at 20°C), the <sup>1</sup>H-NMR spectrum of the crude extract showed that the desired dihydrooxepines were the major products (Scheme IV-5). However, these compounds were poorly stable upon isolation as predicted, given moderate yields. This transformation was tested in DMF at 15°C as well, without furnishing better yield. To improve this step, purification on refrigerated silica-gel column will hence be needed. In the near future, since this improvement was only uncovered lately.



*Scheme IV-5 Results of tandem cyclopropanation/oxa-Cope rearrangement step.*

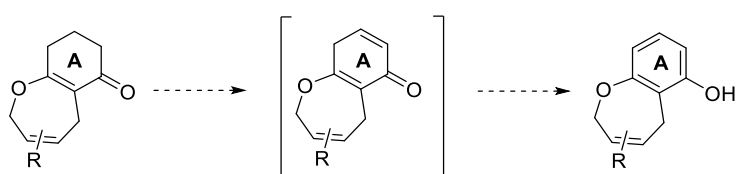
Demonstrated in the methodological part, the cyclopropanation step was moderately regioselective, always giving two regioisomers with a ratio of 3:1 in favor of the desired 3-methylated isomer. The wrong regioisomer could be eliminated later after further steps.

### 1.3.3. Aromatization of 2,5-dihydrooxepine intermediates

With successfully synthesized dihydrooxepine intermediates in hand, aromatization conditions were needed to end these syntheses. Due to the instability of these intermediates, this step was particularly challenging and necessitated protocols adapted to our compounds. Simplified model molecules were first used to screen several aromatization methods.

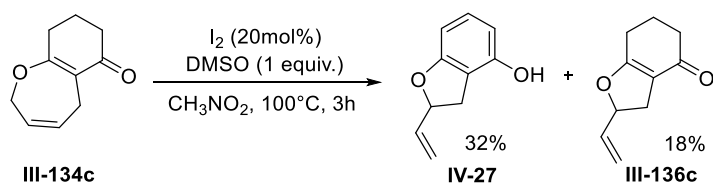
#### 1.3.3.1. Model study for aromatization

The main strategy in this step was to desaturate the cyclohexanone ring A into the desired phenol. To make this transformation, several known conditions were tested, consisting in oxidizing the  $\alpha,\beta$ -position of the carbonyl. In our case, heating should be prohibited (Scheme IV-6).



Scheme IV-6 First aromatization strategy

Under a heating aromatization reaction,<sup>287</sup> a phenol could be obtained but it was fused with a dihydrofuran, which follows our discussion in the previous methodology chapter on the reorganization of 2,5-dihydrooxepines into 2-vinyl-2,3-dihydrofurans. The temperature could easily decompose our 2,5-dihydrooxepines (Scheme IV-7).



Scheme IV-7 Dihydrofurans formations in the heating conditions

Therefore, some room-temperature dehydrogenation conditions of carbonyl compounds were attempted as shown in following Table IV-2. Bromination and iodination conditions were not mild enough to generate the unsaturation in this kind of system, even at low temperature, leading to decomposition (entry 1). Then oxidations using hypervalent iodine reagent, IBX, CAN,  $\text{MnO}_2$ , DDQ or palladium-catalyzed Saegusa–Ito condition were tested, but without

<sup>287</sup> Y.F. Liang, S. Song, L. Ai, X. Lia, N. Jiao, *Green Chemistry* **2016**, 18, 6462-6467.

success. As our model substrates were extremely sensible to temperature and base, a small screening of different bases was also performed to find the right condition for silylation, prior to IBX or Saegusa-Ito oxidation under wild conditions (Table IV-2, entry 13-19).

Table IV-2 Aromatization condition screenings

Entry	Conditions	Results
1	PHBP·HBr <sub>3</sub> , THF, rt, 2h <sup>288</sup>	decomposition
2	LiHMDS (-78°C to 0°C), NBS (0°C), THF, 10min	decomposition
3	LiHMDS (-78°C), TMSCl (-78°C to 0°C); NBS (0°C), THF, 30min	decomposition
4	LDA (-10 °C), I <sub>2</sub> (-78°C to 0°C), THF, 30min	decomposition
5	HTIB, ACN, rt, 2h <sup>289</sup>	decomposition
6	LDA (-10 °C), TMSCl (-10°C to 0°C); MnO <sub>2</sub> (rt), THF, 12h	decomposition
7	CAN, ACN, 0°C, 2h	decomposition
8	IBX, MPO, DMSO, rt, 2h <sup>290</sup>	NR
9	NEt <sub>3</sub> (0°C), TMSOTf (0°C), THF; IBX, MPO, DMSO, rt, 1h	NR
10	LiHMDS (-78°C), TMSOTf (-78°C to 0°C), THF; IBX, MPO, DMSO, rt, 1h	decomposition
11	LiHMDS (-78°C), TMSOTf (-78°C to 0°C), THF; DDQ, MeCN, rt, 3h <sup>291</sup>	decomposition
12	LiHMDS (-78°C), TMSCl (-78°C), THF; Pd(OAc) <sub>2</sub> (0°C), MeCN, 30min <sup>292</sup>	NR
13	TMSOTf, NEt <sub>3</sub> , DCM, 0°C, 1h	formation of <b>III-136c</b>
14	LiHMDS (-78°C), 15min; TMSOTf (-78°C to 0°C), 1h, THF <sup>293</sup>	decomposition
15	tBuOK, TMSCl, 0°C to rt, overnight, THF	decomposition
16	LiH, TMSCl, 0°C to rt, overnight, THF	decomposition
17	LDA, TMSOTf, -78°C, THF, 1h;	decomposition
18	LiH, TBSOTf, 0°C, 1h, THF	decomposition
19	NaH, TBSOTf, 0°C, 1h, THF	NR

<sup>288</sup> C. Bonini, G. Cristiani, M. Funicello, *Synthetic Communications* **2006**, *36*, 1983-1990.

<sup>289</sup> K. H. Lee, K.-Y. Ko, *Bull. Korean Chem. Soc.* **2002**, *23*, 1505-1506.

<sup>290</sup> K. C. Nicolaou, T. Montagnon, P. S. Baran, *Angew. Chem. Int. Ed.* **2002**, *41*, 993-996.

<sup>291</sup> K. Chen, C. Liu, L. Deng, G. Xu, *Steroids* **2010**, *75*, 513-516.

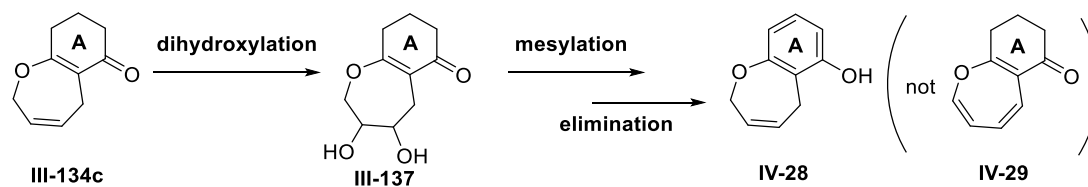
<sup>292</sup> Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011-1013.

<sup>293</sup> L. M. Murray, P. O. Brien, R. J. K. Taylor, *Org. Lett.* **2003**, *5*, 1943-1946.



Disappointingly, no silylation took place with any of these bases. From the NMR of crude extract, we observed that amines promote the isomerization of 2,5-dihydrooxepine to a 2,3-dihydrofuran; stronger lithium bases like LiHMDS or LDA completely decomposed our model substrates, while inorganic bases like LiH and tBuOK may partially isomerize the double bond on the dihydrooxepine rings (the significant NMR signals of dihydrooxepine disappeared). When treated with NaH at 0°C, the starting material remained stable in this condition, but no silylation occurred.

As no classical oxidation could afford the  $\alpha,\beta$ -unsaturated carbonyl motif, an alternative strategy had to be found. The solution serendipitously came from an alternative study that was undertaken in order to dehydrogenate the 2,5-dihydrooxepin ring into an oxepin during our synthetic study toward janoxepin and cinereain. This transformation is known to be difficult in the literature and our aim was first to reproduce Taylor's dihydroxylation strategy<sup>294</sup> with our bicyclic model **III-134c**. It was expected that a dimesylate could be doubly eliminated to generate the oxepine ring. Surprisingly, we did not observe the formation of oxepine **IV-29**, but that of a 2,5-dihydrobenzoxepine, the heterocarbocyclic core of radulanins. We will describe in the following parts the details of this discovery and its application to the synthesis of some radulanins (Scheme IV-8).



Scheme IV-8 Alternative aromatization strategy

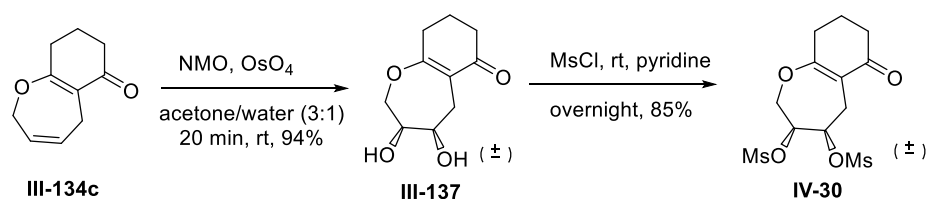
Application of standard Upjohn dihydroxylation conditions<sup>295</sup> (5 mol% OsO<sub>4</sub>, stoichiometric amount of NMO in acetone and water) to 2,5-dihydrooxepine furnished oxepane-diol **III-137** in excellent yield (94%). Activation of this diol for double elimination was investigated next. Treatment with MsCl in pyridine as solvent was found to proceed efficiently, and dimesylate **IV-30** was isolated in 85% yield (Scheme IV-9).

With the dimesylate **IV-30** in hand, a screening of elimination conditions was carried out

<sup>294</sup> R. G. Doveston, Ph. D. thesis "Oxepine-Pyrimidinone Natural Products: The Total Synthesis of (±)-Janoxepin", The University of York, 2012.

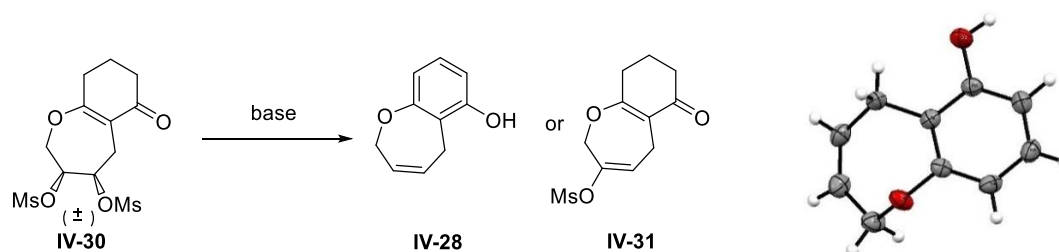
<sup>295</sup> M. Schroeder, *Chem. Rev.* **1980**, *80*, 187–213.

(Table IV-3). TBAF in DMSO gave optimal results, with a new compound isolated in 75% yield (entry 1). The structure of this new synthetic compound was first assigned based upon  $^1\text{H-NMR}$  spectrum. Three aromatic signals appeared at 7.01 (t,  $J = 8.0$  Hz), 6.68 (d,  $J = 7.9$  Hz) and 6.54 ppm (d,  $J = 8.1$  Hz). Besides, the characteristic signals of 2,5-dihydrooxepines were clearly recovered: 5.86 (dt,  $J = 13.3, 5.3, 2.2$  Hz), 5.50 (dtt,  $J = 9.7, 2.7, 1.3$  Hz), 4.59 (m), 3.54 ppm (dd,  $J = 5.2, 2.0$  Hz). The broad singlet at 4.91 ppm strongly suggested the presence of a phenolic OH group. All data together indicated the structure of isolated compound could be our desired dihydrobenzoxepine **IV-28**.



*Scheme IV-9 Dihydroxylation and mesylation*

The structure of dihydrobenzoxepine **IV-28** was then further confirmed by X-ray crystallographic analysis. Alternatively, when DBU,  $\text{Cs}_2\text{CO}_3$  and potassium *tert*-butoxide were employed, the double elimination did not occur, but compound **IV-31** could be isolated in low yields (entry 2).

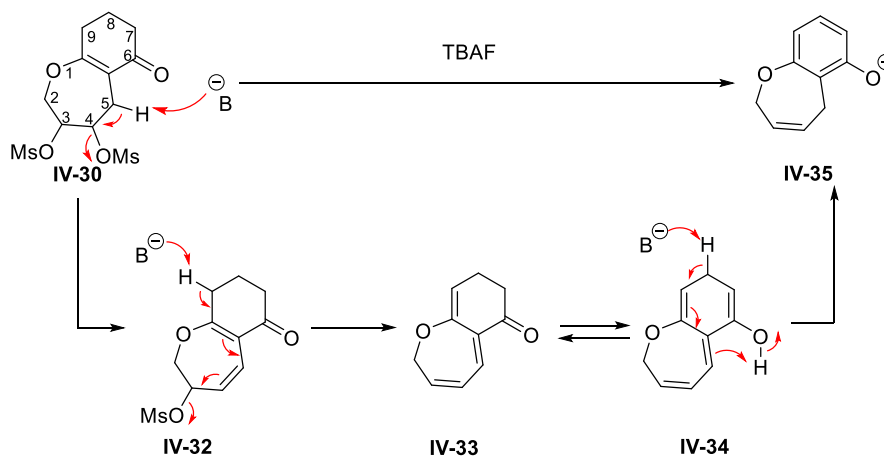


*Table IV-3 Base screening for dehydration*

Entry	Conditions	Results
1	TBAF (5 equiv.), DMSO, rt, 1h	<b>IV-28</b> (75%)
2	DBU, THF, 80°C, 12h	<b>IV-31</b> (25%)
3	$\text{Cs}_2\text{CO}_3$ , THF, 80°C, 12h	<b>IV-31</b> (trace)
4	<i>t</i> BuOK, THF, rt, 16h	<b>IV-31</b> (trace)

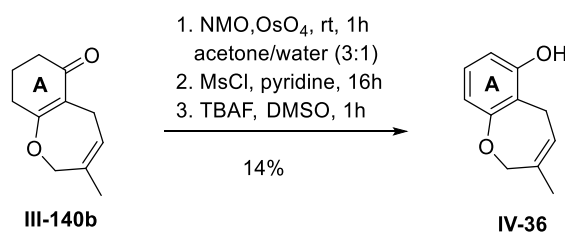
The double elimination mechanism is proposed in Scheme IV-10. The first elimination of mesylate would occur at C4, which generates a conjugated double bond. For the same reason,

the position C9 of **IV-32** could be deprotonated, leading a triene formation. In addition, in the presence of base, the ketone **IV-33** easily converts on enolate **IV-34**, triggering the last isomerization and aromatization. After an acidic work up, the final 2,5-dihydrobenzobenzoxepine **IV-28** could be isolated.



*Scheme IV-10 Mechanism of double elimination to generate 2,5-dihydrobenzobenzoxepine compounds*

This aromatization conditions were tested as well with the 3-methylated substrate **III-140b**, the yield of resulting phenol decreased (14% over three steps). This low yield may be due to the presence of the methyl group, leading to regioselectivity issues during elimination (Scheme IV-11). However, it would be worth trying the dihydroxylation step at 0°C to avoid any problem due to the instability of 2,5-dihydroxepine. Having demonstrated the feasibility of this strategy, no further optimization studies were carried out on model substrates. This three-step aromatization method was applied directly to our total synthesis of radulanins.

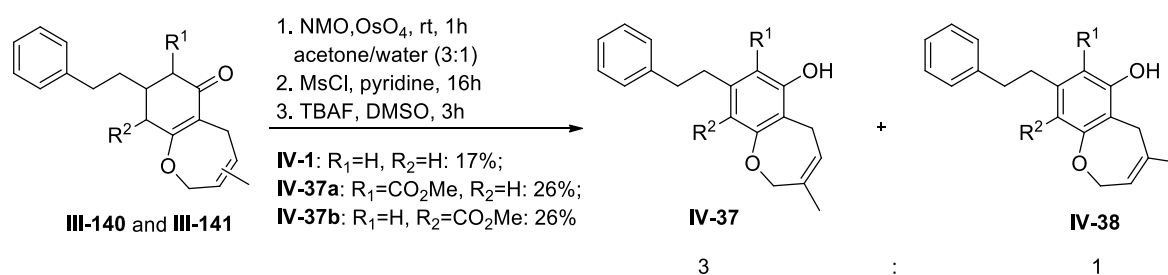


*Scheme IV-11 Aromatization for methylated substrate III-140b*

### 1.3.3.2. End game of radulanin synthesis

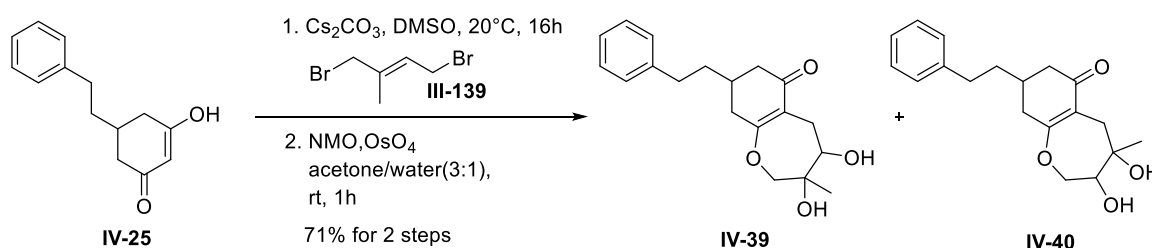
The dihydroxylation-elimination methodology, developed with model substrate **III-134c**, was applied to the dihydrooxepine intermediates in the total synthesis of radulanins under the same conditions, affording encouraging results, but yields remained modest. Treatment with

OsO<sub>4</sub> (5 mol%) and NMO in an acetone/water solvent system took longer reaction time compared with model substrate. A small pad of silica work-up gave a mixture of diastereomeric diol products which were directly engaged in the dimesylation step. Increasing the loading of osmium tetroxide to 1 equiv. or extending the reaction time to 24h was found to be detrimental to the yield. Similar results were obtained when the 2,5-dihydrooxepine-derived diols were subjected to the same mesylation conditions. A complex mixture of products was shown by the <sup>1</sup>H-NMR spectrum of the unpurified product. The double elimination of mesylates was carried out with TBAF in DMSO at rt, but only a low yield of the final products was obtained (from 14% to 26% over 3 steps). No more conversion to product could be observed following prolonged reaction times or loading less TBAF (Scheme IV-12).



*Scheme IV-12 Application of the dihydroxylation-dehydration methodology to the total synthesis*

Considering the instability of the dihydrooxepine ring formed from the key transformation, the yields could be improved by subjecting them directly to the next steps without column purification. When tested with diketone compound **IV-25**, the yield over two steps was largely optimized, and was found comparable to the <sup>1</sup>H-NMR yields of the first step (Scheme IV-13). This route still needs to be completed.

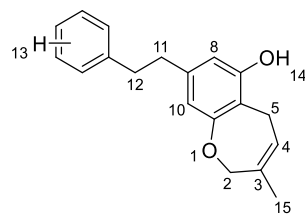


*Scheme IV-13 Optimization of the isolated yield for tandem cyclopropanation/oxa-Cope rearrangement step*

At this stage, radulanin A **IV-1** was obtained and purified perfectly from its 4-methylated isomer with an overall yield of 4%, which still needs some improvement at the aromatization

step.  $^1\text{H}$  NMR data of our synthesized radulanin A was compared to the reported one, all of the signals showed good agreement (Table IV-4).

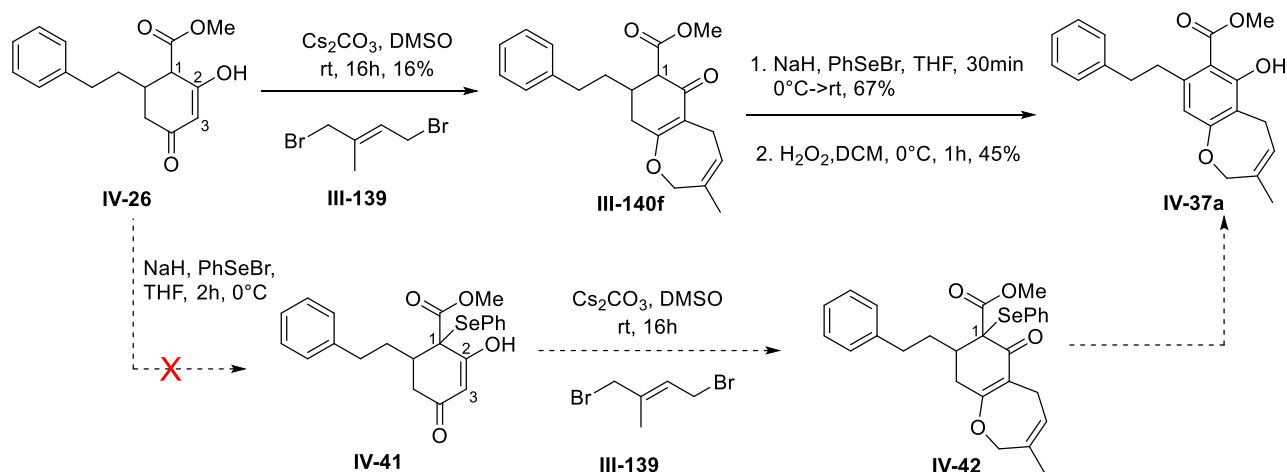
Table IV-4 Comparison of the  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ) data of reported and synthesized radulanin A



$^1\text{H}$ number	Reported ( $\delta$ ppm) <sup>10</sup>	Synthesized ( $\delta$ ppm)
15	1.54 (s)	1.54 (d, J=1.4Hz)
12	2.8-2.7 (m)	2.85 – 2.76 (m)
11		2.88 (ddd, J = 10.3, 6.5, 2.2 Hz)
5	3.4 (d)	3.40 (dd, J = 5.8, 1.9 Hz)
2	4.4 (br s)	4.40 (dq, J = 2.6, 1.4 Hz)
14 (OH)	4.8 (br s)	4.65 (br s)
4	5.6 (m)	5.61 (tt, J = 5.7, 2.9 Hz)
10	6.37 (d)	6.38 (d, J = 1.6 Hz)
8	6.53 (d)	6.54 (d, J = 1.7 Hz),
13	7.32-7.16 (m)	7.33 –7.08 (m)

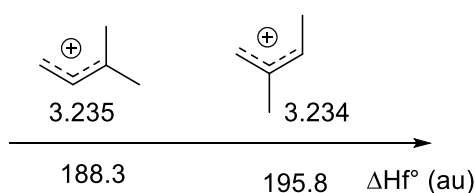
Starting from ester intermediate **IV-26**, an alternative approach to synthesize radulanin H was to use an  $\alpha$ -selenylation on C1, then an oxidation to eliminate the selenoxide could give the desired  $\alpha,\beta$ -unsaturated carbonyl product which may lead to aromatization (Scheme IV-14). The selenide intermediate was observed in 67% yield after generating the anion of **III-140f** with NaH by the reaction with PhSeBr. Selenide oxidation was performed in 45% yield in the presence of hydrogen peroxide to release the methylester of radulanin H. The sequence of silylation using NaH, TMSOTf and oxidation by DDQ, Pd(OAc)<sub>2</sub> or IBX were tested as well, but did not give encouraging results. Besides, a tentative optimization was made by selenylating C1 of **IV-26** before cyclopropanation. Unfortunately, only the double selenylation product was observed at position 1 and 3. This poor selectivity may also explain some byproduct origins in the cyclopropanation step to make intermediate dihydrooxepine **III-140f** and its low yield. However, as previously, purification on arefrigerated column may

also improve this synthetic route.



Scheme IV-14 Selenoxide elimination involved in the aromatization step

As described before, methylated regioisomers were produced at the same time, which were not separable from the desired compounds. These regioisomers were eliminated at this step by taking advantage of the different stabilities of the corresponding methyl-substituted allyl cations (Scheme IV-15). It was reasoned that a methyl group on the central carbon (position 3 in our compounds) has a much smaller stabilizing effect (~5 kcal/mol) in the case of crotyl cation.<sup>296</sup> This research suggests that if the mixture is treated in acid medium, the wrong 4-methylated regioisomers may form more easily the corresponding allyl cations and so may decomposed more rapidly.

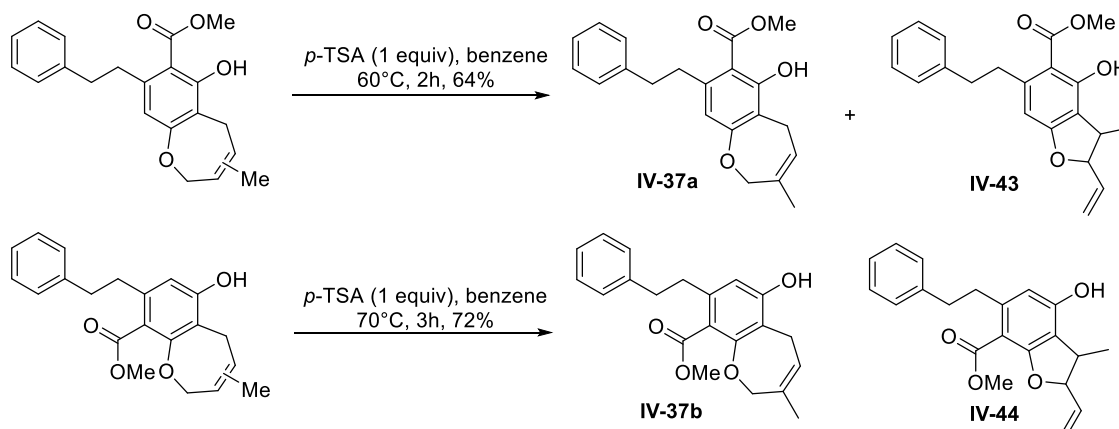


Scheme IV-15 Formation energy of stereoisomeric allyl cations with *ab initio* calculation

This strategy was applied successfully when heating the regioisomeric mixtures of compounds **IV-37a** and **IV-37b** in the presence of p-TSA (1 equiv.) in benzene. Nonetheless, a small amount of desired compounds decomposed in the same time, which could probably be optimized by loading less p-TSA in benzene (Scheme IV-16). According to <sup>1</sup>H-NMR of the

<sup>296</sup> P. V. R Schleyer, H. Mayr, W. Förner, *J. Am. Chem. Soc.* **1978**, 6032-6040.

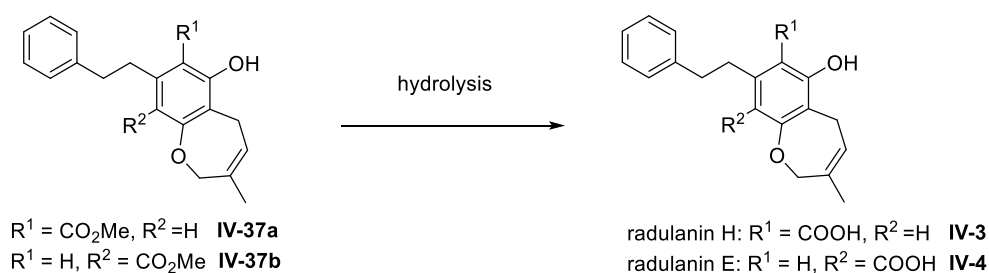
crude mixture, the wrong regioisomers converted to related dihydrofuran derivatives **IV-43** and **IV-44**, which are still needed to be confirmed.



Scheme IV-16 Purifications of **IV-37a** and **IV-37b**

The final hydrolysis of esters was firstly conducted in the presence of KOH or LiOH in a solvent system of THF/H<sub>2</sub>O or MeOH/THF/H<sub>2</sub>O, which only afforded successfully the radulanin H **IV-3** (Table IV-5).

Table IV-5 Final hydrolysis step

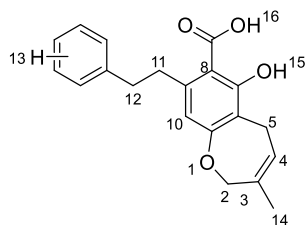


Entry	Substrates	Conditions	Isolated yields
1	<b>IV-37a</b> or <b>IV-37b</b>	KOH (2 equiv.), THF/H <sub>2</sub> O (1:2), 60°C, 16h	<b>IV-3</b> (54%)
2	<b>IV-37a</b> or <b>IV-37b</b>	LiOH (2 equiv.), MeOH/THF/H <sub>2</sub> O (1:1:1), 50°C, 16h	<b>IV-3</b> (70%)
3	<b>IV-37b</b>	KOH (2 equiv.), dioxane/H <sub>2</sub> O (1:2), 60°C, 16h	degradation
4	<b>IV-37b</b>	TMSOK, Et <sub>2</sub> O, rt, 12h <sup>297</sup>	degradation

<sup>297</sup> a) E. D. Laganis, B. L. Chenard, *Tetrahedron Letters* **1984**, 25, 5831-5834; b) T. L. Ho, G. A. Olah, *Proc. Natl. Acad. Sci. USA* **1978**, 75, 4-6.

The  $^1\text{H}$  NMR data of the obtained synthetic radulanin H **IV-3** were in good agreement with spectral data of radulanin H in the literature (Table IV-6). Thus, the second total synthesis was also accomplished.

Table IV-6 Comparison of the  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ) data of reported and synthesized radulanin H



$^1\text{H}$ number	Reported ( $\delta$ ppm) <sup>11</sup>	Synthesized ( $\delta$ ppm)
14	1.64 (s)	1.63 (s)
12	2.89 (t, J = 7.6 Hz)	2.88 (dt, J = 9.7, 6.6 Hz)
11	3.22 (t, J = 7.6 Hz)	3.20 (dt, J = 9.8, 6.7 Hz)
5	3.52 (d, J = 4.4 Hz)	3.51 (d, J = 4.3 Hz)
2	4.50 (s)	4.49 (s)
15 (OH)		
4	5.72 (t, J = 4.4 Hz)	5.71 (m)
10	6.41 (s)	6.41 (s)
13	7.21–7.18 (m), 7.31–7.27 (m)	7.22–7.18 (m), 7.33 – 7.27 (m),
16(COOH)	11.70 (brs)	11.82 (brs)

In general, the ortho-substituted benzoic acid does not esterify as easily as the meta- or para-isomer, and it is more difficult to hydrolyze di-ortho-substituted benzoic acids. The explanation is not clear yet, probably due to the steric hindrance effect.<sup>298</sup> In our case, ortho-hydroxyl substitution in **IV-37a** might facilitate the formation of hydrogen bond, resulting in the ester in the same plan as the aromatic ring. Compared with **IV-37b**, this structural planarity might reduce the steric effects, making **IV-37a** more accessible and easier to be hydrolyzed (Figure IV-3). Therefore, in order to finish the total synthesis of radulanin E, other mild and efficient hydrolysis methods are still under our investigations.

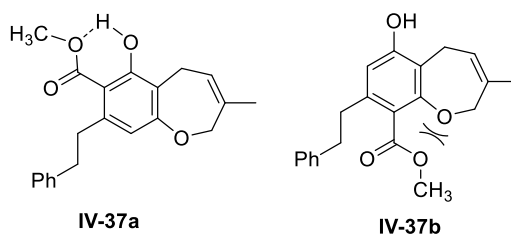


Figure IV-3 Structural analysis of methyl ester of radulanin H and E

<sup>298</sup> A. Arora, *Organic Chemistry: Aromatic, Alcohols Aldehydes & Acids*, Discovery Publishing House, 2006.



#### 1.4. Bioactivity tests of radulanins

Lunularic acid is considered as a common endogenous growth inhibitor and dormancy-inducing factor of a number of hepaticas and algae. It could also inhibit the germination and the growth of cress and lettuce at 1 mM.<sup>299</sup> Based on the structural similarity between lunularic acid and radulanins, the biotests such as herbicide activities and anti-germination activities were carried out on *Arabidopsis thaliana*. Five of our synthetic compounds, radulanin A **IV-1**, radulanin A regioisomer **IV-46**, radulanin H **IV-3**, radulanin H regioisomer **IV-47** and the methylester of radulanin H **IV-37a**, were selected to study their herbicide activities and germination inhibitions. All substrates have shown important phytotoxicities at low concentrations. The details of their inhibition efficiency regarding different substrates are still under our investigation. Indeed, these promising results confirmed our hypothesis of the herbicidal potential of radulanins.

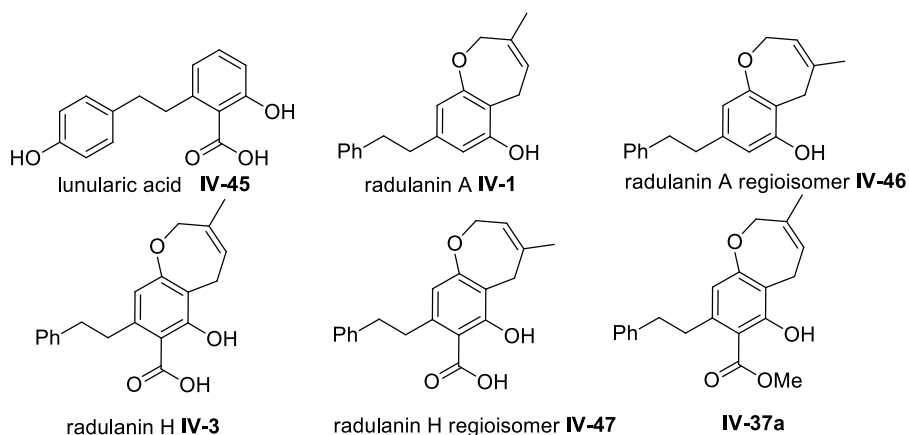


Figure IV-4 Structures of lunularic acid and five tested compounds

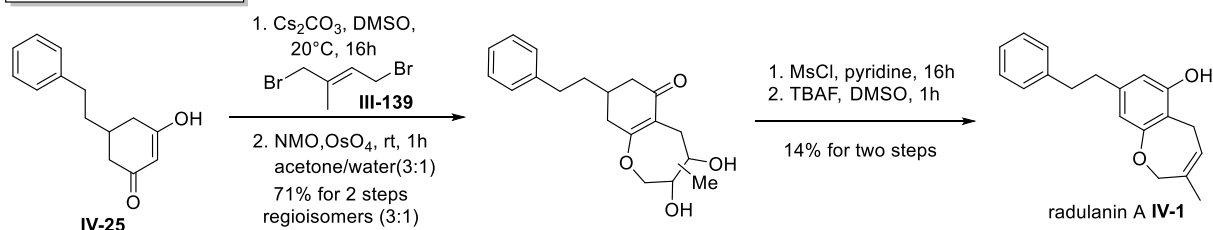
#### 1.5. Conclusion and perspectives

The total synthesis of radulanin A, H and E have been achieved from cheap or known materials by using a tandem cyclopropanation/oxa-Cope rearrangement strategy as a key step to build the carbocyclic skeleton. Their synthetic pathways are reviewed in Scheme IV-17.

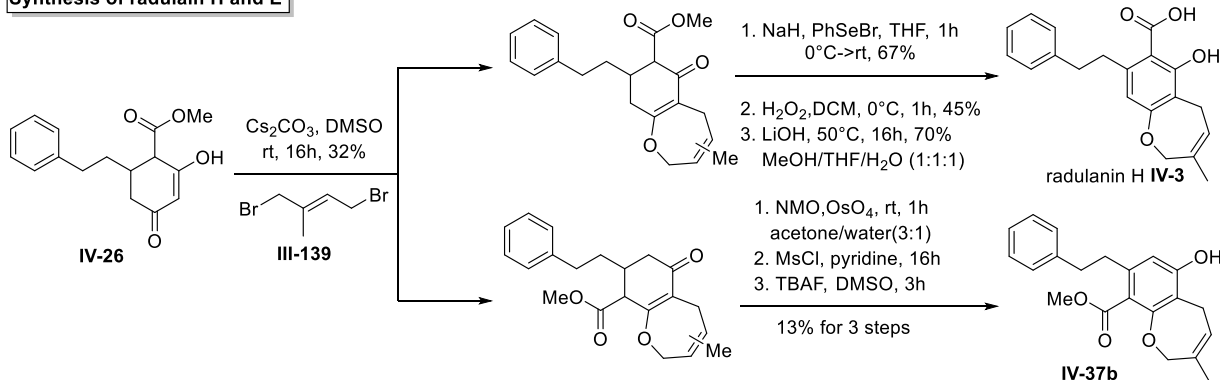
These first attempted total syntheses showed encouraging results. However, some optimization work is still required. For example, low temperature purification should be undertaken in regards with the stability of 2,5-dihydroxypines; while elimination conditions with TBAF for aromatization will be worth to be investigated in order to get better yield of phenol products.

<sup>299</sup> H. Yoshikawa, Y. Ichiki, K. Sakakibara, H. Tamura, M. Suiko, *Biosci. Biotechnol. Biochem.* **2002**, *66*, 840-846.

## Synthesis of radulanin A

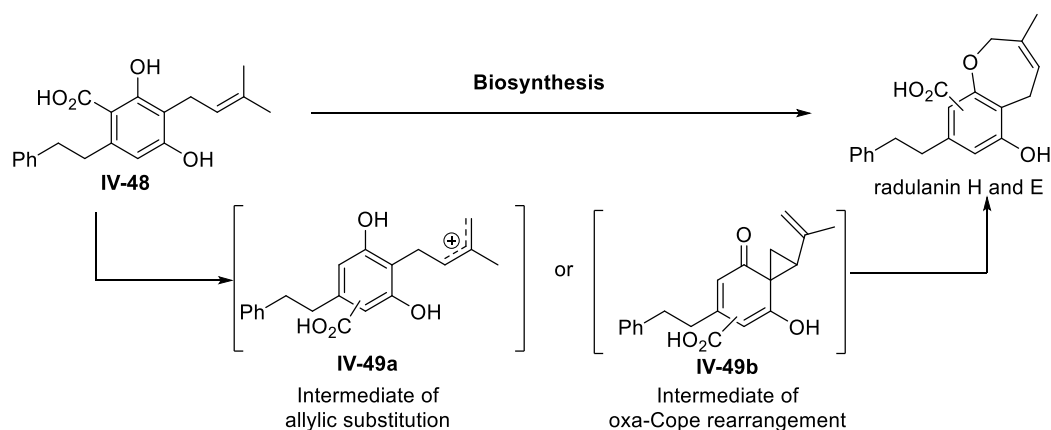


## Synthesis of radulanin H and E



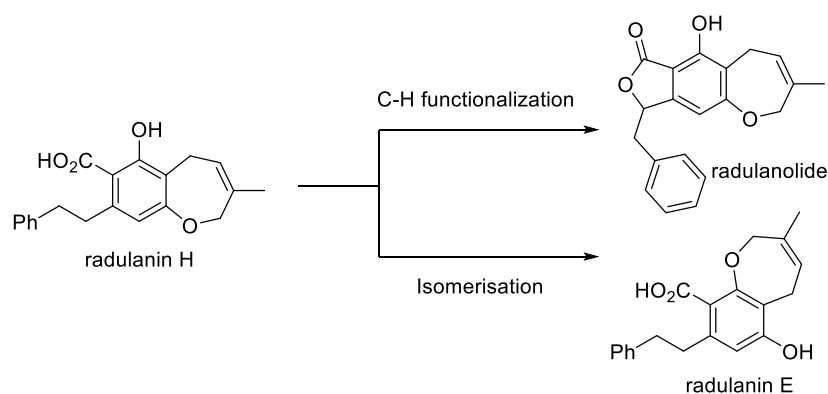
Scheme IV-17 Resume of whole synthetic pathway of radulanin A, H and methyl ester of radulanin E

The biosynthetic pathway to radulanin H and E is proposed to be derived from 2-carboxy-3,5-dihydroxy-4-(3-methyl-2-butenyl) bibenzyl precursor **IV-48**. However, the real transformation pathway is still unknown. Yamaguchi has achieved a biomimetic synthesis by postulating an oxidative intermediate of o-prenylphenol **IV-49a**, which undergoes a Mitsunobu reaction to obtain radulanin H and E (see details before). The new total synthesis realized by tandem cyclopropanation/oxa-Cope rearrangement suggests that an acylvinylcyclopropane **IV-49b** could be also a biogenetic intermediate to generate the dihydrooxepines. Phenols are indeed frequently dearomatized through double ortho alkylation, and in that case, aromatization might be the ideal driving force to afford benzoxepine (Scheme IV-18).



Scheme IV-18 Proposed biosynthetic pathway

Beyond that, some post-transformations of radulanins will be interesting to study with. For example, a C-H functionalization<sup>300</sup> with Pd<sup>II</sup> or hypervalent iodine on the benzylic position of radulanin H might directly convert it into radulanolide (Scheme IV-19). A catalyzed isomerization of radulanin H by specific Lewis acids might afford its isomer radulanin E, although more challengingly.



Scheme IV-19 Possible post-modification to afford more natural products

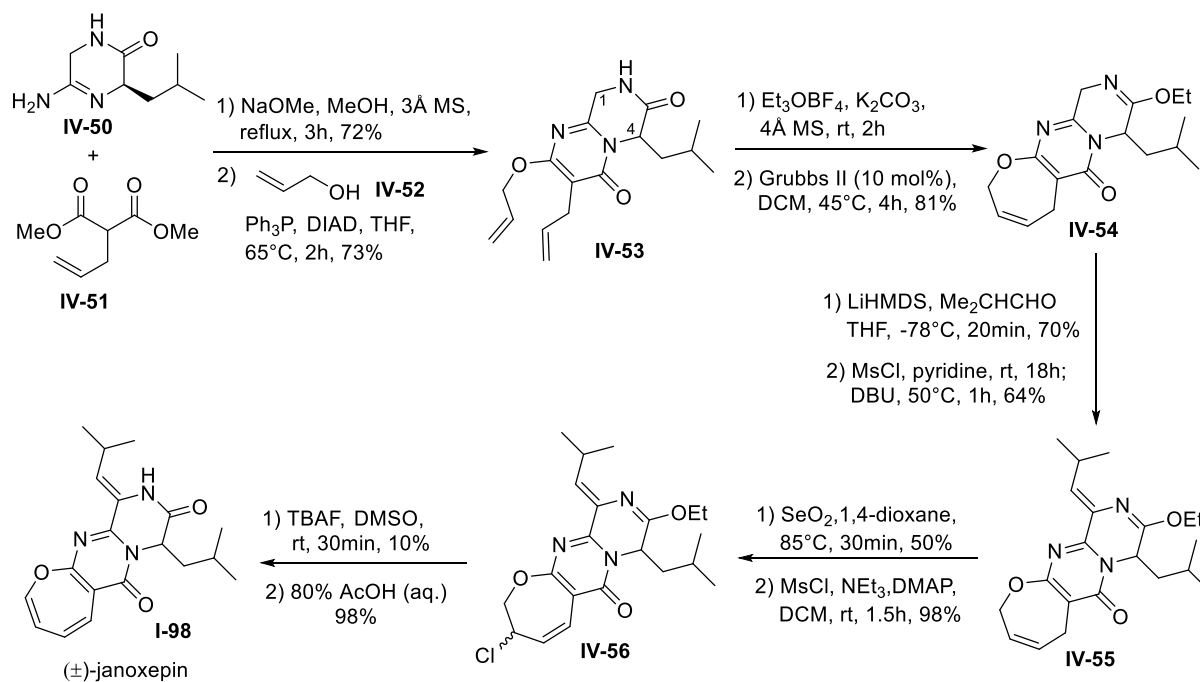
## 2. Total synthesis of janoxepin and cinereain by using the oxa-Cope rearrangement

### 2.1. Taylor's total synthesis of janoxepin

The total synthesis of janoxepine was reported by Taylor and co-workers in 2012.<sup>301</sup> This is also the only total synthesis of an oxepino-DKP natural products. The authors synthesized a protected 2,5-dihydrooxepinopyrimidinone by condensation between amidine **IV-50** and allylmalonate, followed by an *O*-allylation and a ring closing metathesis (RCM) on bis-allyl derivative **IV-53** (Scheme IV-20). The alkylation of C4 was achieved by the deprotonation of imidate **IV-54** with LiHMDS and addition of *iso*-butyraldehyde. A successive mesylation and elimination gave enamine **IV-55** as desired product. Then, the oxepine pattern was obtained by a lengthy sequence of oxidation–chlorination–elimination (Scheme IV-20b), enabling the first total synthesis of (±)-janoxepin in 14 steps and 0.7% yield. As the condensation step requires NaOMe as a base, a racemization was observed during the pyrimidinone preparation step.

<sup>300</sup> a) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315-1345; b) R. N. Zare, S. Banerjee, S. Sathyamoorthi, J. Du Bois, *Chem. Sci.* **2017**, *8*, 7003-7008; c) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885-1898; d) M. S. Sanford, T. W. Lyons. *Chem. Rev.* **2010**, *110*, 1147-1169.

<sup>301</sup> R. G. Doveston, R. Steendam, S. Jones, R.J. K. Taylor, *Org. Lett.* **2012**, *14*, 1122-1125.

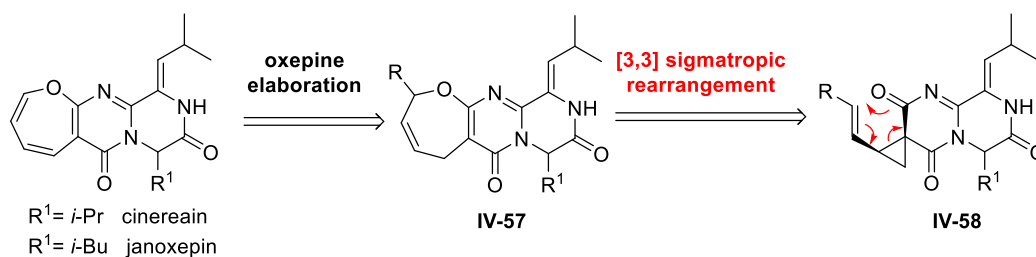


Scheme IV-20 Total synthesis of janoxepin by Taylor and coworkers

## 2.2. Total synthesis of janoxepin and cinereain

### 2.2.1. Revised retrosynthesis of janoxepin and cinereain incorporating the oxa-Cope methodology

Janoxepin and cinereain are two close natural products in the family of oxepino-DKPs. The main synthetic challenge with these structures was to construct the oxepine ring fused to a highly functionalized pyrimidino-DKP pattern. Inspired by the total synthesis of (±)-janoxepin reported by Taylor,<sup>301</sup> the oxepine ring could be generated by the dehydrogenation of a dihydrooxepine, which was also the main structural motif afforded by our methodology of oxa-Cope rearrangement described in chapter III. Therefore, a new retrosynthetic pathway toward janoxepin and cinereain could be envisioned, making use of the oxa-Cope rearrangement as a key step, to set up the dihydrooxepin ring within **IV-61** (Scheme IV-21).



Scheme IV-21 Retrosynthesis of cinereain and janoxepin

In fact, although vinylcyclopropanes derived from *N,N'*-dimethylbarbituric acid did not afford 2,5-dihydrooxepines during our methodological study (amide carbonyl groups being unreactive toward our oxa-Cope rearrangement), the situation would be completely different in the case of substrate **IV-58**. Indeed, among both amide functions present in the pyrimidine-4,6-dione, one is an intracyclic acylimine whose nitrogen lone pair is not available for conjugation to the carbonyl (Figure IV-5). We thus reasoned that this carbonyl group could be electronically available for the oxa-Cope rearrangement, unlike the other one.

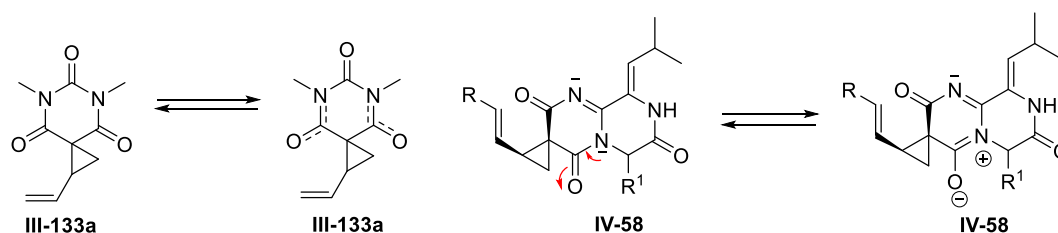
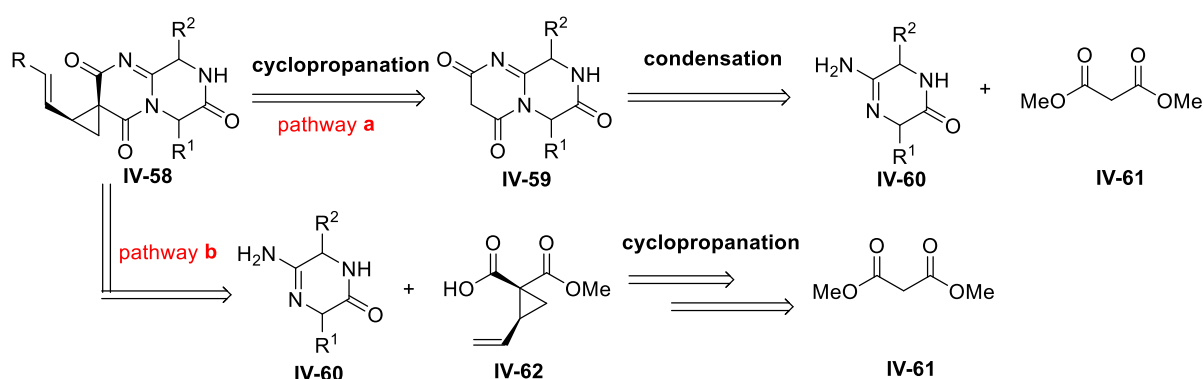


Figure IV-5 Structural comparison between compound **III-133a** and intermediate **IV-58**

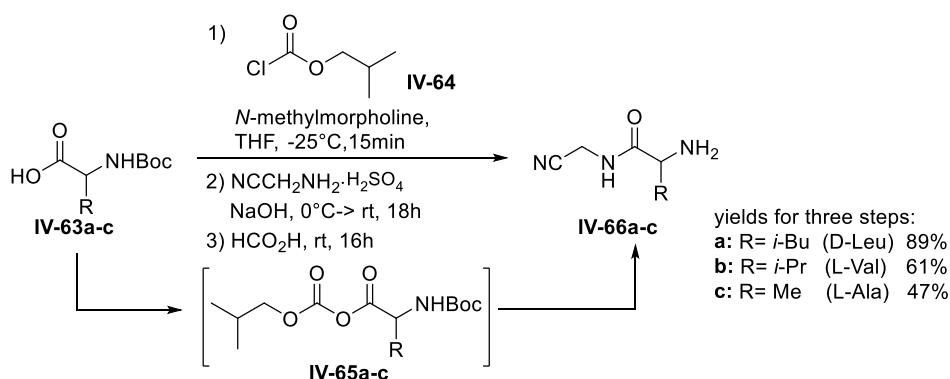
Intermediate **IV-58** could be prepared by two different pathways, depending on when to introduce the vinylcyclopropane motif (Scheme IV-22). Pathway **a** allows the generation of spiro[(2-vinylcyclopropane)-1,5'-(pyrimidine-4',6'-dione)] derivative **IV-58** from pyrimidine-4,6-dione-DKP intermediate **IV-59**, which can be formed by the condensation of amidine **IV-60** and dimethylmalonate **IV-61**. Pathway **b** could afford compound **IV-58** from a peptide coupling reaction between amidine **IV-60** and 1-methoxycarbonyl-2-vinylcyclopropane-1-carboxylic acid **IV-62**, possessing a *syn* configuration between the vinyl and carboxylic acid groups for the oxa-Cope sigmatropic rearrangement. This partner **IV-62** could be prepared by a cyclopropanation on dimethyl malonate.



Scheme IV-22 Two possible retrosyntheses of precursor **IV-58**

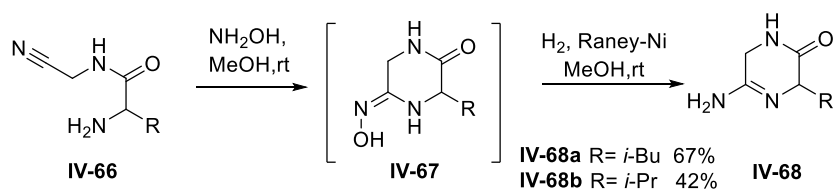
### 2.2.2. Preliminary results to synthesize precursor **IV-58** and subsequent cyclization attempts by direct vinylcyclopropanation (pathway a)

Following Taylor's procedure,<sup>30</sup> the synthesis began with a coupling reaction between corresponding Boc-protected amino acids **IV-63** (D-Leu, L-Val or L-Ala) and aminoacetonitrile bisulfate, through the formation of an intermediate mixed anhydride (Scheme IV-23). The amine functions of compounds **IV-66** were released after deprotection of the Boc group in the presence of formic acid. Due to the high water solubility of products **IV-66**, only D-Leu derivative **IV-66a** was purified with high yield (89%), while L-Ala derivative **IV-66c** was only purified with moderate yield (47%) with a significant loss during the extraction process.



Scheme IV-23 Synthesis of cyano-amide derivatives

According to a known procedure developed by Isobe in 2004,<sup>302</sup> compounds **IV-66a** and **b** were subjected to a one pot oximation–cyclization–hydrogenation transformation, by using hydroxylamine as a cyclization promoter towards oxime **IV-67** and Raney-Ni mediated hydrogenation, to afford cyclic amidines **IV-68a** and **b** (Scheme IV-24). This procedure was applied successfully to L-valine and D-leucine cyano-amide derivatives **IV-66a** and **b**, but due to the high polarity, low solubility and difficult purification of these compounds, the desired cyclic amidine **IV-68a** and **b** were only purified with moderate yield (67% and 42%).

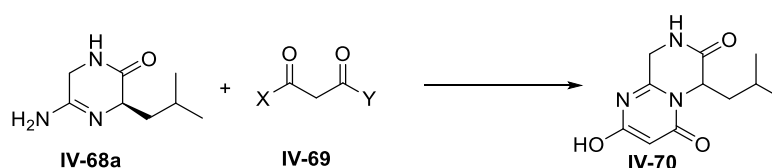


Scheme IV-24 Synthesis of cyclic amidines

<sup>302</sup> M. Kuse, N. Kondo, Y. Ohyabu, M. Isobe, *Tetrahedron* **2004**, *60*, 835-840.

The next step of the synthesis of the pyrimidino-DKP core (**IV-70**) was carried out by using a base-catalyzed condensation of cyclic amidine **IV-68a** with commercially available malonate derivatives **IV-69** (Table IV-7).<sup>294</sup> The only encouraging results were obtained with dimethyl malonate as the condensation partner with **IV-68a** under microwave condition at 130 °C (entry 5-7). The low solubility of compound **IV-68a** may be the main reason to explain the reaction worked only under harsh conditions. Because of the presence of a large amount of MeONa, epimerization was observed as reported in the synthesis of (±)-janoxepin.<sup>301</sup>

Table IV-7 Pyrimidinone formation conditions



Entry	IV-69	Conditions	Results (yields)
1	X=Cl, Y= Cl	DCM/DMF, Et <sub>3</sub> N (2 equiv.), 0°→rt, 2h <sup>303</sup>	NR
2	X=Cl, Y= OMe	DCM/DMF/pyridine, rt, 16h	NR
3	X=OH, Y=OH	Ac <sub>2</sub> O, microwave, 100°C, 20 min	NR
4	X=OMe, Y= OMe	MeONa, MeOH, 3Å MS, reflux, 2h <sup>304</sup>	NR
5	X=OMe, Y= OMe	MeONa (3 equiv.), MeOH, 130°C, μwave, 2h	43%
6	X=OMe, Y= OMe	MeONa (6 equiv.), MeOH, 130°C, μwave, 30 min	67%
7	X=OMe, Y= OMe	MeONa (6 equiv.), MeOH, 140°C, μwave, 30 min	53%

After having obtained successfully compound **IV-70**, the study of the key step of tandem cyclopropanation–oxa-Cope rearrangement could be investigated (Table IV-8). Our previously developed methodology was applied by reacting **IV-70** with *trans*-1,4-dibromo-2-butene under basic conditions (Cs<sub>2</sub>CO<sub>3</sub>) in DMSO at room temperature. Disappointingly, under these conditions (entry 1), only the formation of **IV-71** in 9% yield was observed, but no desired vinylcyclopropane or oxepine product. Alternatively, we envisaged the Tsuji-Trost condition<sup>305</sup> (entries 2-3) to afford the *C*-allylation of our 1,3-dicarbonyl substrate, yet without success. Finally, a diazo-mediated cyclopropanation under rhodium-catalyzed condition were

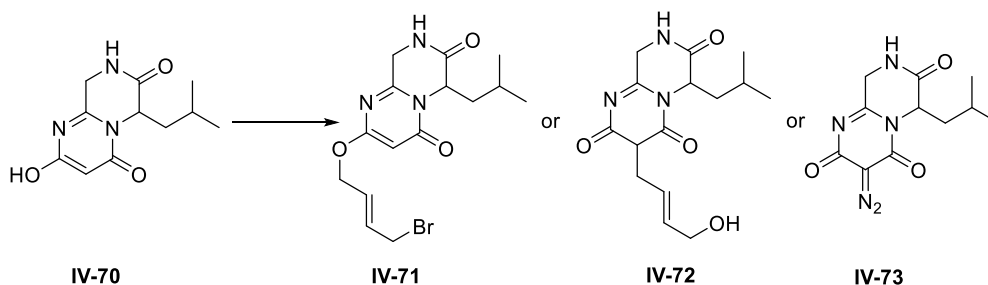
<sup>303</sup> M. Abass, A. S. Mayas, *Heteroatom Chemistry* **2007**, *18*, 19-27.

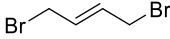
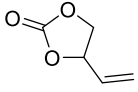
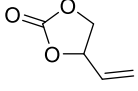
<sup>304</sup> W. Stadlbauer, E. Badawey, G. Hojas, P. Roschger, T. Kappe, *Molecules* **2001**, *6*, 338-352.

<sup>305</sup> S. K. Kang, S. G. Kim, J. S. Lee, *Tetrahedron: Asymmetry* **1992**, *3*, 1139-1140.

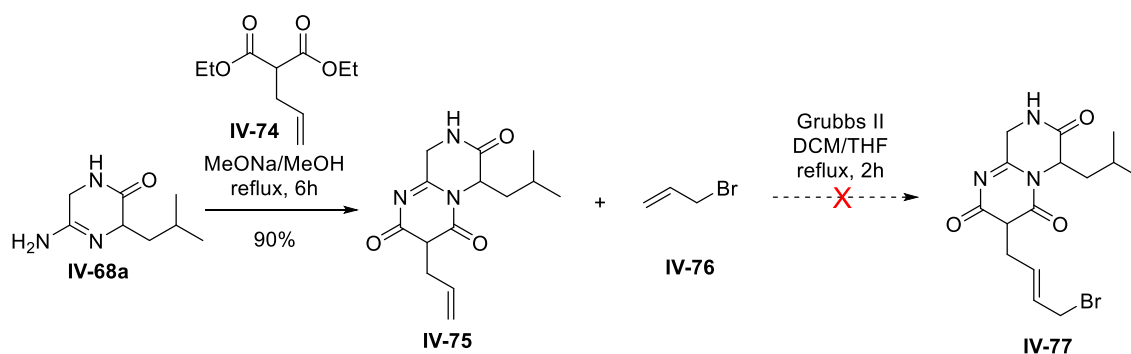
also envisaged but we could not succeed in synthesizing the appropriate diazo intermediate **IV-73** (entry 4).

Table IV-8 Oxepine formation studies



Entry	Conditions	Results (yields)
1	 , Cs <sub>2</sub> CO <sub>3</sub> , DMSO, rt, 16h	<b>IV-71</b> (9%)
2	 , Pd(PPh <sub>3</sub> ) <sub>4</sub> (5mol%), K <sub>2</sub> CO <sub>3</sub> , DMSO, rt, 16h	complex mixture (no <b>IV-72</b> )
3	 , Pd(PPh <sub>3</sub> ) <sub>4</sub> (5mol%), THF/DMSO, rt, 16h	complex mixture (no <b>IV-72</b> )
4	MsN <sub>3</sub> , Et <sub>3</sub> NMeCN, 0° → rt, 1h <sup>306</sup>	complex mixture (no <b>IV-73</b> )

A cross metathesis was finally tested between allylated compound **IV-75** (prepared by the condensation of amidine **IV-68a** with diethyl allylmalonate **IV-74**) and vinyl bromide **IV-76** (Scheme IV-25).<sup>307</sup> Because of the low solubility of compound **IV-75** in DCM or THF, no reaction occurred in the tested conditions. This pathway was thus abandoned.



Scheme IV-25 Cross metathesis to prepare the precursor of cyclopropanation

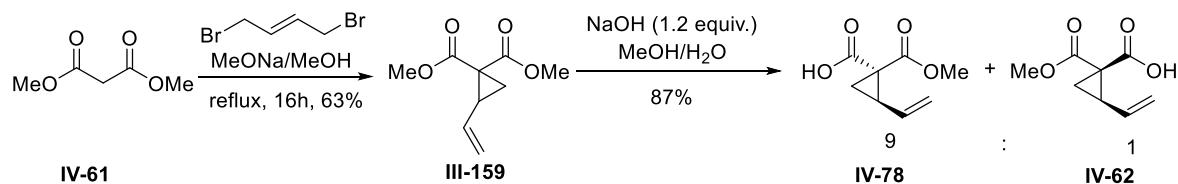
<sup>306</sup> D. F. Taber, R. E. Ruckle, M. J. Hennessy, *J. Org. Chem.* **1986**, *51*, 4077-4078.

<sup>307</sup> D. Amans, V. Bellosta, J. Cossy, *Angew. Chem.* **2006**, *118*, 6002-6006.



### 2.2.3. Preliminary attempts of synthesis of dihydrooxepines IV-81 (pathway b)

Compared to pathway **a**, pathway **b** was designed as a convergent synthesis. The vinylcyclopropyl partner was prepared separately by reacting dimethylmalonate **IV-61** with *trans*-1,4-dibromo-2-butene (Scheme IV-26). Then product **III-159** was monohydrolyzed by using 1.2 equiv. NaOH,<sup>308</sup> which furnished two isomers **IV-78** and **IV-62** with a ratio 9/1 according to <sup>1</sup>H-NMR. As mentioned in the methodological studies, the oxa-Cope rearrangement could only occur when the ketone and vinyl groups are in *cis* position, therefore the pathway envisaged here is not appropriated to prepare the precursor of oxa-Cope rearrangement. However, it would be useful to test the amide coupling/annulation towards the pyrimidine-4,6-dione-DKP core.



Scheme IV-26 Cyclopropanation and monohydrolysis

Thus, before attempting another synthetic method for **IV-62**, the mixture of monoacids **IV-78** and **IV-62** was used to investigate the coupling conditions with cyclic amidine **IV-68b**. Four different conditions were employed (Table IV-9) and to our surprise, when the monoacid was activated as a mixed anhydride by isobutylchloroformate and the amidine by NaH, the reaction led to two interesting products **IV-79** and **IV-81** in 14% and 7% yields, respectively (entry 4).

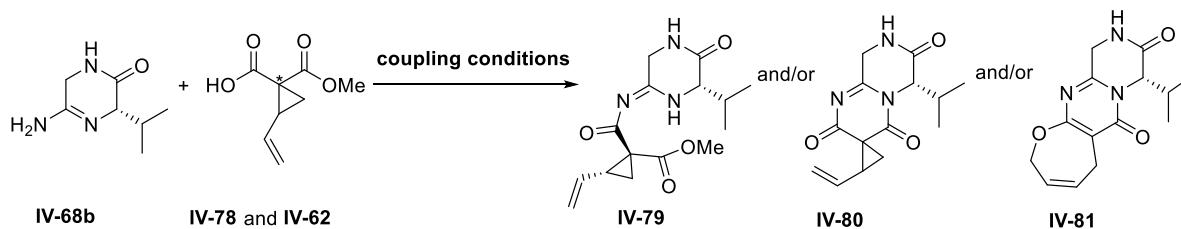
The structure of compound **IV-81** was assigned based upon spectral similarities with the closely related product **IV-82**, reported by Doveston.<sup>294</sup> It showed that these two structures have close chemical shifts and also coupling constants. H-16 was deshielded for our compound **IV-81**, which is coherent with its *i*-Pr substitution.

In particular, the formation of **IV-81** was probably the result of the 10% contamination of *trans*-monoacid **IV-78** by *cis*-isomer **IV-62**. Most importantly, this encouraging result indicated that the formation of the dihydrooxepin ring in **IV-81** is possible if the right monoacid isomer is utilized in the coupling reaction. The reason of the low isolated yield of

<sup>308</sup> N. Takahashi, A. Sudo, T. Endo, *Macromolecules* **2017**, *50*, 5679–5686.

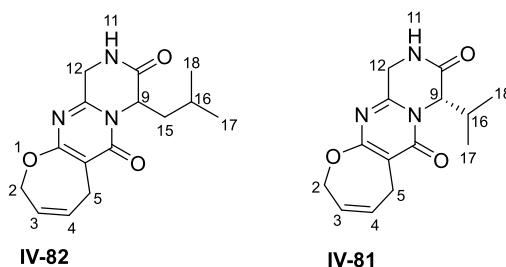
**IV-79** is not clear at this stage of the work, since the reaction has only been attempted once.

Table IV-9 Screening of coupling reaction conditions



Entry	Conditions	Results
1	DMAP, EDCI, DCM, rt	complex mixture
2	<b>IV-78</b> , oxalyl chloride, pyridine, rt, then <b>IV-68b</b>	complex mixture
3	HBTU, DIPEA, DCM/DMF	complex mixture
4	<b>IV-78</b> , isobutylchloroformate, THF, -25°C to 0°C, 30min; then <b>IV-68b</b> , NaH, DMSO/THF, 0°C, 30min, stirring for 2h	<b>IV-79</b> (14%) <b>IV-81</b> (7%)

Table IV- 10 NMR spectral comparison (400Hz, CDCl<sub>3</sub>) between reported **IV-82** and our compound **IV-81**

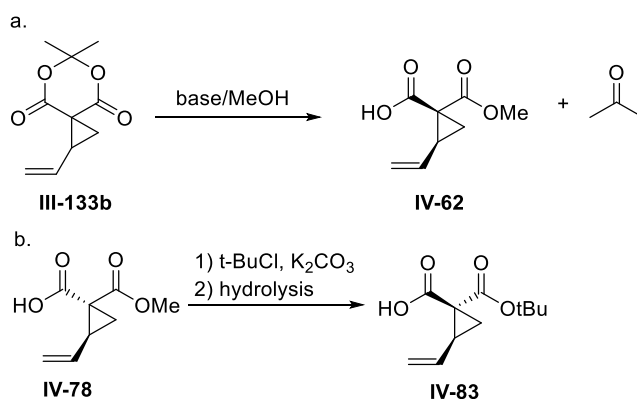


<sup>1</sup> H number	<b>IV-82</b> (δ ppm)	<b>IV-81</b> (δ ppm)
17/18	0.98 (d, J = 6.5 Hz)	1.06 (d, J = 6.8 Hz)
17/18	1.09 (d, J = 6.5 Hz)	1.13 (d, J = 6.9 Hz)
15b	1.61 (ddd)	—
15a	1.72 (ddd)	—
16	1.85-1.79 (m)	2.32-2.23 (m)
5	3.49 (d, J = 6.0 Hz)	3.51 (d, J = 5.7 Hz)
12b	4.30 (dd, J = 17.0, 5.0 Hz)	4.29 (dd, J = 17.5, 4.9 Hz)
12a	4.53 (d, J = 17.0 Hz)	4.56 (d, J = 17.6 Hz)
2b	4.77 (dd, J = 13.5, 6.5 Hz)	4.77 (dd, J = 13.4, 6.4 Hz)
2a	4.84 (dd, J = 13.5, 6.5 Hz)	4.87 (dd, J = 13.5, 6.5 Hz)
9	5.29 (ddd, J = 9.0, 6.0, 1.0 Hz)	5.09 (d, J = 6.6 Hz)
3	6.08-6.02 (m)	6.11 – 6.03 (m)
4	6.25 (dt, J = 10.0, 6.0 Hz)	6.27 (dt, J = 9.9, 6.0 Hz)
11	6.79 (d, J = 5.0 Hz)	3.97 (bs, 1H)

### 2.3. Conclusions and perspectives

These preliminary results on the total synthesis of cinereain and janoxepin are encouraging as the oxa-Cope rearrangement was successfully applied to the synthesis of a dihydrooxepin-DKP. Compared with the total synthesis of janoxepin achieved by Taylor, this fully convergent pathway was performed under mild condition, and may result in enantiopure natural products as final products. In addition, the method for the synthesis cyclic amidines and pyrimidine-4,6-diones could be applied to L-Ala and D-Leu derivatives, which provide the possibility to synthesize a full range of natural oxepino-DKPs.

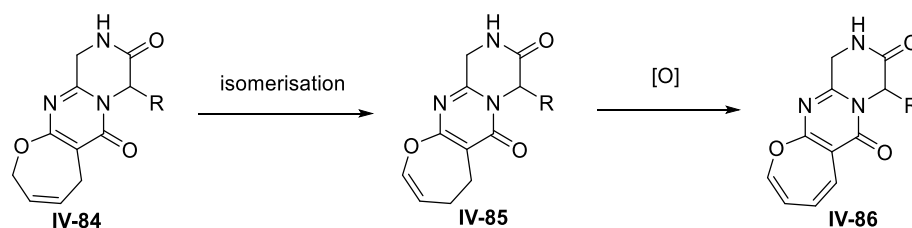
In order to conform this preliminary result, the *cis* isomer needs to be selectively synthesized. To this end, two synthetic pathways are currently being explored. First, the methanolysis of the vinylcyclopropyl derivative of Meldrum's acid (**III-133b**) may directly give the *cis* isomer of monoacid **IV-62** upon reaction of the less hindered (*trans*) ester group with methanolate anions (Scheme IV-27a). Alternatively, the protection of the wrong isomer with a hindered group (*e.g.* *t*-Bu) may favor the hydrolysis of the *cis* methyl ester and afford the expected monoacid **IV-83** (Scheme IV-27b).



Scheme IV-27 Possible strategies to synthesize *cis*-monoacids **IV-62**

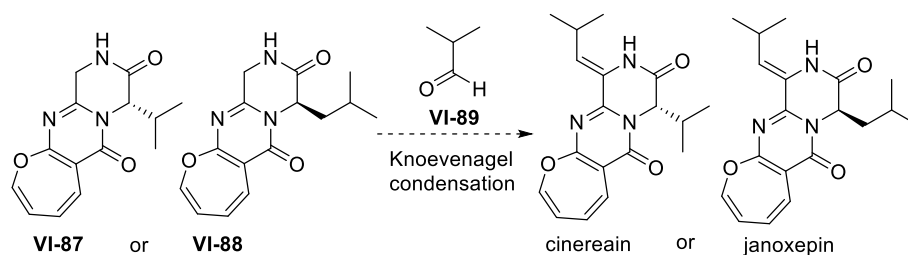
Once dihydrooxepine **IV-84** will have been successfully prepared, two more steps will be needed to complete the total synthesis of janoxepin (R = *i*-Bu) and cinereain (R = *i*-Pr). The oxepine-elaboration by using an oxidation–chlorination–elimination sequence afforded only 5% yield during Taylor's work. Therefore, a new efficient synthetic method should be investigated. Trost reported an alkene isomerization method by using [Ir(*coe*)<sub>2</sub>Cl]<sub>2</sub> to prepare

the allyl vinyl ethers<sup>309</sup> while Daugulis recently used a sterically hindered diamine-palladium adduct to catalyze the olefin isomerization.<sup>310</sup> These ideas inspired us to design another strategy for oxepine elaboration through dihydrooxepine isomerization and then dehydrogenative oxidation (by DDQ<sup>311</sup> or IBX) (Scheme IV-28).



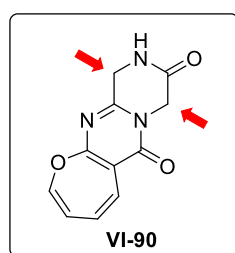
Scheme IV-28 Proposed oxepine elaboration pathway

After the oxepino-DKP will have been installed, a Knoevenagel condensation with isobutyraldehyde at the  $\alpha$  position of the amidine function could be considered to complete the total synthesis of janoxepin and cinereain (Scheme IV-29).



Scheme IV-29 Knoevenagel condensation to finish the total synthesis

Finally, it could also be envisaged to apply C-H functionalization to an unsubstituted oxepino-DKP like VI-90. By this strategy, several natural products and various derivatives could be synthesized at the same time in a collective manner.



<sup>309</sup> a) B. M. Trost, T Zhang, *Org. Lett.* **2006**, *8*, 6007-6010; b) M. G. McLaughlin, M. J. Cook, *J. Org. Chem.* **2012**, *77*, 2058-2063.

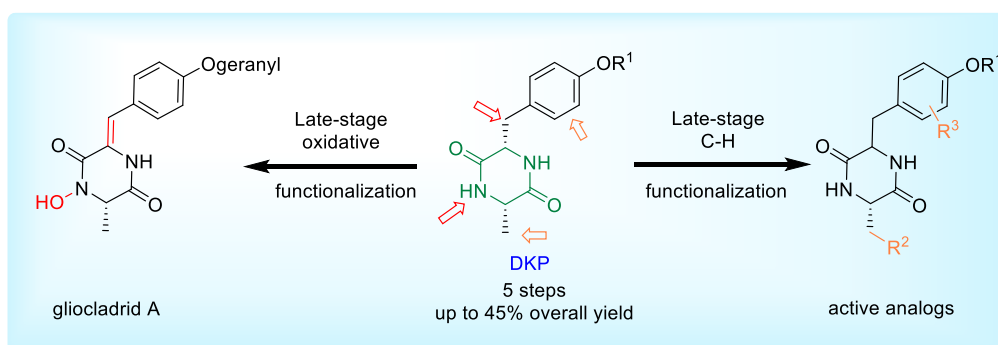
<sup>310</sup> A. L. Kocen, K. Klimovica, M. Brookhart, O. Daugulis, *Organometallics* **2017**, *36*, 787-790.

<sup>311</sup> M. Shimizu, T. Fujimoto, X. Liu, T. Hiyama, *Chemistry Letters* **2004**, *33*, 438-439.

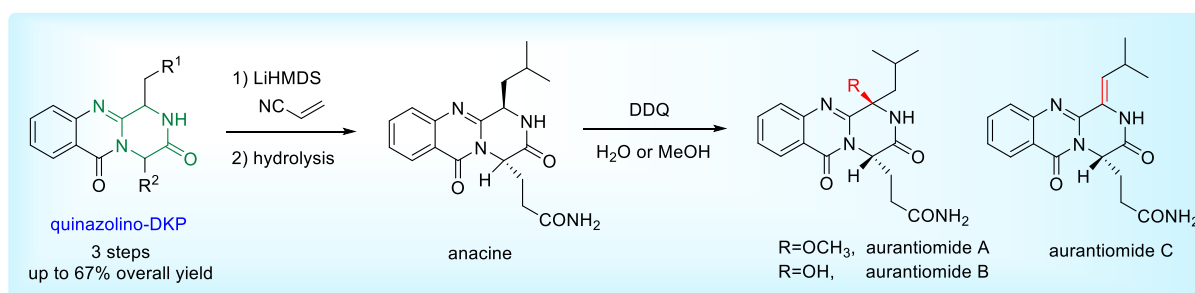
## CHAPTER V. GENERAL CONCLUSION

Biosynthesis has inspired the design of collective synthetic strategies while in parallel, breakthroughs in selective C-H functionalization have opened new doors to implement biomimetic synthesis in practice. To imitate the powerful synthetic logic of nature, from common biomimetic intermediates to natural products, we designed three key intermediates: DKP, quinazolino-DKP and oxepino-DKP. By taking advantages of well-studied peptide synthesis, the two former scaffolds were successfully achieved in high overall yield.

The direct oxidative functionalization of geranyl-DKP or DKP alone is still difficult, and will require more innovative methods to be investigated toward the total synthesis of gliocladrin A. As geranyl-DKP natural products have shown good anticancer activities, other C-H functionalizations on side chains of DKP core might afford some interesting active analogs.

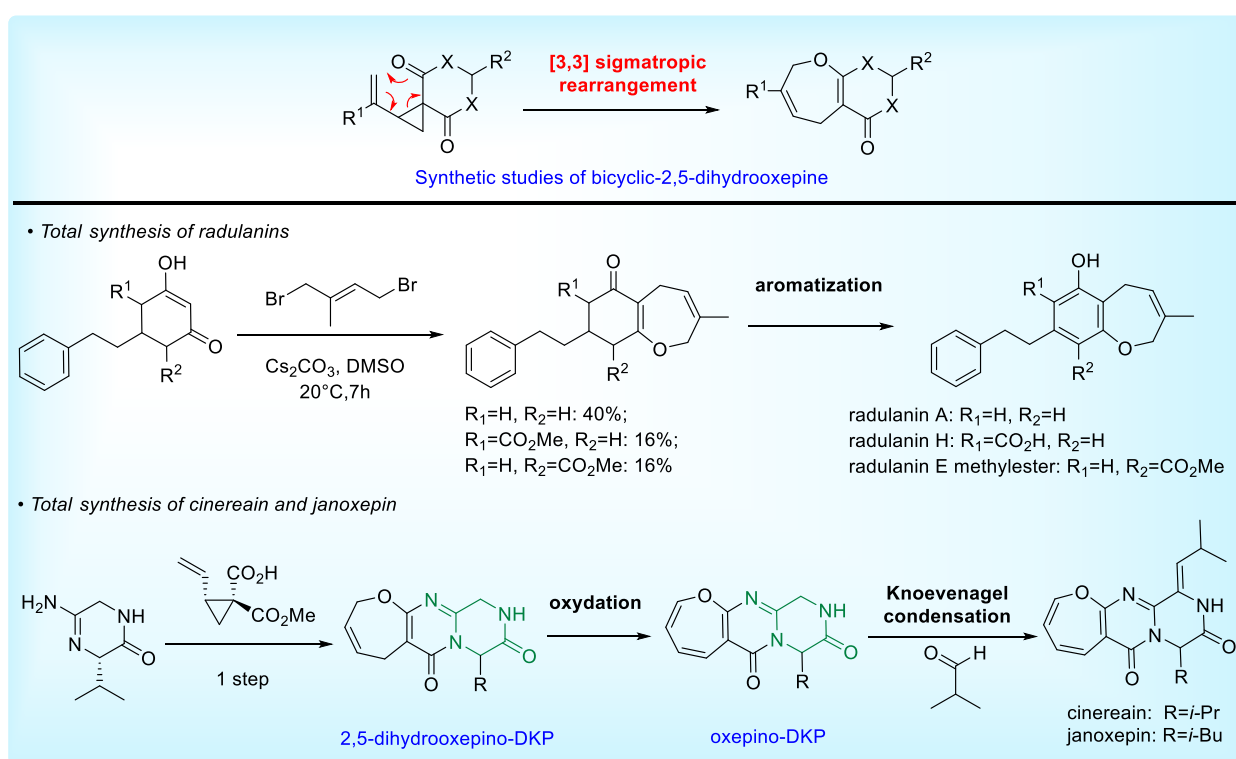


Regarding the quinazolino-DKP core, a regioselective late-stage oxidation operated by DDQ was discovered and brought new synthetic possibilities to make some natural products in collective manner. For example, the total synthesis of aurantiomides A, B and C could be accomplished with two further steps, Micheal addition and DDQ-mediated oxidation, from leucine substituted quinazolino-DKP ( $R^1=i\text{-Pr}$ ,  $R^2 = \text{H}$ ).



The synthetic work on oxepino-DKP has been a challenging process. The classical chemical oxidations and microbial oxidations on quinazolino-DKP did not afford the desired

compound. However, these failures motivated us to develop a temperature-controlled tandem cyclopropanation/oxa-Cope reaction toward the synthesis of 2,5-dihydrooxepines. Besides, the generality, scope and practicality of this synthetic methodology have been elucidated by experimental and computational studies. In consequence, this method has been successfully applied to the intractable total synthesis of radulanins A, H, E and, as well, to the installation of dihydrooxepino-DKP, one oxidative step away from oxepino-DKP. With this achieved 2,5-dihydrooxepino-DKP intermediate, the total synthesis of cinereain and janoxepin could be rapidly accomplished in two stages: oxepine elaboration and Knoevenagel condensation. Moreover, C-H functionalizations on oxepino-DKP might give more possibilities toward more oxepin-based natural products, such as varioxepin A.



Natural products synthesis is a highly developed artform, yet somewhat difficult and esoteric. The use of bio-inspired synthetic strategies to extend molecular complexity and diversity is attractive, but still limited in practice by available synthetic methodologies. During this Ph.D. research, we tried to take advantages of several interdisciplinary approaches. The obtained synergetic results of organic synthesis, biotransformations and DFT studies helped us to deeply understand structure-property-reactivity relationships, contributing to the design of new reactions and new synthetic strategies. Although the collective total synthesis work is not fully completed, the encouraging outcome makes us moving forward to the destination.

## **EXPERIMENTAL SECTION**





## Summary of Experimental Section

<b>1. Chemical experimental procedures and spectroscopic data</b> .....	165
1.1. General information.....	165
1.2. Chapter II: Installations and functionalizations of biomimetic intermediates.....	166
1.3. Chapter III: Tandem Cyclopropanation/Oxa-Cope Rearrangement Studies .....	198
1.4. Chapter IV: Total synthesis of oxepin-based natural products .....	246
1.4.1. Total synthesis of radulanins .....	246
1.4.2. Total synthesis of janoxepin and cinereain.....	267
<b>2. Microbial oxidations</b> .....	278
2.1. Microorganism and culture conditions .....	278
2.2. Biotransformations .....	279
2.3. Analytical studies .....	279
<b>3. Computational methods and results</b> .....	281
3.1. Technical details .....	281
3.2. Computational details on optimized geometries and energies .....	282
<b>4. X-Ray Crystallographic Data</b> .....	285
4.1. Crystallographic information for compound <b>III-137</b> .....	285
4.2. Crystallographic information for compound <b>IV-28</b> .....	286

# 1. Chemical experimental procedures and spectroscopic data

## 1.1. General information

All reactions were performed in flame-dried refluxed reactors fitted with rubber septa under a positive pressure of argon. Solvents (methylene chloride, ether and tetrahydrofuran) were purified using a Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Analytical thin-layer chromatography (TLC) was carried out using alumina plates precoated silica gel plates (silica gel 60, F254, Merck), which were visualized by exposure to ultraviolet light and/or exposure to a basic solution of potassium permanganate or *p*-anisaldehyde stain followed by heating. Flash chromatography was carried out on Kieselgel 60 (40-63  $\mu\text{m}$ ). Infrared spectra were recorded on a PerkinElmer FTIR using neat thin film technique. Absorption maxima ( $\nu_{\text{max}}$ ) are reported in wavenumbers ( $\text{cm}^{-1}$ ). High-resolution mass spectra (HRMS) were obtained on JEOL JMS-GCmate II spectrometer and reported as  $m/z$  (relative intensity). Accurate masses are reported for the molecular ion  $[\text{M}+\text{Na}]^+$ ,  $[\text{M}+\text{H}]^+$ ,  $[\text{M}-\text{H}]^-$ , or  $[\text{M}]$ . The quoted masses are accurate to  $\pm 5$  ppm. Nuclear magnetic resonance spectra ( $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR) were recorded at ambient temperature with a Bruker DPX (400 MHz,  $^1\text{H}$  at 400 MHz,  $^{13}\text{C}$  at 100 MHz) instrument. For  $\text{CDCl}_3$ , DMSO,  $\text{CD}_3\text{COCD}_3$ , and  $\text{CD}_3\text{OD}$  solutions, chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvent ( $\text{CDCl}_3$ :  $\delta_{\text{H}}= 7.27$  and  $\delta_{\text{C}}= 77.1$ ; DMSO:  $\delta_{\text{H}} = 2.50$  and  $\delta_{\text{C}} = 39.5$ ;  $\text{CD}_3\text{COCD}_3$ ,  $\delta_{\text{H}} = 2.05$  and  $\delta_{\text{C}} = 29.8$ ;  $\text{CD}_3\text{OD}$ :  $\delta_{\text{H}} = 3.31$  and  $\delta_{\text{C}} = 49.0$ ). Coupling constants are reported in Hertz (Hz). Data for  $^1\text{H}$ -NMR spectra are reported as follows: chemical shift ppm, referenced to protium (br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, integration, and coupling constants (Hz)). HPLC purifications were performed on an Agilent 1200 series HPLC with a Supelco Analytical Discovery® C18 (25 cm X 10 mm, 5 $\mu\text{m}$ ) RP-HPLC column unless otherwise noted. Microwave assisted reaction was performed using an Anton Paar® Monowave 300 microwave reactor.

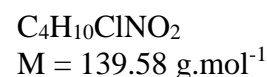
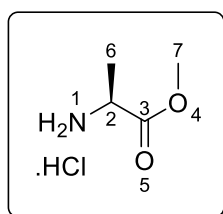
The atom numbers involved in the following molecules are arbitrarily defined to well explain NMR data.

## 1.2. Chapter II: Installations and functionalizations of biomimetic intermediates

### *Procedure A: General procedure to prepare amino acid methylesters:*

To a mixture of amino acid (1 equiv.) in anhydrous MeOH (0.5 M) was added dropwise SOCl<sub>2</sub> (1.5 equiv.) at -20°C under an Ar atmosphere. After 30 min stirring, the reaction mixture was brought to room temperature for 3 more hours, and then refluxed for 30 min. The organic solvent was concentrated under reduced pressure, and then the crude solid was washed with Et<sub>2</sub>O to give the title product as a white solid (100%).

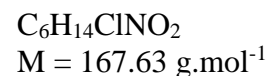
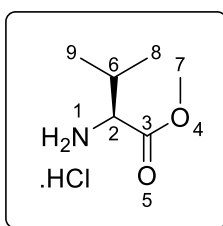
#### methyl L-alaninate hydrochloride (II-25)



<sup>1</sup>H NMR  $\delta = 8.77$  (s, 2H; H-1), 4.32 (s, 1H; H-2), 3.84 (s, 3H; H-7), 1.77 ppm (400 MHz, CDCl<sub>3</sub>) (s, 3H; H-6).

All data were consistent with those reported in the literature.<sup>1</sup>

#### methyl L-valinate hydrochloride (II-52)

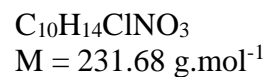
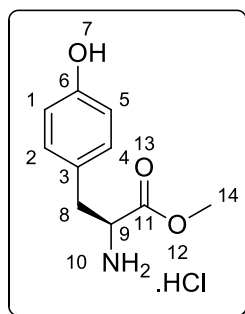


<sup>1</sup>H NMR  $\delta = \delta 3.93$  (d, J = 4.6 Hz, 1H; H-2), 3.85 (s, 3H; H-7), 2.39 – 2.19 (m, (400 MHz, MeOD) 1H; H-6), 1.07 (d, J = 2.8 Hz, 3H; H-8/9), 1.06 ppm (d, J = 2.8 Hz, 3H; H-8/9).

All data were consistent with those reported in the literature.<sup>2</sup>

<sup>1</sup> T. Rehm, V. Stepanenko, X. Zhang, F. Würthner, F. Gröhn, K. Klein, C. Schmuck, *Org. Lett.* **2008**, *10*, 1469-1472.

## methyl L-tyrosinate hydrochloride

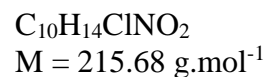
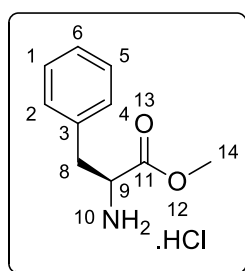


**$^1\text{H}$  NMR**  $\delta = 7.08$  (d,  $J = 6.1$  Hz, 2H; H-2, H-4),  $6.79$  (d,  $J = 6.0$  Hz, 2H; H-1, H-5),  $4.25$  (s, 1H; H-9),  $3.81$  (s, 3H; H-14),  $3.22$ - $3.04$  ppm (m, 2H; H-8).

**$^{13}\text{C}$  NMR**  $\delta = 170.4, 158.2, 132.3, 130.7, 125.5, 117.6, 116.0, 56.2, 54.5, 53.0$  (101 MHz, MeOD) ppm.

All data were consistent with those reported in the literature.<sup>3</sup>

## methyl L-phenylalaninate hydrochloride (II-49)



**$^1\text{H}$  NMR**  $\delta = 7.34$ - $7.16$  (m, 5H,  $H_{\text{ar}}$ ),  $3.75$  (dd,  $J = 5.2, 7.9$  Hz, 1H, H-9),  $3.72$  (s, 3H,  $\text{CH}_3$ ),  $3.09$  (dd,  $J = 13.5, 5.2$  Hz, 1H, H-8a),  $2.86$  (dd,  $J = 13.5, 7.9$  Hz, 1H, H-8b),  $1.44$  ppm (s, 2H,  $\text{NH}_2$ ).

**$^{13}\text{C}$  NMR**  $\delta = 175.4, 137.2, 129.2, 128.5, 126.8, 55.8, 51.9, 41.1$  ppm. (101 MHz,  $\text{CDCl}_3$ )

All data were consistent with those reported in the literature.<sup>4</sup>

Procedure B: preparation of Fmoc-amino acid chlorides

To a suspension of Fmoc-amino acid in dry dichloromethane (0.5 M) was added neat thionyl chloride (1.5 equiv.), and the resulting mixture was heated to reflux for 1.5 h. The homogeneous solution was cooled to room temperature and concentrated *in vacuo*. The

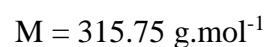
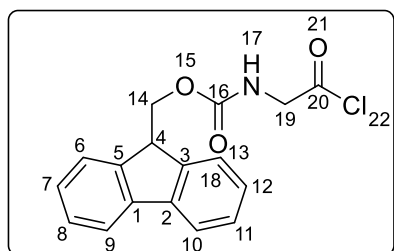
<sup>2</sup> K. Manna, S. Xu, A. D. Sadow, *Angew. Chem. Int. Ed.* **2011**, *50*, 1865–1868.

<sup>3</sup> A. Proteau-Gagné, V. Bournival, K. Rochon, Y. L. Dory, L. Gendron, *ACS Chem. Neurosci.* **2010**, *1*, 757–769.

<sup>4</sup> X. Fan, Y. Z. Li, X. Y. Zhang, G. R. Qu, *Heteroat. Chem.* **2006**, *17*, 382–388.

residue was redissolved in dichloromethane and concentrated *in vacuo* again. The solid was dissolved in a minimum amount of dichloromethane. Petroleum ether was added until no further precipitation occurred. The precipitate was filtered, washed with petroleum ether and dried *in vacuo*.

**(9H-fluoren-9-yl)methyl (2-chloro-2-oxoethyl)carbamate**

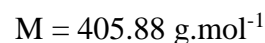
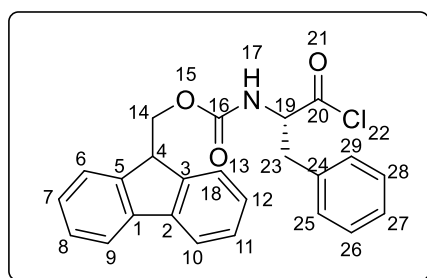


**$^1\text{H NMR}$**   $\delta = 7.77$  (d,  $J = 7.5$  Hz, 2H;  $H_{Ar}$ ),  $7.58$  (d,  $J = 7.4$  Hz, 2H;  $H_{Ar}$ ),  $7.41$  (t,  $J = 7.4$  Hz, 2H;  $H_{Ar}$ ),  $7.32$  (t,  $J = 7.3$  Hz, 2H;  $H_{Ar}$ ),  $5.34$  (br s, 1H; H-17),  $4.47$  (d,  $J = 6.8$  Hz, 2H; H-19),  $4.37$  (d,  $J = 6.1$  Hz, 2H; H-14),  $4.24$  ppm (t,  $J = 6.7$  Hz, 1H; H-4).

**$^{13}\text{C NMR}$**   $\delta = 172.3, 156.1, 143.7, 141.4, 127.9, 127.3, 125.1, 120.2, 67.6, 52.4,$  (101 MHz,  $\text{CDCl}_3$ )  $47.1$  ppm.

Analytical data are consistent with those reported in literature.<sup>5</sup>

**(9H-fluoren-9-yl)methyl (1-chloro-1-oxo-3-phenylpropan-2-yl)carbamate (II-53)**



<sup>5</sup> G. Zagotto, A. Ricci, E. Vasquez, A. Sandoli, S. Benedetti, M. Palumbo, C. Sissi, *Bioconjugate Chem.* **2011**, *22*, 2126–2135.

---

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.77 (d, J = 7.5 Hz, 2H ; H<sub>Ar</sub>), 7.60 – 7.47 (m, 2H; H<sub>Ar</sub>), 7.45 – 7.28 (m, 7H; H<sub>Ar</sub>, H-17), 7.18 (d, J = 6.8 Hz, 1H ; H<sub>Ar</sub>), 5.12 (d, J = 7.4 Hz, 1H ; H-23a), 4.88 (d, J = 8.0 Hz, 1H ; H-23b), 4.42 (d, J = 6.9 Hz, 2H ; H-14), 4.20 (t, J = 6.7 Hz, 1H ; H-19), 3.24 (m, 1H ; H-4).

Analytical data are consistent with those reported in literature.<sup>6</sup>

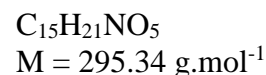
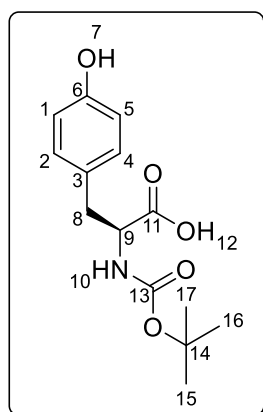
---

<sup>6</sup> J. Cianci, J. B.Baell, A. J. Harvey, *Tetrahedron Letters* **2007**, 48, 5973-5975.

**methyl (tert-butoxycarbonyl)-L-tyrosinate (II-22)**

To a suspension of L-tyrosine (6 g, 1 equiv.) in 1:1 water/dioxane (50 mL, 0.4 M) at 0 °C were added Et<sub>3</sub>N (4.5 mL, 1 equiv.) and di-tert-butyl dicarbonate (8 g, 1.1 equiv.) and the mixture was stirred for 4h at ambient temperature. The dioxane was removed in vacuo, the remaining aqueous phase was washed with a small amount of Et<sub>2</sub>O. The aqueous layer was acidified to pH= 2-4 using 5% aqueous potassium bisulfate and the mixture was extracted with ethyl acetate. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to give clear oil which was coevaporated with dichloromethane to give the title compound as colorless ropy foam (8.3 g, 89% yield) which was used without further purifications.

**R<sub>f</sub>** = 0.23 (5% MeOH in DCM)



**<sup>1</sup>H NMR**  $\delta$  = 8.20 (br s, 1H; H-7), 6.98 (d, J = 7.9 Hz, 2H; H-2 and H-4), 6.72 (d, (400 MHz, CDCl<sub>3</sub>) J = 7.9 Hz, 2H; H-1 and H-5), 5.10-5.02 (m, 1H; H-10), 4.61-4.52 (m, 1H; H-9), 3.09-2.98 (m, 2H; H-8), 1.42 ppm (s, 9H; H<sub>Boc</sub>);

**<sup>13</sup>C NMR**  $\delta$  = 176.1, 155.0, 130.7, 127.6, 115.8, 54.6, 37.2, 28.5, 14.3 ppm (101 MHz, CDCl<sub>3</sub>)

Analytical data are consistent with those reported in literature.<sup>7</sup>

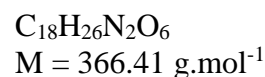
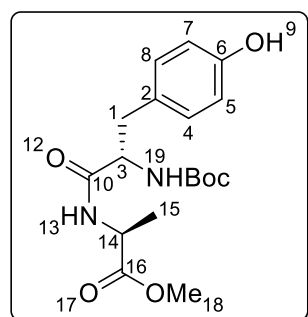
**methyl (tert-butoxycarbonyl)-L-tyrosyl-L-alaninate (II-20)**

To a stirred solution of Boc-protected L-tyrosine (8.3 g, 1.0 equiv.) and L-alanine methyl ester hydrochloride (4.0 g, 1.0 equiv.) in DMF (0.3 M) were added sequentially HBTU (12

<sup>7</sup> P. Jana; S. Maity; D. Haldar, *Cryst. Eng. Comm.* **2011**, *13*, 973–978.

g, 1.1 equiv.), HOBt (4.4 g, 1.0 equiv.), and Et<sub>3</sub>N (8.9 mL, 2.2 equiv.) at rt. After 3h stirring, the reaction was quenched with 5% KHSO<sub>4</sub> to pH 4 and diluted in DCM. The mixture was at first washed with H<sub>2</sub>O three times, then extracted with DCM. The combined organic layers were washed with sat. NaHCO<sub>3</sub> and finally brine, and then dried over Na<sub>2</sub>SO<sub>4</sub>. The concentrated crude product which was purified by flash column (gradient of cyclohexane /ethyl acetate = 1:1 to 6:4) to afford desired product (10.4 g, 97% yield) as an amorphous solid.

Rf = 0.3 (cyclohexane/EtOAc = 1:3)



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.04 (d, J = 8.4 Hz, 2H; H-2 and H-4), 6.74 (d, J = 8.4 Hz, 2H; H-5 and H-7), 6.42 (d, J = 7.2 Hz, 1H; H-13), 6.13 (br s, 1H, H-9), 5.04 (br s, 1H, H-19), 4.63-4.41 (m, 1H; H-14), 4.30-4.26 (m, 1H; H-3), 3.72 (s, 3H; H-18), 3.14-2.89 (m, 2H; H-1), 1.42 (s, 9H; H<sub>Boc</sub>), 1.35 ppm (d, J = 7.2 Hz, 3H; H-15)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 173.1, 171.2, 155.7, 155.3, 130.7, 128.2, 115.8, 80.6, 56.0, 52.7, 48.4, 37.8, 28.5, 18.6 ppm.

$[\alpha]_D^{25} = +0.9$  (c = 1.00, CDCl<sub>3</sub>). (literature:  $[\alpha]_D^{25} = +0.9$  (c = 1.00, CDCl<sub>3</sub>))

Analytical data are consistent with those reported in literature.<sup>8</sup>

### (3S,6S)-3-(4-hydroxybenzyl)-6-methylpiperazine-2,5-dione (II-19)

**Method a:** Compound **II-20** (100 mg, 1.0 equiv.) was dissolved in 1:5 TFA/DCM (3 mL, 0.1 M) and stirred for 1h30. The solvent was evaporated, and traces of TFA were removed by vacuum azeotropic evaporation with toluene 3 times. The residue was dissolved in 4:1 toluene/*s*-BuOH (5 mL), and the solution was heated at reflux for 3 h. Cyclo(L-Tyr-L-Ala) is precipitated in form of a white solid. The product was collected by filtration and washed with cold methanol, dried in vacuo to get 71% yield of **II-19** (35 mg) as a white solid.

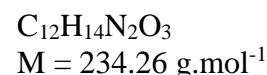
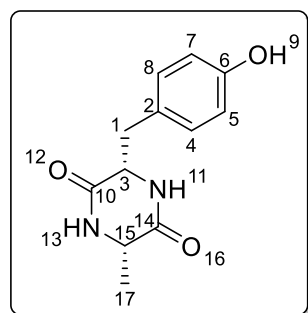
<sup>8</sup> Q. Wang, Y. Wang, M. Kurosu, *Org. Lett.* **2012**, *14*, 3372-3375.



**Method b:** Compound **II-20** (200 mg, 1.0 equiv.) was dissolved in 1:5 TFA/DCM (6 mL, 0.1M) and stirred for 1h30. The solvent was evaporated, and traces of TFA were removed under vacuum by azeotropic evaporation with toluene 3 times. Then the crude mixture was dissolved in a mixture of cold methanol/20% aq. NH<sub>3</sub> (4:1, 0.1 M) in water at 0°C and the solution was stirred at rt for 16 h. Cyclo(L-Tyr-L-Ala) was precipitated as a white solid. The product was collected by filtration and washed with cold water, dry in vacuo to get 85% yield of compound **II-19** (110 mg).

**Method c:** A suspension of compound **II-20** in H<sub>2</sub>O (0.1 M) was irradiated at 200 °C for 5 min by utilizing an Anton Paar Monowave 300 microwave synthesizer. The residue was collected and washed with cold water to afford DKP **II-19** (100% yield) as a white solid.

R<sub>f</sub> = 0.15 (10% MeOH in DCM)



**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  = 7.01 (d, J = 8.3 Hz, 2H; H-4, H-8), 6.72 (d, J = 8.3 Hz, 2H; H-5, H-7), 4.23 (s, 1H; H-9), 3.77 (q, J = 6.7 Hz, 1H; H-15), 3.18 (dd, J = 14.1, 3.3 Hz, 1H; H-1a), 2.85 (dd, J = 13.7, 4.3 Hz, 1H; H-1b), 0.61 ppm (d, J = 7.0 Hz, 3H; H-17).

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  = 9.20 (br s, 1H; H-9), 8.01 (br s, 1H; H-11/13), 7.97 (s, 1H; H-11/13), 6.93 (d, J = 8.5 Hz, 2H; H-4, H-8), 6.65 (d, J = 8.5 Hz, 2H; H-5, H-7), 4.07 (t, J = 4.8 Hz, 1H; H-3), 3.62 (q, J = 6.9 Hz, 1H; H-15), 3.01 (dd, J = 13.6, 3.8 Hz, 1H; H-1a), 2.73 (dd, J = 13.4, 4.8 Hz, 1H; H-1b), 0.54 ppm (d, J = 7.0 Hz, 3H; H-17).

**<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>)  $\delta$  = 167.7, 165.8, 156.0, 131.3, 126.0, 114.8, 55.6, 49.8, 19.8 ppm.

$[\alpha]_D^{25} = +42$  (c = 0.50, DMSO) (literature:  $[\alpha]_D^{25} = +43.7$  (c = 0.06, DMSO))

**Mp** = > 240°C (decompose).

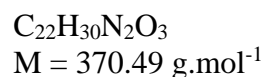
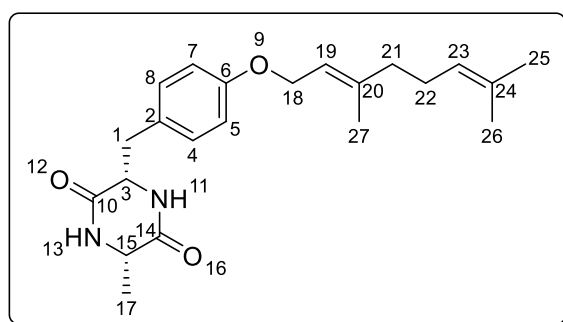
Analytical data are consistent with those reported in literature.<sup>9</sup>

<sup>9</sup> M. Nakao, Y. Toriuchi, S. Fukayama, S. Sano, *Chem. Lett.* **2014**, 43, 340–342.

**(3S,6S)-3-(4-(((E)-3,7-dimethylocta-2,6-dien-1-yl)oxy)benzyl)-6-methylpiperazine-2,5-dione (I-47)**

Cyclo(L-Tyr-L-Ala) **II-19** (50 mg, 1.0 equiv.) was dissolved in DMSO then  $K_2CO_3$  (44 mg, 1.5 equiv.), TBAI (32 mg, 0.4 equiv.) and geranyl bromide (63  $\mu$ L, 1.5 equiv.) were added to the stirring solution at rt. The mixture was stirred at rt without light for 16h, then quenched with  $H_2O$  which give a white precipitate, filtered and dried under vacuum. The crude product could be recrystallized in  $Et_2O$  to afford compound **I-47** as a white solid (48 mg, 61% yield).

**Rf** = 0.25 (cyclohexane/EtOAc 1 :9)



**$^1H$  NMR**  $\delta$  = 7.13 (d,  $J$  = 8.6 Hz, 2H; H-4, H-8), 6.89 (d,  $J$  = 8.6 Hz, 2H; H-5, H-7), 6.24 (s, 1H; H-11/13), 6.06 (s, 1H; H-11/13), 5.47 (dd,  $J$  = 6.5, 5.4 Hz, 1H; H-19), 5.09 (dd,  $J$  = 6.8, 5.5 Hz, 1H; H-23), 4.52 (d,  $J$  = 6.5 Hz, 2H; H-18), 4.27-4.18 (m, 1H; H-3), 4.01 (q,  $J$  = 7.0 Hz, 1H; H-15), 3.24 (dd,  $J$  = 14.0, 3.8 Hz, 1H; H-1a), 2.98 (dd,  $J$  = 14.1, 8.0 Hz, 1H; H-1b), 2.18-2.01 (m, 4H; H-21, H-22), 1.73 (s, 3H; H-27), 1.68 (s, 3H; H-25/26), 1.61 (s, 3H; H-25/26), 1.16 ppm (d,  $J$  = 7.0 Hz, 3H; H-17).

**$^{13}C$  NMR**  $\delta$  = 168.4, 167.2, 158.5, 141.6, 132.0, 130.9, 126.9, 123.9, 119.4, (101 MHz,  $CDCl_3$ ) 115.4, 65.1, 56.5, 51.0, 39.7, 39.2, 26.4, 25.9, 20.2, 17.9, 16.8 ppm.

**IR** (neat):  $\tilde{\nu}$  = 3186, 2972, 2924, 1666, 1511, 1465, 1337, 1241, 1113, 1055  $cm^{-1}$ .

**HRMS** ( $EI^+$ ): Calcd. for  $C_{12}H_{14}N_2O_3^+$ : 234.0999

Found 234.0995

$[\alpha]_D^{25}$  = -53 ( $c$  = 0.095,  $CHCl_3$ )

**Mp** = > 218  $^{\circ}C$  (decompose)

Comparison with the literature:<sup>10</sup>

<b>H</b>	<b>Isolated (600 MHz, DMSO-d<sub>6</sub>, ppm)</b>	<b>Synthesized (400 MHz, DMSO-d<sub>6</sub>, ppm)</b>
17	0.50 (d, J = 6.9 Hz)	0.53 (d, J = 7.0 Hz)
25, 26	1.62 (s), 1.55 (s)	1.63 (s), 1.57 (s)
27	1.66 (s)	1.68 (s)
21, 22	1.99 (m), 2.04 (m)	2.17-1.87 (m)
1	3.04 (dd, J = 13.5, 6.4 Hz) 2.75 (dd, J = 13.5, 4.8 Hz)	3.06 (dd, J = 13.5, 3.6 Hz) 2.78 (dd, J = 13.7, 4.8 Hz)
15	3.61 (q, J = 6.9 Hz)	3.67 – 3.57 (m)
3	4.09 (m)	4.11 (m)
18	4.47 (d, J = 6.3 Hz)	4.49 (d, J = 6.3 Hz)
23	5.05 (= t, J = 6.6 Hz)	5.12-5.01 (m)
19	5.36 (t, J = 6.3 Hz)	5.38 (dd, J = 6.4, 5.2 Hz)
2NH	7.99 (s), 8.07 (s)	8.07 (d, J = 1.8 Hz), 8.00 (d, J = 1.9 Hz)
aromatic	7.02 (d, J = 8.5 Hz), 6.82 (d, J = 8.5 Hz)	7.05 (d, J = 8.7 Hz), 6.84 (d, J = 8.7 Hz)

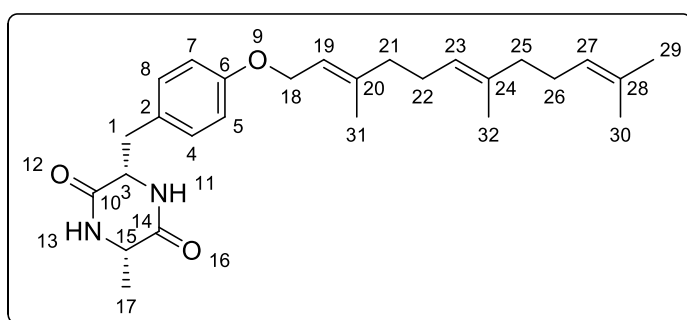
<b>C</b>	<b>Isolated (150 MHz, DMSO-d<sub>6</sub>, ppm)</b>	<b>Synthesized (101 MHz, DMSO-d<sub>6</sub>, ppm)</b>
27	16.5	16.4
26	17.7	17.6
17	19.8	19.7
25	25.6	25.8
22	25.9	29.3
1	37.5	37.5
21	39.0	43.2
15	49.8	49.7
3	55.6	55.5
18	64.4	64.3
5, 7	114.4	114.3
19	119.9	120.0
23	123.9	123.8
2	127.8	127.0
24	131.1	131.0
4, 8	131.4	131.3
20	140.0	140.0
6	157.4	157.3
10	166.0	166.0
14	167.8	167.7

<sup>10</sup> Y. Yao, L. Tian, J. Q. Cao, Y. H. Pei, *Pharmazie* **2007**, *62*, 478-479

**(3S,6S)-3-methyl-6-(4-(((2E,6E)-11-methyldodeca-2,6,10-trien-1-yl)oxy)benzyl)piperazine-2,5-dione (II-26)**

Cyclo(L-Tyr-L-Ala) **II-19** (20 mg, 1.1 equiv.) was dissolved in DMF (0.5 mL), then Cs<sub>2</sub>CO<sub>3</sub> (39 mg, 1.5 equiv.) TBAI (31 mg, 0.4 equiv.) and farnesyl bromide (22 mg, 1.0 equiv.) were successively added to the stirring solution at rt. The mixture was stirred at rt protected from light for 16 h, then quenched with H<sub>2</sub>O which give a white precipitate, filtered and dry under vacuum. The crude product could be recrystallized in Et<sub>2</sub>O to afford white solid **II-26** (18 mg, 52% yield).

R<sub>f</sub> = 0.22 (4% MeOH in DCM)



C<sub>25</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub>  
M = 410.56 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR**  
(400 MHz, CDCl<sub>3</sub>)

$\delta$  = 7.13 (d, J = 8.5 Hz, 2H; H-4, H-8), 6.88 (d, J = 8.6 Hz, 2H; H-5, H-7), 6.39 (s, 1H; H-11/13), 6.16 (s, 1H; H-11/13), 5.47 (t, J = 6.1 Hz, 1H; H-19), 5.19-5.01 (m, 2H; H-23, H-27), 4.51 (d, J = 6.5 Hz, 2H; H-18), 4.30-4.11 (m, 1H; H-3), 4.00 (q, J = 6.9 Hz, 1H; H-15), 3.23 (dd, J = 14.0, 3.8 Hz, 1H; H-1a), 2.99 (dd, J = 14.0, 7.9 Hz, 1H; H-1b), 2.10-1.91 (m, 8H; H-21, H-22, H-25, H-26), 1.73 (s, 3H; H-31/32), 1.68 (s, 3H; H-31/32), 1.60 (s, 6H; H-29, H-30), 1.15 ppm (d, J = 7.0 Hz, 3H; H-17).

**<sup>13</sup>C NMR**  
(101 MHz, CDCl<sub>3</sub>)

$\delta$  = 168.6, 167.4, 158.6, 141.6, 135.6, 131.5, 130.9, 127.0, 124.5, 123.8, 119.5, 115.4, 65.1, 56.5, 51.0, 39.8, 39.7, 39.2, 26.9, 26.4, 25.8, 20.2, 17.8, 16.8, 16.2 ppm.

**IR** (neat):

$\tilde{\nu}$  = 3228, 2924, 2853, 1682, 1608, 1469, 1378, 1336, 1261, 1148, 1043, 774, 695 cm<sup>-1</sup>.

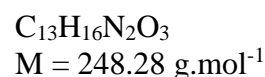
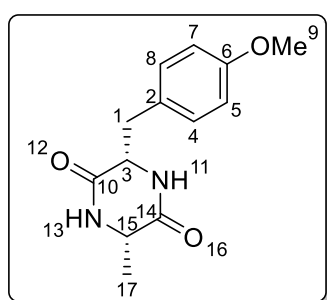
$[\alpha]_D^{25} = -8$  (c = 0.10, CHCl<sub>3</sub>)

**Mp** = >212 °C (decompose)

**(3S,6S)-3-(4-methoxybenzyl)-6-methylpiperazine-2,5-dione (II-27)**

Cyclo(L-Tyr-L-Ala) **II-19** (50 mg, 1.0 equiv.) was dissolved in DMF then  $K_2CO_3$  (58 mg, 2 equiv.) and MeI (90 mg, 3 equiv.) were added to the stirred solution at rt. The mixture was stirred at 60°C for 5h, then quenched with HCl 1M and extracted with DCM:*n*-BuOH (3:1). The gathered organic phase was dried over  $MgSO_4$  and dry under vacuum. The crude product was purified by column with MeOH/DCM (1:9), which afforded a white solid as desired compound (32 mg, 62% yield).

R<sub>f</sub> = 0.31 (MeOH/DCM = 1 : 9)



**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  = 7.11 (d, *J* = 8.5 Hz, 2H; H-4, H-8), 6.86 (d, *J* = 8.5 Hz, 2H; H-5, H-7), 4.25 (t, *J* = 3.9 Hz, 1H; H-15), 3.83-3.66 (m, 1H; H-3), 3.75 (s, 3H; H-9), 3.22 (dd, *J* = 14.0, 3.7 Hz, 1H; H-1a), 2.89 (dd, *J* = 14.0, 4.6 Hz, 1H; H-1b), 0.58 ppm (d, *J* = 7.1 Hz, 3H; H-17).

**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  = 160.1, 158.5, 143.5, 132.8, 128.2, 115.0, 57.5, 55.9, 51.4, 39.6, 20.4 ppm.

Analytical data are consistent with those reported in literature.<sup>11</sup>

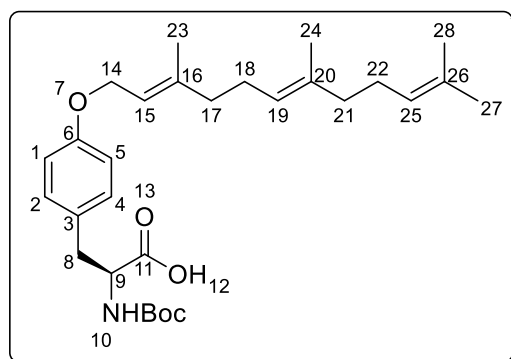
**(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)phenyl)propanoic acid (II-23)**

To a suspension of *N*-Boc-L-tyrosine in MeOH, thionyl chloride was added dropwise at 0°C, then the resulting mixture was stirred at rt for 16h. The methyl ester of *N*-Boc-L-tyrosine was obtained after removing the solvent under vacuum and purified by washing with Et<sub>2</sub>O. The given white solid was directly dissolved in anhydrous DMF, and Cs<sub>2</sub>CO<sub>3</sub> and farnesyl bromide were added sequentially at rt. After stirring for 1h30, the reaction was quenched by addition of aqueous KHSO<sub>4</sub> (5%) to pH = 4, and extracted with EtOAc. The combined

<sup>11</sup> P. Cledera, M. Villacampa, C. Avendaño, J. C. Menéndez, *ARKIVOC* **2011**, 3, 72-98.

organic phases were washed with H<sub>2</sub>O, brine, dried over MgSO<sub>4</sub>. After filtration and evaporation, the Boc form of **II-24** was purified by flash chromatography column of silica gel. The obtained pure compound was then hydrolyzed with NaOH in 1:1 MeOH/H<sub>2</sub>O. After 16h, the hydrolysis reaction was quenched with aqueous KHSO<sub>4</sub> (5%) to pH = 2, and extracted with EtOAc. After drying over MgSO<sub>4</sub> and concentrated, the desired product **II-24** was obtained as a yellow oil (163 mg, 78% yield over three steps).

Rf = 0.26 (cyclohexane/EtOAc = 1:1)



C<sub>29</sub>H<sub>43</sub>NO<sub>5</sub>  
M = 485.67 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 7.09 (d, J = 8.6 Hz, 2H; H-2, H-4), 6.85 (d, J = 8.6 Hz, 2H; H-1, H-5), 5.48 (t, J = 6.0 Hz, 1H; H-15), 5.10 (dd, J = 14.0, 6.9 Hz, 2H; H-19, H-25), 4.90 (d, J = 4.3 Hz, 1H; H-10), 4.56-4.49 (m, 1H; H-9), 4.51 (d, J = 6.5 Hz, 2H; H-14), 3.21-2.90 (m, 2H; H-8), 2.16-1.92 (m, 8H; H-17, H-18, H-21, H-22), 1.73 (s, 3H; H-23), 1.68 (s, 3H; H-24), 1.60 (s, 6H; H-27, H-28), 1.42 ppm (s, 9H; H<sub>Boc</sub>).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 176.8, 158.1, 155.5, 141.3, 135.5, 131.4, 130.5, 127.9, 124.4, 124.0, 119.6, 114.7, 80.2, 64.9, 54.6, 53.5, 39.8, 39.7, 28.4, 28.1, 26.8, 26.4, 17.8, 16.7, 16.1 ppm.

**IR** (neat):  $\tilde{\nu}$  = 3368, 2975, 2930, 1696, 1612, 1511, 1450, 1367, 1241, 1166, 1026, 830 cm<sup>-1</sup>.

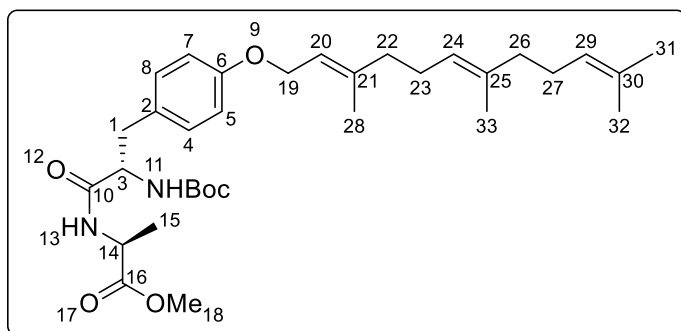
**HRMS** (EI<sup>+</sup>): Calcd for C<sub>9</sub>H<sub>8</sub>O<sub>3</sub><sup>+</sup>: 164.0468 Found 164.0464

**Methyl ((S)-2-((tert-butoxycarbonyl)amino)-3-(4-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)phenyl)propanoyl)-L-alaninate (II-24)**

To a mixture of **II-24** (100 mg, 1.0 equiv.) was added EDC (42 μL, 1.2 equiv.), HOBT (37 mg, 1.2 equiv.) and DMAP (2.4 mg, 0.1 equiv.) in dry DCM (1.5 mL). Then a mixture of alanine methyl ester hydrochloride (33 mg, 1.2 equiv.) pretreated with Et<sub>3</sub>N (34 μL, 1.2 equiv.) in DCM (0.5 mL) was added to the former mixture at 0°C. Then the reaction was warmed up to rt, and stirred for 16h. The reaction was quenched with a saturated NH<sub>4</sub>Cl

solution and extracted with DCM. After drying and evaporation of the organic phase in vacuo, the desired product was purified by flash chromatography on silica gel (with a gradient solvent system cyclohexane/EtOAc =9:1 to 3:1), affording compound II-25 as a light yellow solid (76 mg, 67%).

**Rf** = 0.45 (cyclohexane/EtOAc = 1:1)



$C_{33}H_{50}N_2O_6$   
 $M = 570.77 \text{ g}\cdot\text{mol}^{-1}$

**$^1\text{H NMR}$**   $\delta = 7.10$  (d,  $J = 8.4$  Hz, 2H; H-4, H-8),  $6.83$  (d,  $J = 8.5$  Hz, 2H; H-5, H-7),  $6.40$  (d,  $J = 7.2$  Hz, 1H; H-13),  $5.48$  (t,  $J = 6.2$  Hz, 1H; H-20),  $5.10$  (dd,  $J = 14.1, 7.2$  Hz, 2H; H-24, H-29),  $4.98$  (s, 1H, H-11),  $4.55$ - $4.49$  (m, 1H; H-3),  $4.50$  (d,  $J = 6.5$  Hz, 2H; H-19),  $4.29$  (br s, 1H; H-14),  $3.71$  (s, 3H; H-18),  $3.05$  (dd,  $J = 13.9, 6.3$  Hz, 1H),  $2.96$  (dd,  $J = 13.9, 6.7$  Hz, 1H),  $2.19$  –  $1.90$  (m, 8H; H-22, H-33, H-26, H-27),  $1.73$  (s,  $J = 7.6$  Hz, 3H; H-28),  $1.68$  (s, 3H; H-33),  $1.60$  (s, 6H; H-31, H-32),  $1.42$  (s, 9H; H<sub>Boc</sub>),  $1.34$  ppm (d,  $J = 7.1$  Hz, 3H; H-15).

**$^{13}\text{C NMR}$**   $\delta = \delta 173.0, 171.0, 158.1, 141.4, 135.4, 131.5, 130.5, 128.4, 124.5, 123.8, 119.6, 115.0, 65.0, 55.7, 52.6, 48.3, 39.8, 39.7, 37.6, 28.4, 26.9, 26.4, 25.8, 18.6, 17.8, 16.8, 16.1$  ppm.

**IR** (neat):  $\tilde{\nu} = 3308, 2973, 2925, 2854, 1743, 1661, 1514, 1454, 1367, 1242, 1164, 1051, 750 \text{ cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd for  $C_{33}H_{50}N_2O_6^+$ : 570.3669 Found 248.0989

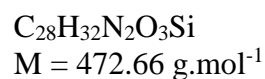
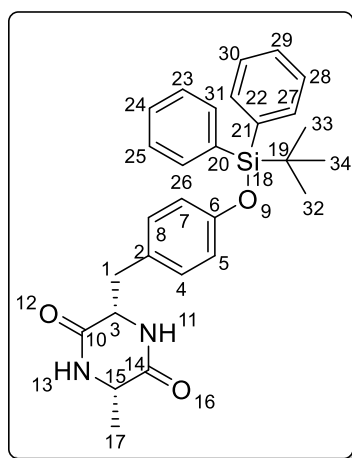
**Mp** = 68-69°C

### (3S,6S)-3-(4-((tert-butyldiphenylsilyl)oxy)benzyl)-6-methylpiperazine-2,5-dione (II-81)

To a solution of DKP **II-19** (100 mg, 1.0 equiv.) and imidazole (47 mg, 1.6 equiv.) in DMF (1.4 mL) was added TBDPSCI (127 mg, 1.3 equiv.) at rt. After 16h stirring, the reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine and dried over  $\text{MgSO}_4$ . The solvent was evaporated to get crude product. It was purified by flash chromatography with a gradient of solvents (2% to 10%) MeOH in DCM, and yielded

67 mg (38%) of product **II-81** as a yellow solid.

**Rf** = 0.18 (10% MeOH in DCM)



**<sup>1</sup>H NMR**  
(400 MHz, CDCl<sub>3</sub>)

$\delta$  = 7.78-7.63 (m, 4H; H<sub>Ar</sub>-TBDPS), 7.47-7.32 (m, 6H; H<sub>Ar</sub>-TBDPS), 6.93 (d, *J* = 8.5 Hz, 2H; H-4, H-8), 6.72 (d, *J* = 8.5 Hz, 2H; H-5, H-7), 5.75 (br s, 1H; H-11/13), 5.66 (br s, 1H; H-11/13), 4.16 (m, 1H; H-3), 3.98 (q, *J* = 7.1 Hz, 1H; H-15), 3.16 (dd, *J* = 14.1, 3.7 Hz, 1H; H-1a), 2.88 (dd, *J* = 14.1, 8.3 Hz, 1H; H-1b), 1.12 (d, *J* = 7.0 Hz, 3H; H-17), 1.09 ppm (s, 9H; H<sub>tBu</sub>-TBDPS).

**IR** (neat):  $\tilde{\nu}$  = 3672, 2971, 2901, 1677, 1509, 1406, 1394, 1254, 1066, 702 cm<sup>-1</sup>

**HRMS** (EI<sup>+</sup>): Calcd for C<sub>33</sub>H<sub>50</sub>N<sub>2</sub>O<sub>6</sub><sup>+</sup>: 472.2182 Found 472.2194

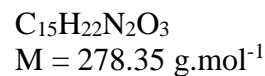
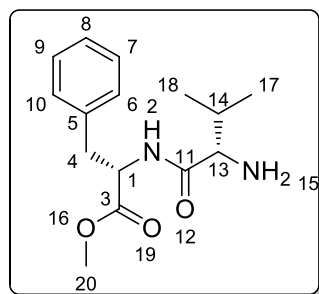
**Mp** = 225-227°C

### methyl L-valyl-L-phenylalaninate (**II-50**)

To a flask containing *N*-Boc-L-Val (240 mg, 1.0 equiv.), HBTU (557 mg, 1.4 equiv.) and HOBT (205 mg, 1.3 equiv.) in DCM (4 mL) was added a solution of phenylalanine methyl ester hydrochloride (290 mg, 1.1 equiv.) and Et<sub>3</sub>N (0.4 mL, 2.8 equiv.) in DMF/DCM (1:2, 1.5 mL). The reaction was stirring at rt for 2h, then quenched with H<sub>2</sub>O and extracted with DCM. After drying over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo, the crude product was purified by flash chromatography (eluting with a gradient system Et<sub>2</sub>O/ cyclohexane= 3:7 to 1:1) to afford a white solid. Then this solid was treated with 20% TFA in DCM. After 1h30, the mixture was washed with a saturated solution of Na<sub>2</sub>CO<sub>3</sub> and extracted with DCM. The organic phase was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent furnished title compound **II-50** (234 mg) in 85% over two-step yield, as a white solid.

**Rf** = 0.21 (Et<sub>2</sub>O/ cyclohexane 1:1)





**$^1\text{H}$  NMR**  $\delta = 7.80 - 7.64$  (m, 1H; H-2), 7.34-7.12 (m, 5H; H<sub>Ar</sub>), 4.97 – 4.86 (m, 1H; H-8), 3.77 – 3.69 (m, 3H; H-20), 3.25-3.20 (m, 1H; H-13), 3.17 (dd,  $J = 13.9, 5.7$  Hz, 1H; H-4a), 3.08 (dd,  $J = 13.9, 7.3$  Hz, 1H; H-4b), 2.24 (m, 1H; H-14), 1.28 (br s, 2H; NH<sub>2</sub>), 0.98 – 0.90 (m, 3H; H-17/18), 0.70 ppm (d,  $J = 6.9$  Hz, 3H; H-17/18).

**$^{13}\text{C}$  NMR**  $\delta = 174.2, 172.4, 136.3, 129.3, 128.7, 127.2, 60.2, 52.8, 52.4, 38.5, 30.8, 19.8, 16.0$  ppm.

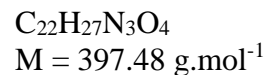
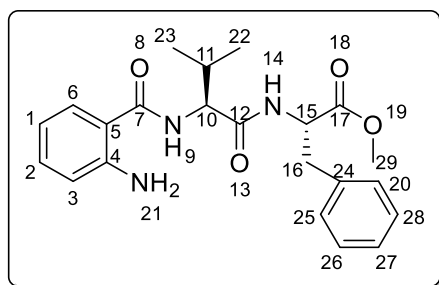
**IR** (neat):  $\tilde{\nu} = 3331, 3273, 2967, 1750, 1687, 1649, 1524, 1444, 1390, 1296, 1247, 1174, 764, 750 \text{ cm}^{-1}$ .

**Mp** = 105°C

#### methyl (2-aminobenzoyl)-L-valyl-L-phenylalaninate (**II-51**)

To a solution of **II-50** (50 mg, 1.0 equiv.) in distilled EtOAc (1.5 mL, 0.1M) was added DMAP (22 mg, 1.0 equiv.), and isatoic anhydride (31 mg, 1.05 equiv.). Then the reaction was refluxed for 8h. When accomplished, the reaction mixture was filtered over Celite® and the filtrate was concentrated on a rotary evaporator. After purification by flash chromatography (with a gradient eluting solvent MeOH/DCM= 2:98 to 5:95), the desired product **II-51** was obtained as a white solid (46 mg, 65% yield).

**Rf** = 0.5 (5% MeOH/DCM)



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.36 (dd, *J* = 7.9, 1.4 Hz, 1H; H-27), 7.21 (m, 4H; H-1, 2, 3, 6), 7.13-7.06 (m, 2H; H-20, H-25), 6.73-6.64 (m, 2H; H-26, H-28), 6.62 (d, *J* = 8.5 Hz, 1H; H-9), 6.37 (d, *J* = 7.7 Hz, 1H; H-14), 5.49 (br s, 2H; NH<sub>2</sub>), 4.89 (dt, *J* = 7.8, 6.2 Hz, 1H; H-15), 4.40 (dd, *J* = 8.5, 6.6 Hz, 1H; H-10), 3.73 (s, 3H; H-29), 3.15 (dd, *J* = 13.9, 5.8 Hz, 1H; H-16a), 3.07 (dd, *J* = 13.9, 6.4 Hz, 1H; H-16b), 2.17 (m, 1H; H-11), 0.99 (d, *J* = 4.6 Hz, 3H; H22/23), 0.97 (d, *J* = 4.7 Hz, 3H; H22/23).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 171.8, 171.0, 169.2, 149.0, 135.7, 132.8, 129.4, 128.8, 127.6, 127.3, 117.4, 116.9, 115.6, 58.4, 53.3, 52.5, 38.0, 31.3, 19.3, 18.3 ppm.

**IR** (neat):  $\tilde{\nu}$  = 3411, 3291, 2956, 1743, 1656, 1618, 1587, 1529, 1449, 1380, 1307, 1253, 1214, 1158, 1032, 745, 698 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub><sup>+</sup>: 397.2002 Found 397.2011.

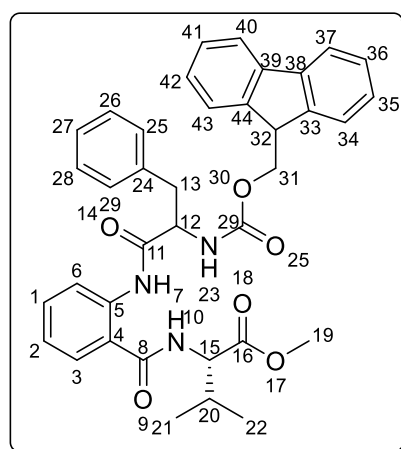
$[\alpha]_D^{25}$  = + 11.0 (*c* = 0.10, CHCl<sub>3</sub>)

**Mp** = 189-190°C (decompose)

**methyl (2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)benzoyl-L-valinate (II-55)**

The compound **II-73a** (225 mg, 1.0 equiv.) was solubilized in DCM (9 mL, 0.1M) and mixed with Fmoc-Phe-Cl **II-53** (360mg, 1.14 equiv.). 1 M K<sub>2</sub>CO<sub>3</sub> (aq.) 9 mL was added after 30 min stirring and then kept stirring for a further 1 h. The organic phase was then separated from the reaction mixture and the aqueous phase was extracted with DCM. The combined organic phase was washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to furnish desired product (yellow amorphous solid) without further purification (500 mg, 90% yield).

**Rf** = 0.23 (Et<sub>2</sub>O/pentane 1 :1)



C<sub>37</sub>H<sub>37</sub>N<sub>3</sub>O<sub>6</sub>  
M = 619.72 g.mol<sup>-1</sup>

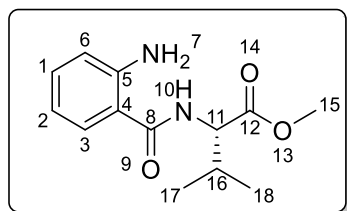
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 11.43 (s, 1H; H-7), 8.60 (d, J = 8.2 Hz, 1H; H-3), 7.76 (d, J = 7.4 Hz, 2H; H<sub>ar</sub>), 7.63-7.48 (m, 4H; H<sub>ar</sub>), 7.39 (t, J = 7.2 Hz, 2H; H<sub>ar</sub>), 7.33 – 7.27 (m, 3H; H<sub>ar</sub>), 7.23-7.13 (m, 5H; H<sub>ar</sub>), 6.66 (d, J = 8.1 Hz, 1H; H-23), 5.42 (d, J = 7.5 Hz, 1H; H-10), 4.77-4.59 (m, 2H; H-15, H-12), 4.40-4.32 (d, J = 4.3 Hz, 2H; H-31), 4.23 (t, J = 6.9 Hz, 1H; H-32), 3.76 (s, 3H; H-19), 3.31 (dd, J = 13.9, 4.8 Hz, 1H; H-13a), 3.17 (dd, J = 13.7, 6.8 Hz, 1H; H-13b), 2.25-2.10 (m, 1H; H-20), 0.91 ppm (d, J = 6.6 Hz, 6H; H-21, H-22).

**IR** (neat):  $\tilde{\nu}$  = 3322, 2924, 1723, 1593, 1517, 1447, 1263, 1064, 754, 631 cm<sup>-1</sup>.

### methyl (2-aminobenzoyl)-L-valinate (**II-73a**)

To a suspension of valine methyl ester hydrochloride (500 mg, 1.0 equiv.) in distilled EtOAc (20 mL, 0.1M) was added DMAP (371 mg, 1 equiv.), and isatoic anhydride (507 mg, 1.05 equiv.). Then the reaction was refluxed for 24h. When accomplished, the reaction mixture was filtered over Celite<sup>®</sup> and the filtrate was concentrated on a rotary evaporator. After purification by flash chromatography (with a gradient eluting solvent DCM/EtOAc = 10:0 to 9:1), the desired product **II-73a** was obtained as a white solid (568 mg, 65% yield).

**Rf** = 0.35 (DCM/EtOAc 9:1)



C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>  
M = 250.30 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.41 (dd, J = 8.2, 1.4 Hz, 1H; H-2), 7.24-7.17 (m, 1H; H-6), 6.69-6.63 (m, 2H; H-1, H-3), 6.56 (d, J = 8.1 Hz, 1H; H-10), 5.47 (s, 2H; NH<sub>2</sub>), 4.71 (dd, J = 8.6, 5.0 Hz, 1H; H-11), 3.76 (s, 3H; H-15), 2.25 (qd, J = 6.8, 1.7 Hz, 1H; H-16), 0.99 ppm (dd, J = 9.4, 6.9 Hz, 6H; H-17, H-18).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 179.1, 172.9, 166.1, 139.5, 132.7, 127.5, 117.5, 116.9, 57.2, 52.4, 31.7, 19.2, 18.2 ppm.

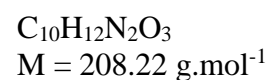
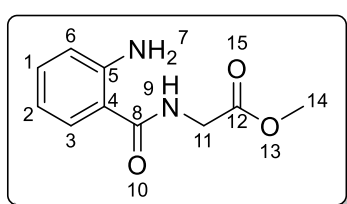
Analytical data are consistent with those reported in literature.<sup>12</sup>

<sup>12</sup> L. Z. Flores-López, M. Parra-Hake, R. Somanathan, F. Ortega, G. Aguirre, *Synthetic Communications* **2000**, *30*, 147-155.

**methyl (2-aminobenzoyl)glycinate (II-73b)**

To a suspension of glycine methyl ester hydrochloride (3.0 g, 1.0 equiv.) in distilled EtOAc (200 mL, 0.1M) was added DMAP (3.2 g, 1.1 equiv.), and isatoic anhydride (4.1 g, 1.05 equiv.). Then the reaction was refluxed for 15 h. When accomplished, the reaction mixture was filtered over Celite® and the filtrate was concentrated on a rotary evaporator. After purification by flash chromatography (with a gradient eluting solvent DCM/EtOAc = 10:0 to 9:1), the desired product II-73b was obtained as a white solid (4.6 g, 91% yield).

R<sub>f</sub> = 0.37 (DCM/EtOAc 4:1)



**<sup>1</sup>H NMR**  $\delta = 7.46\text{-}7.37$  (m, 1H, H-2),  $7.25\text{-}7.20$  (m, 1H; H-6),  $6.69\text{-}6.57$  (m, 2H; H-1, H-3),  $6.57$  (br s, 1H; H-9),  $5.51$  (br s, 2H; NH<sub>2</sub>),  $4.21$  (d, J = 5.1 Hz, 2H; H-11),  $3.80$  ppm (s, 3H; H-14).

**<sup>13</sup>C NMR**  $\delta = 170.9, 169.3, 149.3, 132.8, 127.6, 117.5, 116.8, 115.2, 52.6, 41.6$  ppm.

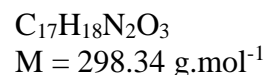
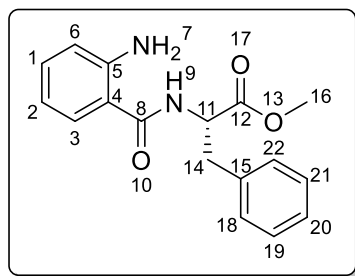
Analytical data are consistent with those reported in literature.<sup>13</sup>

**methyl (2-aminobenzoyl)-L-phenylalaninate (II-73c)**

To a suspension of phenylalanine methyl ester hydrochloride (500 mg, 1.0 equiv.) in distilled EtOAc (23 mL, 0.1 M) was added DMAP (312 mg, 1.1 equiv.), and isatoic anhydride (398 mg, 1.05 equiv.). Then the reaction was refluxed for 24 h. When accomplished, the reaction mixture was filtered over Celite® and the filtrate was concentrated on a rotary evaporator. After purification by flash chromatography (with a gradient eluting solvent DCM/EtOAc = 10:0 to 9:1), desired product II-73c was obtained as a white solid (426 mg, 62% yield).

R<sub>f</sub> = 0.57 (DCM/EtOAc 4:1)

<sup>13</sup> J. Escalante, P. Flores, J. M. Priego, *Heterocycles* **2004**, *63*, 2019 – 2032.



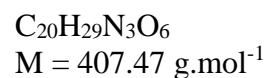
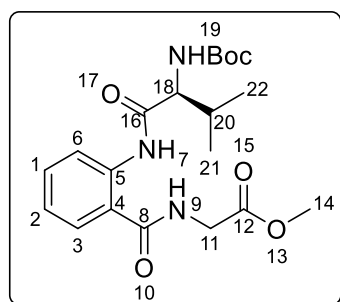
**<sup>1</sup>H NMR**  $\delta = 7.33\text{--}7.11$  (m, 6H; H<sub>ar</sub>),  $6.72\text{--}6.56$  (m, 2H; H<sub>ar</sub>),  $6.47$  (d, J = 7.0 Hz, 1H; H-9),  $5.47$  (s, 2H; NH<sub>2</sub>),  $5.08\text{--}5.00$  (m, 1H; H-11),  $3.76$  (s, 3H; H-16),  $3.27$  (dd, J = 13.8, 5.7 Hz, 1H; H-14a),  $3.20$  ppm (dd, J = 13.8, 5.7 Hz, 1H; H-14b).

Analytical data are consistent with those reported in literature.<sup>14</sup>

**methyl (S)-2-(2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)benzoyl glycinate (II-75)**

To a solution of Boc-L-Val (3 g, 1.05 equiv.) and EEDQ (3.6 g, 1.1 equiv.) in DCM (70 mL, 0.2M) at room temperature was added **II-73b** (2.8 g, 1 equiv.) at 0°C. The reaction mixture was stirred for 30 min and stirring for a further 18 h at rt. The organic phase was then washed with 1M HCl 3 times then extracted with DCM, then washed with saturated aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O and brine. The combined organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to furnish a crude mixture, and purified by flash chromatography to get an off-white crystalline solid (5 g, 89%) as title compound **II-75**.

**R<sub>f</sub>** = 0.22 (Et<sub>2</sub>O/pentane 7 :3)



<sup>14</sup> S. N. Khattab, N. S. Haiba, A. M. Asal, A. A. Bekhit, A. Amer, H. M. Abdel-Rahman, A. El-Faham, *Bioorg. Med. Chem.* **2015**, *23*, 3574–3585.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 11.30 (br s, 1H; H-7), 8.49 (d, J = 8.2 Hz, 1H; H-3), 7.55 (d, J = 7.7 Hz, 1H; H-6), 7.38 (t, J = 7.6 Hz, 1H; H-2), 7.31 (br s, 1H; H-9), 7.00 (t, J = 7.3 Hz, 1H; H-1), 5.24 (d, J = 8.4 Hz, 1H; H-19), 4.23 – 4.00 (m, 3H; H-11, H-18), 3.73 (s, 3H; H-14), 2.20 (dd, J = 12.1, 6.0 Hz, 1H; H-20), 1.39 (d, J = 13.3 Hz, 9H; H<sub>Boc</sub>), 0.96 (d, J = 6.8 Hz, 3H; H-21/22), 0.88 ppm (d, J = 6.7 Hz, 3H; H-21/22).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 170.8, 170.3, 168.9, 155.9, 138.9, 132.8, 127.1, 123.1, 121.3, 119.9, 79.8, 77.4, 77.1, 76.8, 60.9, 52.5, 41.5, 31.1, 28.3, 19.3, 17.5 ppm.

**IR** (neat):  $\tilde{\nu}$  = 3423, 3150, 2954, 1720, 1639, 1591, 1528, 1433, 1408, 1371, 1282, 1248, 1211, 1058, 969, 755, 721, 523 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>20</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub><sup>+</sup>: 407.2051 Found 407.2043

$[\alpha]_D^{25} = -40$  (c = 0.27, DMSO)

**Mp** = 64°C

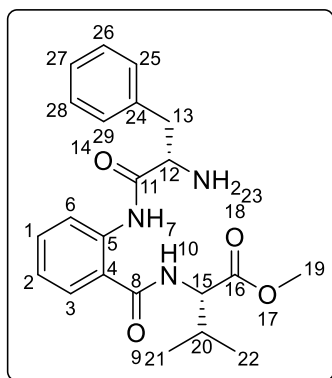
**General procedure C: synthesis of tripeptide (II-54, II-63, II-65, II-66):**

The amino acid methyl ester (Gly, Phe, Val) (1.0 equiv.) was added to a suspension of isatoic anhydride and DMAP (2.0 equiv.) in EtOAc (0.5 M) at rt. The reaction mixture was heated to reflux for 18 h. Then the reaction was cooled to room temperature, filtered through Celite® and washed with water and brine. The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to furnish a yellowbrown solid, which was used without further purification. The obtained compound was after then solubilized in DCM (0.15M) and mixed with Fmoc-AA-Cl (Phe, Ala, Val, Gly) (1.1 equiv.). 1 M Na<sub>2</sub>CO<sub>3</sub> (aq.) was added after 30 min stirring and then kept stirring for a further 1 h. The organic phase was then separated from the reaction mixture and the aqueous phase extracted with DCM. The combined organic phase was washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The crude amide product was treated with piperidine in DCM (0.1 M) and concentrated in vacuo after stirring at rt for 30 min. The resulting crude product was purified by flash column chromatography on silica gel (DCM/MeOH) to furnish the desired tripeptide product.

**methyl (2-((S)-2-amino-3-phenylpropanamido)benzoyl)-L-valinate (II-54)**

According to procedure C, from L-valine methyl ester hydrochloride **II-52** (50 mg, 0.3 mmol), yielded a yellow solid, 49mg (41% overall yield).

Rf = 0.35 (DCM/EtOAc/MeOH 80:15:5)



$C_{22}H_{27}N_3O_4$   
 $M = 397.47 \text{ g}\cdot\text{mol}^{-1}$

**$^1\text{H NMR}$**   
 (400 MHz,  $\text{CDCl}_3$ )

$\delta = 11.76$  (s, 1H; H-7), 8.78 (d,  $J = 8.3$  Hz, 1H; H-3), 7.72-7.60 (m, 2H;  $H_{\text{ar}}$ ), 7.52-7.21 (m, 6H;  $H_{\text{ar}}$ ), 6.78 (d,  $J = 8.6$  Hz, 1H; H-10), 4.91 (dd,  $J = 8.6, 4.8$  Hz, 1H; H-12), 3.95-3.88 (m, 3H; H-19, H-15), 3.48 (dd,  $J = 13.7, 3.9$  Hz, 2H; H-13a), 2.95 (dd,  $J = 13.7, 9.4$  Hz, 1H; H-13b), 2.45-2.35 (m, 1H; H-20), 2.27 (br s, 2H;  $\text{NH}_2$ ), 1.15-1.12 (d,  $J = 10.9$  Hz, 3H; H-21/22), 1.13-1.10 ppm (d,  $J = 6.9$  Hz, 3H; H-21/22).

**$^{13}\text{C NMR}$**   
 (101 MHz,  $\text{CDCl}_3$ )

$\delta = 182.13, 166.26, 160.99, 151.11, 147.26, 135.30, 135.07, 130.42, 129.01, 127.77, 127.18, 127.10, 127.04, 120.14, 82.61, 77.36, 57.22, 52.28, 36.94, 23.30$  ppm.

**IR** (neat):

$\tilde{\nu} = 3673, 3304, 2933, 2851, 1740, 1649, 1582, 1512, 1446, 1274, 1207, 756, 739 \text{ cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ):

Calcd. for  $C_{22}H_{27}N_3O_4^+$ : 397.2002

Found 306.1446

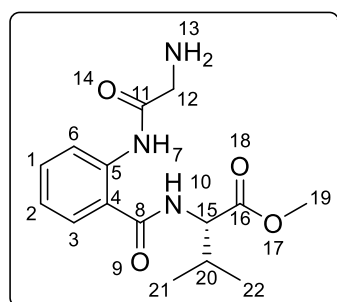
$[\alpha]_D^{25} = -8$  ( $c = 0.10, \text{CHCl}_3$ )

**Mp** = 95-97°C

### methyl (2-(2-aminoacetamido)benzoyl)-L-valinate (II-63)

According to procedure **C**, from L-valine methyl ester hydrochloride **II-52** (30 mg, 0.18 mmol), yielded a yellow oil, 17 mg (38% overall yield).

Rf = 0.32 (DCM/MeOH 9 :1)



$C_{15}H_{21}N_3O_4$   
 $M = 307.35 \text{ g}\cdot\text{mol}^{-1}$

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 11.54 (s, 1H; H-7), 8.62 (d, *J* = 8.3 Hz, 1H; H-10), 7.56 (d, *J* = 7.8 Hz, 1H; H-6), 7.49 (t, *J* = 7.9 Hz, 1H; H-2), 7.11 (t, *J* = 7.6 Hz, 1H; H-1), 6.68 (d, *J* = 8.6 Hz, 1H; H-3), 4.78 (dd, *J* = 8.7, 4.8 Hz, 1H; H-15), 3.78 (s, 3H; H-19), 3.52 (s, 2H; H-12), 2.38-2.19 (m, 1H; H-20), 1.98 (br s, 2H; NH<sub>2</sub>), 1.01 (d, *J* = 6.9 Hz, 3H; H-21/22), 0.98 ppm (d, *J* = 6.9 Hz, 3H; H-21/22).

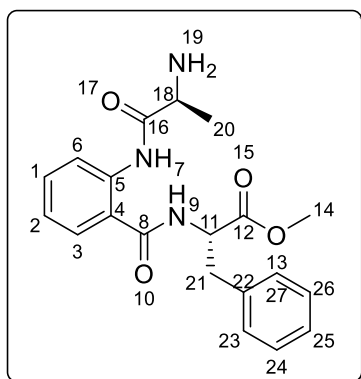
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 172.2, 168.5, 138.8, 132.7, 127.0, 123.1, 121.6, 121.5, 57.3, 52.4, 46.4, 31.6, 19.0, 18.0 ppm.

**IR** (neat):  $\tilde{\nu}$  = 3307, 3061, 2928, 1737, 1644, 1582, 1507, 1444, 1282, 1205, 157, 753, 699 cm<sup>-1</sup>.

### methyl (2-((S)-2-aminopropanamido)benzoyl)-L-phenylalaninate (II-65)

According to procedure C, from L-phenylalanine methyl ester hydrochloride **II-49** (257 mg, 1.2 mmol) yield a colourless liquid, 75 mg (17% overall yield).

**R<sub>f</sub>** = 0.42 (5% MeOH in DCM)



C<sub>20</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>  
M = 369.4210 g.mol<sup>-1</sup>

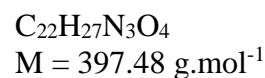
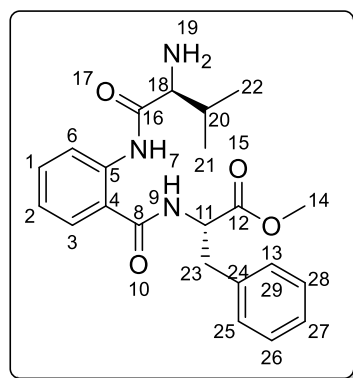
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 11.45 (br s, 1H; H-7), 8.46 (d, *J* = 8.4 Hz, 1H; H-3), 7.32-6.87 (m, 8H; H<sub>ar</sub>), 6.50 (d, *J* = 7.1 Hz, 1H; H-9), 4.94 (q, *J* = 5.8 Hz, 1H; H-18), 3.62 (s, 3H; H-14), 3.54 – 3.38 (m, 1H; H-11), 3.10 (d, *J* = 33.1 Hz, 2H; H-21), 1.25 ppm (d, *J* = 6.9 Hz, 3H; H-20).

### methyl (2-((S)-2-amino-3-methylbutanamido)benzoyl)-L-phenylalaninate (II-66)

According to procedure C, from L-phenylalanine methyl ester hydrochloride **II-49** (45 mg, 0.2 mmol), yielded a yellow liquid, 26 mg (33% overall yield).

**R<sub>f</sub>** = 0.21 (100% Et<sub>2</sub>O)





**$^1\text{H}$  NMR**  $\delta = 11.60$  (br s, 1H; H-7), 8.77 – 8.51 (m, 1H; H-3), 7.54 – 7.05 (m, 8H;  $\text{H}_{\text{ar}}$ ), 6.61 (d,  $J = 7.5$  Hz, 1H; H-9), 5.11 (dt,  $J = 7.6, 5.6$  Hz, 1H; H-11), 3.79 (s, 3H; H-14), 3.40-3.28 (m, 2H; H-23), 3.22 (dd,  $J = 13.9, 5.6$  Hz, 1H; H-18), 2.38-2.25 (m, 1H; H-20), 1.60 (br s, 2H;  $\text{NH}_2$ ) 1.05 (d,  $J = 6.9$  Hz, 3H; H-21/22), 0.91 ppm (d,  $J = 6.9$  Hz, 3H; H-21/22).

**$^{13}\text{C}$  NMR**  $\delta = 174.2, 171.8, 168.2, 139.0, 135.8, 132.8, 129.5, 128.9, 127.5, 126.9, 123.1, 121.7, 121.2, 61.7, 53.5, 52.7, 37.9, 31.7, 19.9, 16.6$  ppm.

**IR** (neat):  $\tilde{\nu} = 3288, 2960, 1742, 1649, 1600, 1582, 1513, 1446, 1276, 1216, 1076, 879, 751, 701 \text{ cm}^{-1}$ .

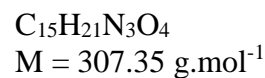
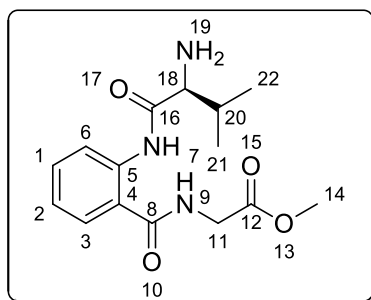
**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_4^+$ : 397.2002 Found 397.1986.

$[\alpha]_D^{25} = +34$  ( $c = 0.10, \text{CHCl}_3$ )

#### methyl (S)-(2-(2-amino-3-methylbutanamido)benzoyl)glycinate (II-64)

To a solution of Boc-L-Val (57 mg, 1.05 equiv.) and EEDQ (68 mg, 1.1 equiv.) in DCM (1.25 mL, 0.2 M) at room temperature was added **II-73b** (52 mg, 1 equiv.) at  $0^\circ\text{C}$ . The reaction mixture was stirred for 30 min at  $0^\circ\text{C}$  and stirred for a further 18 h at rt. The organic phase was then washed with 1 M HCl 3 times then extracted with DCM, then washed with saturated aqueous  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$  and brine. The combined organic phase was dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo to furnish a crude mixture, and purified by flash chromatography to get an off-white crystalline solid. Then the obtained solid was treated with TFA/DCM (1:5) for 2h. The reaction was quenched with 10%  $\text{K}_2\text{CO}_3$  solution and extracted with EtOAc. After dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo, a yellow liquid was yield as pure compound (64 mg, 80% overall yield).

**Rf** = 0.19 (DCM/MeOH 95 :5)



**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta = 11.64$  (s, 1H; H-7), 8.61 (dd,  $J = 8.4, 0.8$  Hz, 1H; H-3), 7.56 (dd,  $J = 7.8, 1.3$  Hz, 1H; H-6), 7.50-7.39 (m, 1H; H-1), 7.06 (td,  $J = 7.7, 1.1$  Hz, 1H; H-2), 6.97 (br s, 1H; H-9), 4.20 (d,  $J = 5.2$  Hz, 2H; H-11), 3.76 (s, 3H; H-14), 3.33 (d,  $J = 4.2$  Hz, 1H; H-18), 2.28 (dtd,  $J = 13.7, 6.9, 4.1$  Hz, 1H; H-20), 1.59 (br s, 2H;  $\text{NH}_2$ ), 1.00 (d,  $J = 6.9$  Hz, 3H; H-21/22), 0.87 ppm (d,  $J = 6.9$  Hz, 3H; H-21/22).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta = 174.2, 170.3, 168.8, 139.0, 132.8, 127.1, 123.1, 121.7, 120.9, 77.5, 77.2, 76.8, 61.7, 41.7, 38.7, 31.6, 19.8, 16.5$  ppm.

**IR** (neat):  $\tilde{\nu} = 3308, 2959, 2872, 1749, 1650, 1599, 1582, 1513, 1446, 1370, 1281, 1209, 1174, 757 \text{ cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_4^+$ : 307.1532 Found 307.1522.

$[\alpha]_D^{25} = -9$  ( $c = 0.10, \text{CHCl}_3$ )

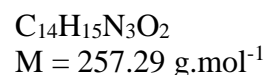
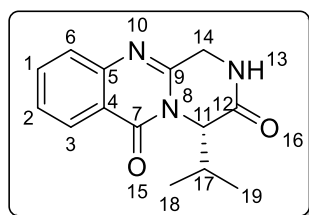
***General procedure D: synthesis of quinazolino-DKP (II-67 to II-71):***

The corresponding tripeptide was mixed with zinc triflate or scandium triflate in DMF. The solution was heated at  $140^\circ\text{C}$  in a sealed tube for 2-16 h, while monitoring with TLC. The reaction was quenched with  $\text{H}_2\text{O}$  and extracted with ethyl acetate three times. After drying over  $\text{Na}_2\text{SO}_4$ , evaporated under vacuum, the crude product was purified by flash column chromatography to furnish desired product.

**(S)-4-isopropyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (II-68)**

According to procedure **D** from compound **II-63** (8 mg), yielded 2 mg of **II-68** with  $\text{Sc}(\text{OTf})_3$  (30% yield), 3.7 mg, with  $\text{Zn}(\text{OTf})_2$  (56% yield) as a yellow solid.

**Rf** = 0.15 (100%  $\text{Et}_2\text{O}$ )



**$^1\text{H NMR}$**   $\delta = 8.30$  (dd,  $J = 8.0, 1.2$  Hz, 1H; H-3), 7.80-7.76 (m, 1H; H-1), 7.64 (d,  $J = 8.1$  Hz, 1H; H-6), 7.51 (t,  $J = 7.6$  Hz, 1H; H-2), 6.79 (d,  $J = 3.8$  Hz, 1H; H-13), 5.28 (dd,  $J = 7.9, 0.9$  Hz, 1H; H-11), 4.72 (d,  $J = 17.1$  Hz, 1H; H-14a), 4.45 (dd,  $J = 17.1, 5.3$  Hz, 1H; H-14b), 2.31 (dq,  $J = 13.9, 6.9$  Hz, 1H; H-17), 1.16 (d,  $J = 6.8$  Hz, 3H; H-18/19), 1.09 ppm (d,  $J = 6.9$  Hz, 3H; H-18/19).

**$^{13}\text{C NMR}$**   $\delta = 169.1, 160.8, 148.6, 147.0, 134.9, 127.3, 127.2, 126.9, 120.3, 60.8, 25.4, 31.8, 19.9, 18.9$  ppm.

**IR** (neat):  $\tilde{\nu} = 3305, 2922, 2333, 2076, 1988, 1675, 1595, 1522, 1449, 1268, 1033, 756 \text{ cm}^{-1}$ .

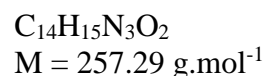
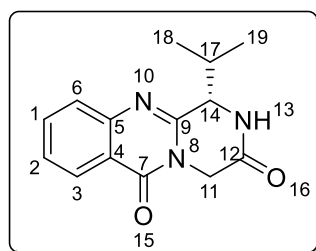
$[\alpha]_D^{25} = +50$  ( $c = 0.01$ , DMSO) (literature:  $[\alpha]_D^{25} = +132$  ( $c = 0.22$ ,  $\text{CHCl}_3$ ))

Analytical data are consistent with those reported in literature.<sup>15</sup>

#### (S)-1-isopropyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (II-69)

A suspension of **II-75** in distilled water (0.03 M) was irradiated by microwave at 120°C during 2h. The reaction mixture was cooled and filtered. Compound **II-69** was obtained as a white solid (83% yield).

**Rf** = 0.33 (100%  $\text{Et}_2\text{O}$ )



**$^1\text{H NMR}$**   $\delta = 8.30$  (dd,  $J = 8.0, 1.1$  Hz, 1H; H-3), 7.84-7.74 (m, 1H; H-1), 7.68 (d,  $J = 7.8$  Hz, 1H; H-6), 7.56-7.45 (m, 1H; H-2), 6.69 (br s, 1H; H-13), 5.00 (d,  $J = 18.9$  Hz, 1H; H-14), 4.53 – 4.32 (m, 2H; H-11), 2.55-2.40 (m, 1H; H-17), 1.12 (d,  $J = 6.9$  Hz, 3H; H-18/19), 1.00 ppm (d,  $J = 6.7$  Hz, 3H; H-18/19).

<sup>15</sup> P. Cledera, C. Avendaño, J. C. Menéndez, *J. Org. Chem.* **2000**, *65*, 1743-1749.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.30 (dd, *J* = 8.0, 1.1 Hz, 1H; H-3), 7.84-7.74 (m, 1H; H-1), 7.68 (d, *J* = 7.8 Hz, 1H; H-6), 7.56-7.45 (m, 1H; H-2), 6.69 (br s, 1H; H-13), 5.00 (d, *J* = 18.9 Hz, 1H; H-14), 4.53 – 4.32 (m, 2H; H-11), 2.55-2.40 (m, 1H; H-17), 1.12 (d, *J* = 6.9 Hz, 3H; H-18/19), 1.00 ppm (d, *J* = 6.7 Hz, 3H; H-18/19).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 166.0 (C-12), 160.9 (C-7), 150.0 (C-5), 147.1 (C-9), 135.0 (C-1), 127.5 (C-2), 127.3 (C-6), 126.9 (C-3), 120.0 (C-4), 62.0 (C-14), 44.9 (C-11), 35.1 (C17), 19.4 (C-18/19), 17.1 (C-18/19) ppm.

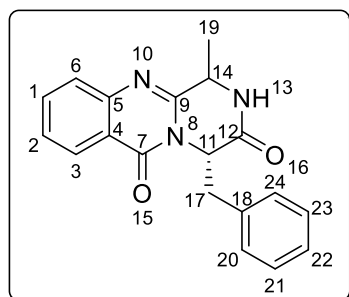
**IR** (neat):  $\tilde{\nu}$  = 3365, 3149, 3103, 2964, 1689, 1667, 1481, 1356, 1249, 1171, 869, 769 cm<sup>-1</sup>.

**HRMS** (ESI<sup>+</sup>): Calcd. for [C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>+H]<sup>+</sup>: 258.1235 Found 258.1237.

$[\alpha]_D^{25} = -22$  (c = 0.29, DMSO) (literature:  $[\alpha]_D^{25} = -26$  (c = 0.28, DMSO))

**Mp** = 194-196°C

**(1*S*,4*S*)-4-benzyl-1-methyl-1,2-dihydro-6*H*-pyrazino[2,1-*b*]quinazoline-3,6(4*H*)-dione (II-70)**



C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>

M = 319.36 g.mol<sup>-1</sup>

Trans isomer

According to procedure **D** from compound **II-65** (13 mg), yielded 2 mg of **II-78** with Sc(OTf)<sub>3</sub> (14% yield), 2.3 mg with Zn(OTf)<sub>2</sub> (20% yield) as an orange solid.

**Rf** = 0.62 (100% Et<sub>2</sub>O)

**Mp** = 145-148°C

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.35 (d, *J* = 8.2 Hz, 1H; H-3), 7.79 (t, *J* = 7.5 Hz, 1H; H-1), 7.65 (d, *J* = 8.2 Hz, 1H; H-6), 7.54 (t, *J* = 7.5 Hz, 1H; H-2), 7.29-7.24 (m, 1H; H-22), 7.19 (t, *J* = 7.3 Hz, 2H; H-21, H-23), 6.98 (d, *J* = 7.1 Hz, 2H; H-20, H-24), 5.75-5.59 (m, 2H; H-11, H-13), 3.49 (s, 2H; H-17), 3.05 – 2.91 (m, 1H; H-14), 1.45 ppm (d, *J* = 6.6 Hz, 3H; H-19).

Cis isomer

According to procedure **D** from compound **II-54d** (13 mg), yielded 1 mg of **II-58** with

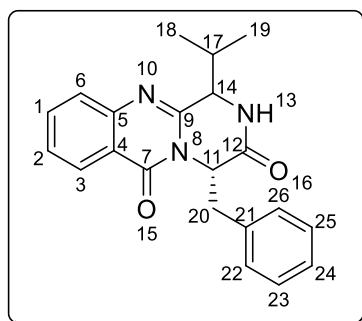
Sc(OTf)<sub>3</sub> (8% yield), 1.3 mg, with Zn(OTf)<sub>2</sub> (12% yield) as a yellow solid.

R<sub>f</sub> = 0.16 (100% Et<sub>2</sub>O)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 8.36 (d, J = 7.8 Hz, 1H; H-3), 7.80 (t, J = 7.3 Hz, 1H; H-1), 7.62 (d, J = 8.3 Hz, 1H; H-6), 7.54 (t, J = 7.2 Hz, 1H; H-2), 7.22 – 7.15 (m, 3H; H-21, 22, 23), 6.99-6.90 (m, 2H; H-20, H-24), 5.94 (br s, 1H; H-13), 5.54 (q, J = 4.0 Hz, 1H; H-14), 4.53 (dt, J = 13.7, 6.8 Hz, 1H; H-11), 3.62 (dd, J = 14.4, 6.2 Hz, 1H; H-17a), 3.50 (d, J = 14.1 Hz, 1H; H-17b), 0.72 ppm (d, J = 7.1 Hz, 3H; H-19).

Analytical data are consistent with those reported in literature.<sup>16</sup>

**(1S,4S)-4-benzyl-1-isopropyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (II-71)**



C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>  
M = 347.42 g.mol<sup>-1</sup>

*Trans isomer*

According to procedure **D** from compound **II-66** (13 mg), yielded 1.4 mg of **II-71** with Sc(OTf)<sub>3</sub> (10% yield), 2.1 mg with Zn(OTf)<sub>2</sub> (15% yield) as a white solid.

R<sub>f</sub> = 0.67 (100% Et<sub>2</sub>O)

Mp = 81 °C

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 8.36 (dd, J = 8.0, 1.2 Hz, 1H; H-3), 7.79 (ddd, J = 8.5, 7.2, 1.5 Hz, 1H; H-1), 7.62 (d, J = 8.0 Hz, 1H; H-6), 7.59-7.48 (m, 1H; H-2), 7.28-7.24 (m, 1H; H-24), 7.17 (t, J = 7.5 Hz, 2H; H-23, H-25), 6.92 (d, J = 7.1 Hz, 2H; H-22, H-26), 5.69 (br s, 1H; H-13), 5.67 (t, J = 4.3 Hz, 1H; H-11), 3.54-3.40 (m, 2H; H-20), 2.77 (m, 1H; H-17), 2.72 (d, J = 2.3 Hz, 1H; H-14), 0.87 (d, J = 7.3 Hz, 3H; H-18/19), 0.72 ppm (d, J = 6.7 Hz, 3H; H-18/19).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 187.5, 168.4, 161.1, 150.0, 147.2, 135.0, 134.9, 130.0, 128.9, 128.0, 127.5, 127.3, 127.1, 120.2, 58.0, 57.2, 37.4, 29.6, 19.2, 15.0 ppm.

<sup>16</sup> M. C. Tseng, Y. H. Chu, *Tetrahedron* **2008**, *64*, 9515-9520.

**IR** (neat):  $\tilde{\nu}$  = 3204, 2964, 2924, 1682, 1598, 1570, 1470, 1390, 1335, 1276, 1260, 1150, 766, 749, 699  $\text{cm}^{-1}$ .

Cis isomer

According to procedure **D** from compound **II-66** (13 mg), yielded 1 mg of **II-71** with  $\text{Sc}(\text{OTf})_3$  (7% yield), 1.4 mg with  $\text{Zn}(\text{OTf})_2$  (10% yield) as a white solid.

**Rf** = 0.27 (100%  $\text{Et}_2\text{O}$ )

**$^1\text{H}$  NMR**  $\delta$  =  $\delta$  8.33 (dd,  $J$  = 8.0, 1.0 Hz, 1H; H-3), 7.87-7.75 (m, 1H; H-1), (400 MHz,  $\text{CDCl}_3$ ) 7.66 (d,  $J$  = 8.0 Hz, 1H; H-6), 7.54 (dd,  $J$  = 11.1, 4.0 Hz, 1H; H-2), 7.23 (m, 3H; H-23, 24, 25), 7.15 (m, 2H; H-22, H-26), 6.26 (br s, 1H; H-13), 5.56-5.40 (m, 1H; H-11), 4.04 (dd,  $J$  = 8.5, 3.7 Hz, 1H; H-14), 3.56-3.43 (m, 2H; H-20), 1.15 (dt,  $J$  = 13.4, 6.7 Hz, 1H; H-17), 0.95 (d,  $J$  = 6.7 Hz, 3H; H-18/19), 0.81 ppm (d,  $J$  = 6.6 Hz, 3H; H-18/19).

**$^{13}\text{C}$  NMR**  $\delta$  = 196.1, 167.1, 161.7, 154.7, 146.9, 136.1, 135.0, 130.1, 128.9, (101 MHz,  $\text{CDCl}_3$ ) 127.5, 127.3, 127.0, 62.2, 57.8, 53.2, 38.2, 35.0, 20.1, 19.0 ppm.

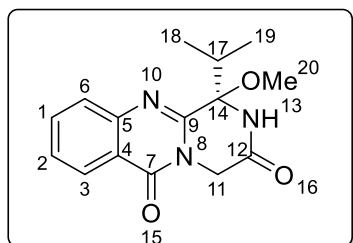
**IR** (neat):  $\tilde{\nu}$  = 3204, 2964, 2924, 1682, 1598, 1570, 1470, 1390, 1335, 1276, 1260, 1150, 766, 749, 699  $\text{cm}^{-1}$ .

Analytical data are consistent with those reported in literature.<sup>17</sup>

**(R)-1-isopropyl-1-methoxy-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (II-92a)**

To a sealed tube containing compound **II-69** (50 mg, 1.0 equiv.) was added DDQ (90 mg, 2.0 equiv.) and MeOH (50  $\mu\text{L}$ ) in DCM (2 mL, 0.1M) at rt. The reaction was heated to 60°C for 16h. The reaction was quenched with  $\text{Na}_2\text{SO}_3$  and extracted with EtOAc. After washing with brine, drying over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo, the crude product was purified by flash chromatography (eluting with EtOAc/PE (3:7 to 1:1)) to afford the title compound as a white solid (44 mg, 77%).

**Rf** = 0.40 (EtOAc/PE 1:1)



$\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3$   
 $M = 287.32 \text{ g}\cdot\text{mol}^{-1}$

<sup>17</sup> F. Hernández, F. L. Buenadicha, C. Avendaño, M. Söllhuber, *Tetrahedron: Asymmetry* **2001**, *12*, 3387-3398.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.30 (m, 1H; H-3), 7.82-7.79 (m, 2H; H-6, H-1), 7.64-7.46 (m, 1H; H-2), 7.21 (br s, 1H; H-13), 4.81 (d, *J* = 19.2 Hz, 1H; H-11a), 4.65 (d, *J* = 19.2 Hz, 1H; H-11b), 3.22 (s, 3H; H-20), 3.07-2.88 (m, 1H; H-17), 1.14 (d, *J* = 7.0 Hz, 3H; H-18/19), 0.91 ppm (d, *J* = 6.8 Hz, 3H; H-18/19).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 166.4 (C-12), 160.8 (C-7), 148.4 (C-9), 146.7 (C-5), 135.0 (C-1), 128.1 (C-2), 128.0 (C-6), 126.8 (C-3), 120.3 (C-4), 90.4 (C-14), 51.4 (C-20), 45.2 (C-11), 35.3 (C-17), 17.3 (C-18/19), 14.8 ppm (C-18/19).

**IR** (neat):  $\tilde{\nu}$  = 3223, 2965, 2924, 2854, 1680, 1607, 1469, 1423, 1377, 1336, 1297, 1260, 1165, 1087, 1049, 775, 734 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>3</sub>O<sub>3</sub><sup>+</sup>: 244.0712 Found 244.0708.

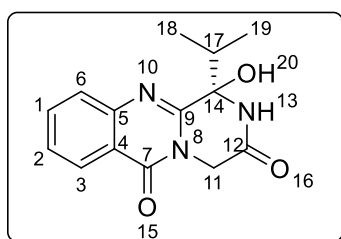
$[\alpha]_D^{25} = +2.6$  (*c* = 0.50, CHCl<sub>3</sub>)

**Mp** = 185-188°C

**(R)-1-hydroxy-1-isopropyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (II-92b)**

To a sealed tube containing compound **II-69** (10 mg, 1.0 equiv.) was added DDQ (18 mg, 2.0 equiv.) in wet DCM (0.5 mL, 0.1M) at rt. The reaction was heated to 60°C for 16 h. The reaction was quenched with Na<sub>2</sub>SO<sub>3</sub> and extracted with EtOAc. After washing with brine, drying over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo, the crude product was purified by flash chromatography (eluting with EtOAc/PE (3:7 to 1:1)) to afford title compound **II-92b** as a white solid (4.2 mg, 39%).

**R<sub>f</sub>** = 0.37 (EtOAc/PE 1:1)



C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>  
M = 273.29 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  = 8.94 (s, 1H; H-13), 8.17 (m, 1H; H-3), 7.91-7.83 (m, 1H; H-1), 7.72 (d, *J* = 8.1 Hz, 1H; H-6), 7.59 (t, *J* = 7.5 Hz, 1H; H-2), 6.71 (s, 1H; H-20), 4.74 (d, *J* = 18.0 Hz, 1H; H-11a), 4.39 (d, *J* = 18.1 Hz, 1H; H-11b), 2.92-2.81 (m, 1H; H-17), 1.11 (d, *J* = 7.1 Hz, 3H; H-18/19), 0.95 ppm (d, *J* = 6.8 Hz, 3H; H-18/19).

**<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>)  $\delta$  = 166.29 (C-12), 159.96 (C-7), 151.83 (C-9), 146.58 (C-5), 134.77 (C-1), 127.46 (C-2), 127.31 (C-6), 126.10 (C-3), 119.80

(C-4), 84.39 (C-14), 44.83 (C-11), 34.17 (C-17), 17.35 (C-18/19), 14.72 ppm (C-18/19).

**IR** (neat):  $\tilde{\nu}$  = 3228, 2924, 2853, 1682, 1608, 1469, 1378, 1336, 1261, 1148, 1043, 774, 695  $\text{cm}^{-1}$ .

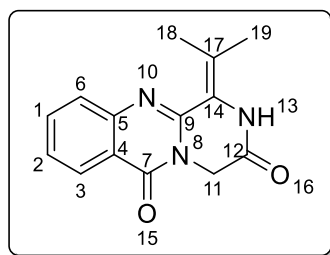
$[\alpha]_D^{25} = + 1.0$  (c = 0.20,  $\text{CHCl}_3$ )

**Mp** = 188-190°C

### 1-(propan-2-ylidene)-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (**II-95**)

Compound **II-9a** (5 mg, 1.0 equiv.) was dissolved in acetonitrile (0.5 mL), and then irradiated at 80°C under microwave condition for 20 min. A white precipitate was formed and collected by filtration. The compound was further purified by flash chromatography eluting with EtOAc/PE (3:7) to afford the title compound (3.5 mg, 85%).

**Rf** = 0.29 (EtOAc/PE 3:7)



$\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2$   
 $M = 255.28 \text{ g}\cdot\text{mol}^{-1}$

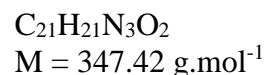
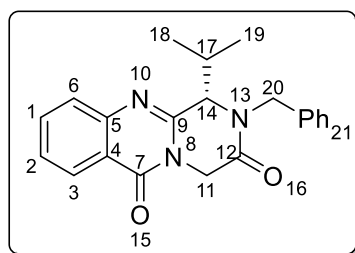
**$^1\text{H}$  NMR**  $\delta$  =  $\delta$  8.29 (m, 1H; H-3), 7.85-7.68 (m, 2H; H-1, H-6), 7.62 (s, 1H; H-13), 7.59-7.45 (m, 1H; H-2), 4.75 (s, 2H; H-11), 2.40 ppm (s, 3H; H-18/19), 2.00 ppm (s, 3H; H-18/19).

### (S)-2-benzyl-1-isopropyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazoline-3,6(4H)-dione (**II-96**)

To a flask containing **II-69** (20 mg, 1.0 equiv.) in THF/DMF (1:1, 0.8mL) was added NaH (3 mg, 1.0 equiv.) and TBAI (29 mg, 1.0 equiv.) at 0°C. After stirring for 10 min, BnBr (65  $\mu\text{L}$ , 93 mg, 7 equiv.) was added and the reaction kept stirring for 16 h at rt. The reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  solution and extracted with EtOAc. After drying over  $\text{MgSO}_4$  and evaporated in vacuo, the crude mixture was purified by flash chromatography (with a gradient solvent system EtOAc/cyclohexane = 1: 9 to 2:3) to afford the title compound as yellow oil (19 mg, 69% yield).

**Rf** = 0.29 (EtOAc/cyclohexane = 3:7)





**$^1\text{H}$  NMR**  
 (400 MHz,  $\text{CDCl}_3$ )

$\delta = 8.28$  (dd,  $J = 8.0, 1.2$  Hz, 1H; H-3),  $7.75$  (ddd,  $J = 8.5, 7.2, 1.5$  Hz, 1H; H-1),  $7.61$  (d,  $J = 7.8$  Hz, 1H; H-6),  $7.52$ - $7.46$  (m, 1H; H-2),  $7.33$ - $7.25$  (m, 3H;  $\text{H}_{\text{Ph}}$ ),  $7.24$ - $7.19$  (m, 2H;  $\text{H}_{\text{Ph}}$ ),  $5.56$  (d,  $J = 15.0$  Hz, 1H; H-20a),  $5.29$  (d,  $J = 18.5$  Hz, 1H; H-11a),  $4.33$  (d,  $J = 18.5$  Hz, 1H; H-11b),  $4.23$  (d,  $J = 7.1$  Hz, 1H; H-14),  $4.12$  (d,  $J = 14.3$ , 1H; H-20b),  $2.32$  (dq,  $J = 13.7, 6.9$  Hz, 1H; H-17),  $1.17$  (d,  $J = 6.8$  Hz, 3H; H-18/19),  $0.98$  ppm (d,  $J = 6.8$  Hz, 3H; H-18/19).

**$^{13}\text{C}$  NMR**  
 (101 MHz,  $\text{CDCl}_3$ )

$\delta = 164.56, 160.69, 149.76, 147.06, 135.55, 134.86, 129.14, 128.25, 128.21, 127.48, 127.41, 126.89, 120.14, 66.23, 49.75, 45.47, 33.94, 20.32, 19.09$  ppm.

**IR** (neat):

$\tilde{\nu} = 2968, 2927, 1673, 1607, 1470, 1445, 1392, 1168, 1077, 1057, 775, 696 \text{ cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ):

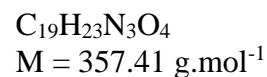
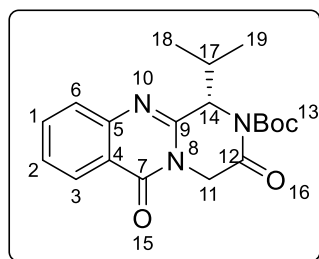
Calcd. for  $C_{21}H_{21}N_3O_2^+$ : 347.1634

Found 347.1637.

**tert-butyl (S)-1-isopropyl-3,6-dioxo-1,3,4,6-tetrahydro-2H-pyrazino[2,1-b]quinazoline-2-carboxylate (II-97)**

To a flask containing **II-69** (110 mg, 1 equiv.),  $\text{Boc}_2\text{O}$  (118 mg, 1.15 equiv.) and DMAP (12 mg, 0.2 equiv.) in THF (4.3 mL, 0.1 M) was added  $\text{Et}_3\text{N}$  at rt and the reaction was monitored by TLC. After 1h, the solvent was directly evaporated and purified by flash chromatography (with  $\text{EtOAc}/\text{cyclohexane} = 1:9$ ) to afford the title compound as white crystalline powder (186 mg 68% yield).

**Rf** = 0.38 ( $\text{EtOAc}/\text{cyclohexane} = 3:7$ )



---

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta = 8.27$ (dd, $J = 8.0, 0.8$ Hz, 1H; H-3), $7.83$ - $7.75$ (m, 1H; H-1), $7.71$ (d, $J = 7.8$ Hz, 1H; H-6), $7.56$ - $7.47$ (m, 1H; H-2), $5.43$ (d, $J = 19.3$ Hz, 1H; H-11a), $5.13$ (d, $J = 10.1$ Hz, 1H; H-14), $4.28$ (d, $J = 19.3$ Hz, 1H; H-11b), $2.14$ (m, 1H; H-17), $1.56$ (s, 9H; H <sub>Boc</sub> ), $1.14$ (d, $J = 6.7$ Hz, 3H; H-18/19), $1.05$ ppm (d, $J = 6.7$ Hz, 3H; H-18/19).	
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta = 164.2, 160.7, 149.9, 146.8, 135.0, 131.1, 127.7, 127.0, 124.8, 120.2, 85.1, 77.5, 77.2, 76.8, 64.5, 46.3, 33.2, 28.1, 19.9, 19.5$ ppm.	
<b>IR</b> (neat):	$\tilde{\nu} = 2972, 1779, 1732, 1684, 1609, 1475, 1369, 1290, 1252, 1152, 774$ cm <sup>-1</sup> .	
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd. for C <sub>19</sub> H <sub>23</sub> N <sub>3</sub> O <sub>4</sub> <sup>+</sup> : 357.1689	Found 357.1694
<b><math>[\alpha]_D^{25}</math></b>	= + 21 (c = 0.10, CHCl <sub>3</sub> )	
<b>Mp</b>	= 69 °C	

### 1.3. Chapter III: Tandem Cyclopropanation/Oxa-Cope Rearrangement Studies

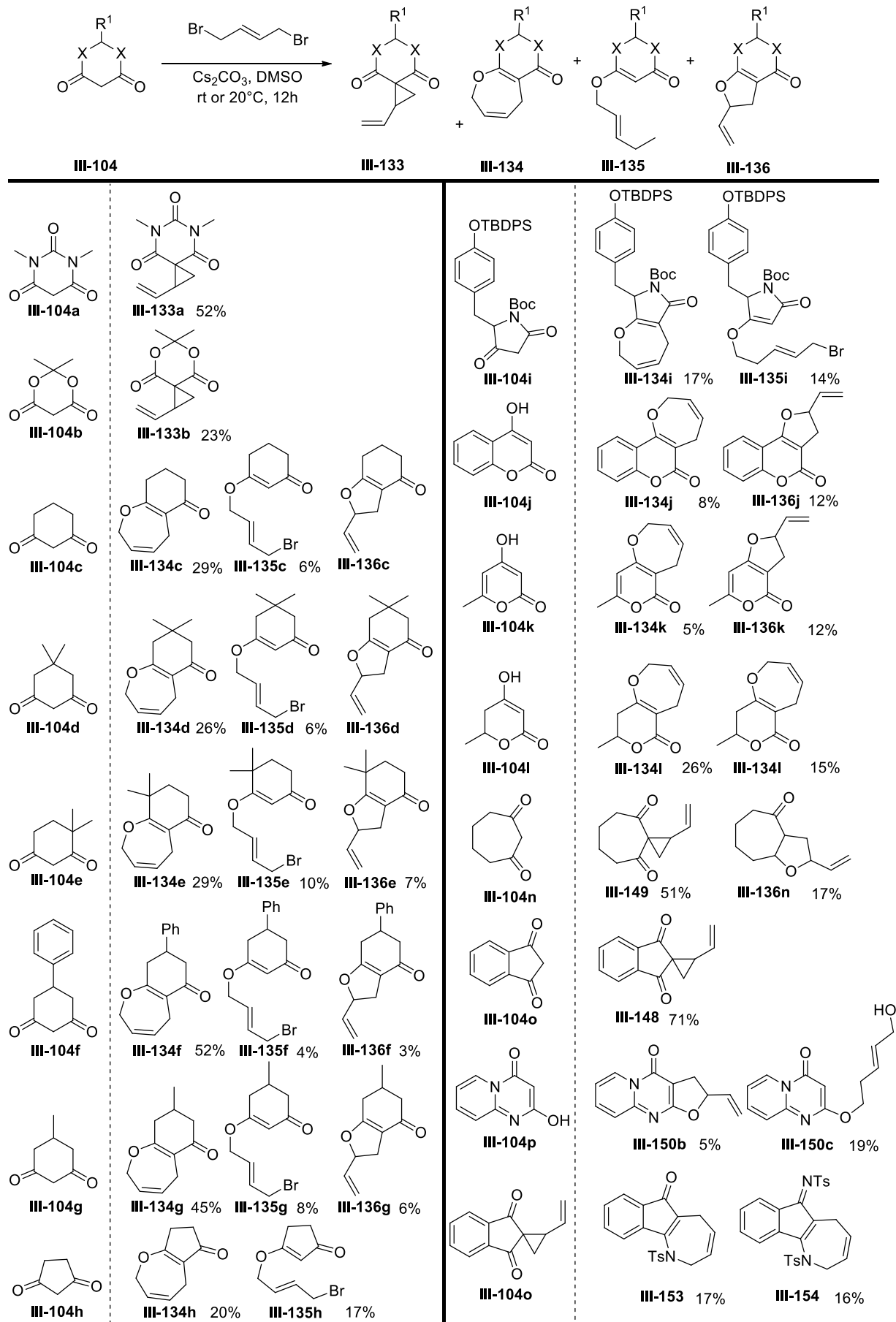
#### General procedure A

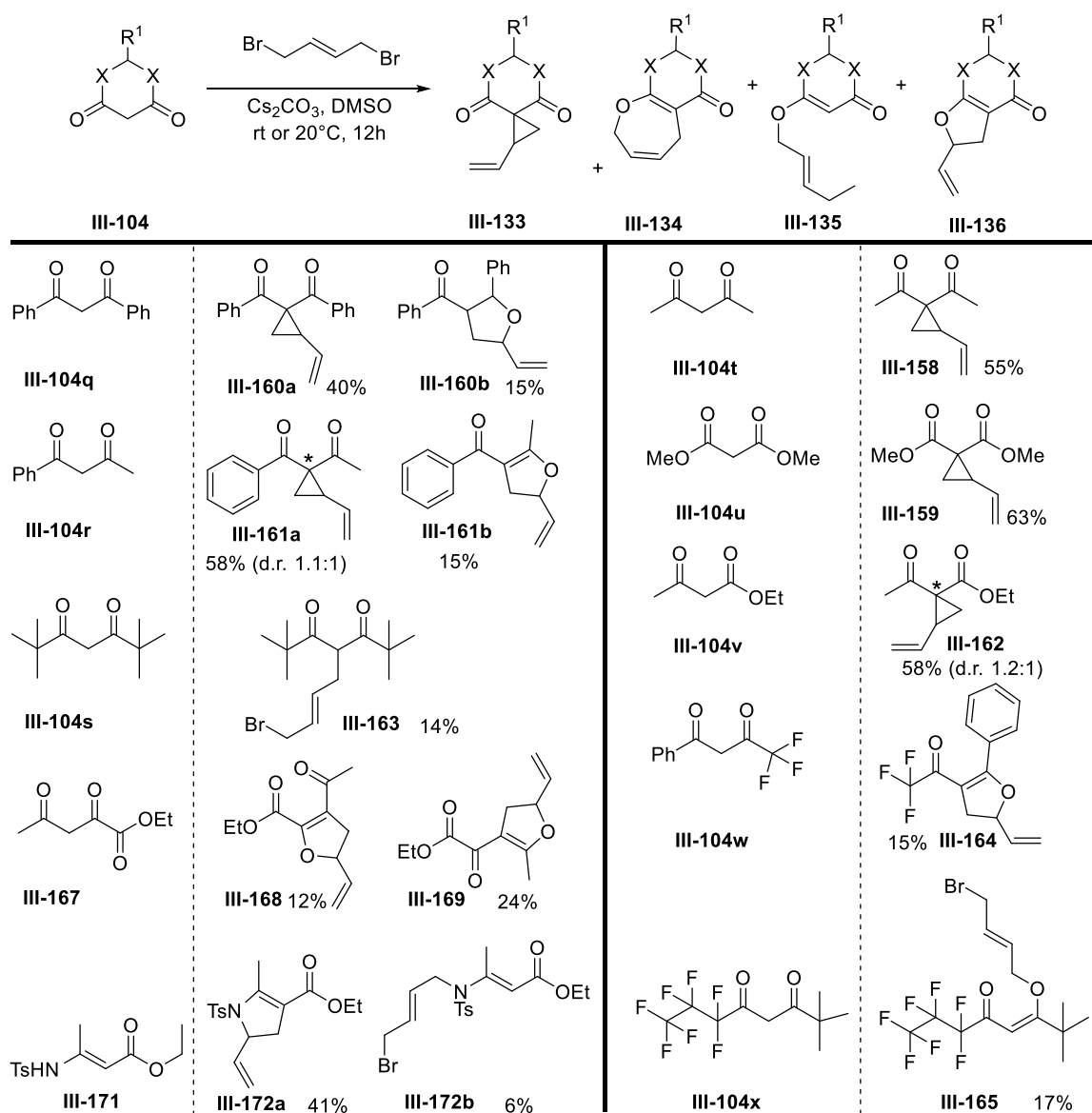
Cs<sub>2</sub>CO<sub>3</sub> or K<sub>2</sub>CO<sub>3</sub> (1.1 equiv.) was added to a solution of diketone (1.0 equiv.) in DMSO or DMF at 0.1M and stirred for 20 min, then a solution of dibromobutene (1.1 equiv.) in DMSO or DMF corresponding was added to the mixture at 20°C, kept stirring at 20°C for another 12h. The reaction was diluted with diethyl ether and quenched with water at 0°C. The organic layer was washed 3 times with brine and then the aqueous phases were extracted 3 times with diethyl ether. The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure at room temperature. The residue was then purified by flash chromatography on silica gel.

#### General procedure B

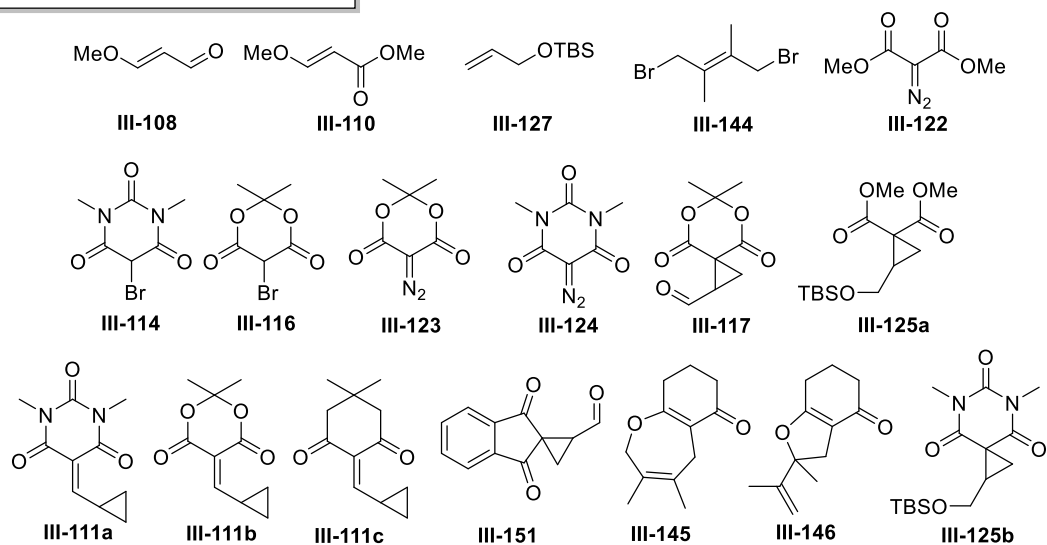
Cs<sub>2</sub>CO<sub>3</sub> (1.1 equiv.) was added to a solution of diketone (1.0 equiv.) in DMSO at 0.1M and stirred for 20min. Then a solution of dibromobutene in DMSO (1.1 equiv.) was added to the mixture at room temperature. The reaction mixture was kept stirring at 80°C for another 3h. The reaction was diluted with diethyl ether and quenched with water at rt. The organic layer was washed 3 times with brine and then the aqueous phases were extracted 3 times with diethyl ether. The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure at 40°C. The residue was then purified by flash chromatography on silica gel.

A summary of cited molecules in **Chapter III** is resumed in following pages, all the yields presented here are obtained at room temperature. Some cyclic products, involved in the total synthesis of radulanins, will be detailed in **Chapter IV**.





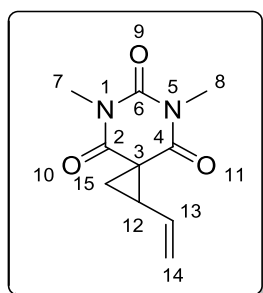
Other products involved in Chapter III



**5,7-dimethyl-1-vinyl-5,7-diazaspiro[2.5]octane-4,6,8-trione (III-133a)**

According to general procedure A, the reaction was carried out with 1,3 dimethyl barbituric acid (500 mg),  $K_2CO_3$  (1.3 g) and trans-1,4-dibromo-2-butene (685 mg) in DMF (32 mL), flash chromatography on silica gel (diethylether/pentane= 1:4) gave the following product as a light yellow solid (yield 347 mg, 52% yield):

**Rf** = 0.25 (Et<sub>2</sub>O/pentane 1:4)



$C_{10}H_{12}N_2O_3$   
**M** = 208.22 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 5.93 (ddd, *J* = 17.2, 10.2, 9.4 Hz, 1H; H-13), 5.39 (dd, *J* = 17.2, 0.9 Hz, 1H; H-14a), 5.26 (dd, *J* = 10.3, 1.2 Hz, 1H; H-14b), 3.32 (s, 3H; H-7/8), 3.31 (s, 3H; H-7/8), 2.84 (q, *J* = 9.1 Hz, 1H; H-12), 2.29 (dd, *J* = 9.2, 3.8 Hz, 1H; H-15), 2.17 ppm (dd, *J* = 8.7, 3.8 Hz, 1H; H-15).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 168.2 (C-2/4), 166.4 (C-2/4), 152.0 (C-6), 132.0 (C-13), 121.3 (C-14), 45.2 (C-3), 35.4 (C-12), 29.0 (C-7/8), 28.8 (7/8), 27.5 (C-15) ppm.

**IR** (neat):  $\tilde{\nu}$  = 2951, 2921, 2851, 1737, 1462, 1379, 1250, 1066 cm<sup>-1</sup>.

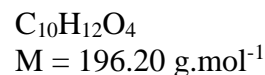
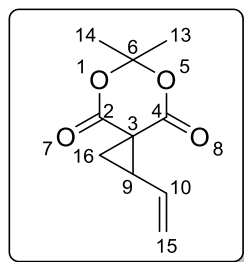
**HRMS** (EI<sup>+</sup>): Calcd. for  $C_{10}H_{12}N_2O_3^+$ : 208.0848 Found 208.0838.

**Mp** = 108-109°C

**6,6-dimethyl-1-vinyl-5,7-dioxaspiro[2.5]octane-4,8-dione (III-133b)**

According to general procedure A, the reaction was carried out with 2,2-dimethyl-[1,3]dioxane-4,6-dione (50 mg),  $K_2CO_3$  (145 mg) and trans-1,4-dibromo-2-butene (75 mg) in DMF (3.5 mL). Flash chromatography on silica gel (diethylether/pentane= 1:4) gave the following product as a light yellow oil (yield 16 mg, 23% yield):

**Rf** = 0.3 (pentane/Et<sub>2</sub>O 4:1)



**$^1\text{H NMR}$**   $\delta = 5.86 - 5.67$  (m, 1H; H-10), 5.45 (dd,  $J = 17.1, 0.9$  Hz, 1H; H-15a), 5.33 (dd,  $J = 10.2, 1.0$  Hz, 1H; H-15b), 2.76 (dd,  $J = 18.1, 9.1$  Hz, 1H; H-9), 2.35 (dd,  $J = 9.1, 4.5$  Hz, 1H; H-16a), 2.21 (dd,  $J = 8.6, 4.5$  Hz, 1H; H-16b), 1.76 (d,  $J = 0.5$  Hz, 3H; H-13/14), 1.71 ppm (d,  $J = 0.5$  Hz, 3H; H-13/14).

**$^{13}\text{C NMR}$**   $\delta = 167.7, 165.4, 131.5, 122.4, 105.3, 43.2, 31.7, 27.8, 27.7, 24.8$  ppm.

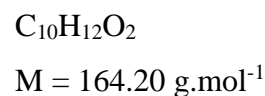
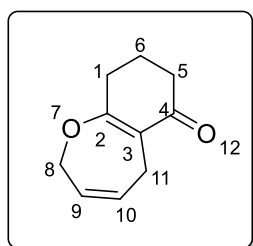
**IR** (neat):  $\tilde{\nu} = 3005, 1742, 1326, 1279, 1261, 1197, 967, 765, 750 \text{ cm}^{-1}$

All analytical data matched those found in the literature.<sup>18</sup>

### 5,7,8,9-tetrahydrobenzo[b]oxepin-6(2H)-one (III-134c)

According to general procedure A, the reaction was carried out with 1,3-cyclohexanedione (224 mg, 2 mmol),  $\text{Cs}_2\text{CO}_3$  (720 mg, 2.2 mmol) and trans-1,4-dibromo-2-butene (470 mg, 2.2 mmol) in 20 mL DMSO at 20°C, flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:6 to 1:1) gave product **III-134c** as a light yellow oil (95 mg, 0.58 mmol, 29% yield) and product **III-135c** as brown oil (29 mg, 0.12 mmol, 6% yield).

**Rf** = 0.4 (ethyl acetate/petroleum ether 2/8)



**$^1\text{H NMR}$**   $\delta = 6.26$  (dt,  $J = 9.7, 6.2$  Hz, 1H; H-10), 6.00 (dtt,  $J = 9.7, 6.6, 1.2$  Hz, 1H; H-9), 4.69 (d,  $J = 6.7$  Hz, 2H; H-8), 3.27 (dd,  $J = 6.2, 1.1$  Hz, 2H; H-11), 2.34 (dd,  $J = m$ , 4H; H-1 H-5), 1.94-1.78 ppm (m, 2H; H-6).

<sup>18</sup> B. M. Trost, P. J. Morris, S. J. Sprague, *J. Am. Chem. Soc.* **2012**, *134*, 17823–17831.

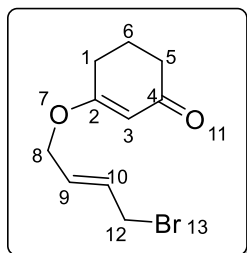
**$^{13}\text{C}$  NMR**  $\delta = 198.8$  (C-4),  $174.6$  (C-2),  $137.9$  (C-10),  $126.4$  (C-9),  $113.0$  (C-3),  
(101 MHz,  $\text{CDCl}_3$ )  $65.9$  (C-8),  $37.2$  (C-1),  $31.5$  (C-5),  $22.1$  (C-11),  $20.5$  ppm (C-6).

**IR** (neat):  $\tilde{\nu} = 3372, 2943, 1640, 1590, 1393, 1287, 1254, 1188, 1071, 1009$   $\text{cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{10}\text{H}_{12}\text{O}_2^+$ : 165.0832 Found 165.0830.

### (E)-3-((4-bromobut-2-en-1-yl)oxy)cyclohex-2-en-1-one (III-135c)

**Rf** = 0.21 (ethyl acetate/petroleum ether 5/5)



$\text{C}_{10}\text{H}_{13}\text{O}_2\text{Br}$

$M = 245.12$   $\text{g}\cdot\text{mol}^{-1}$

**$^1\text{H}$  NMR**  $\delta = 5.97$  (m, 2H, H-9; H-10),  $5.34$  (s, 1H; H-3),  $4.40$  (d,  $J = 5.3$  Hz, 2H; H-8),  $3.97$  (d,  $J = 7.2$  Hz, 2H; H-12),  $2.44$  (t,  $J = 6.3$  Hz, 2H; H-5),  $2.40$ - $2.32$  (t,  $J = 6.6$  Hz, 2H; H-1),  $2.11$ - $1.93$  ppm (m, 2H; H-6).

**$^{13}\text{C}$  NMR**  $\delta = 177.3$  (C-4),  $175.0$  (C-2),  $136.4$  (C-3),  $130.6$  (C-10),  $128.1$  (C-9),  
(101 MHz,  $\text{CDCl}_3$ )  $67.6$  (C-8),  $37.0$  (C-5),  $31.2$  (C-12),  $29.9$  (C-1),  $21.3$  ppm (C-6).

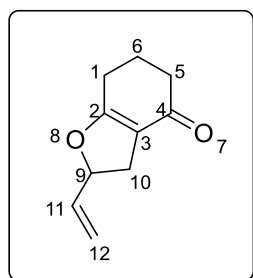
**IR** (neat):  $\tilde{\nu} = 2923, 2855, 1723, 1597, 1402, 1230, 1180, 1136, 925, 835, 734$   $\text{cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{10}\text{H}_{13}\text{O}_2^+$  (-Br): 165.0911 Found 165.0913.

### 2-vinyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (III-136c)

According to general procedure B, the reaction was carried out with 1,3-cyclohexanedione (22.4 mg),  $\text{Cs}_2\text{CO}_3$  (72 mg) and trans-1,4-dibromo-2-butene (47 mg) in DMSO at  $80^\circ\text{C}$ . Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 3:7 to 2:3) gave product **III-136c** as a yellow-brown oil (20 mg, 63% yield).

**Rf** = 0.18 (ethyl acetate/petroleum ether 3/7)



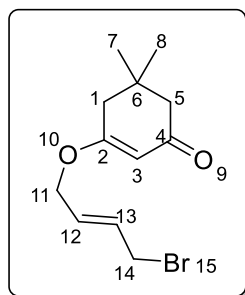
$\text{C}_{10}\text{H}_{12}\text{O}_2$

$M = 164.20$   $\text{g}\cdot\text{mol}^{-1}$





Rf = 0.25 (ethyl acetate/petroleum ether 5/5)



$C_{12}H_{17}O_2Br$   
 $M = 273.17 \text{ g}\cdot\text{mol}^{-1}$

**$^1H$  NMR** (400 MHz,  $CDCl_3$ )  $\delta = 6.03$  (dt,  $J = 14.8, 7.3$  Hz, 1H; H-13),  $5.90$  (dt,  $J = 15.3, 5.4$  Hz, 1H; H-12),  $5.33$  (s, 1H; H-3),  $4.39$  (d,  $J = 5.3$  Hz, 2H; H-11),  $3.97$  (d,  $J = 7.3$  Hz, 2H; H-14),  $2.30$  (s, 2H; H-5),  $2.21$  (s, 2H; H-1),  $1.07$  ppm (s, 6H; 2 $CH_3$ ).

**$^{13}C$  NMR** (101 MHz,  $CDCl_3$ )  $\delta = 199.6$  (C-4),  $175.5$  (C-2),  $130.5$  (C-3),  $128.2$  (C-12),  $102.2$  (C-13),  $67.6$  (C-11),  $50.9$  (C-5),  $42.9$  (C-14),  $32.7$  (C-1),  $31.2$  (C-6),  $28.4$  ppm (C-7 and C-8).

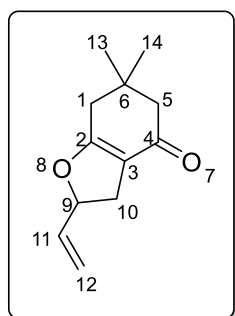
**IR** (neat):  $\tilde{\nu} = 2959, 2870, 1651, 1607, 1464, 1362, 1219, 1146, 968, 824 \text{ cm}^{-1}$ .

**HRMS** (EI<sup>+</sup>): Calcd. for  $C_{12}H_{17}O_2Br^+$ : 273.0485 Found 273.0490.

### 6,6-dimethyl-2-vinyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (**III-136d**)

According to general procedure B, the reaction was carried out with 5,5-dimethyl-1,3-cyclohexanedione (28 mg),  $Cs_2CO_3$  (72 mg) and trans-1,4-dibromo-2-butene (47 mg) in DMSO at  $80^\circ C$ . Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:6 to 1:3) gave the product **III-136d** as a yellow oil (18 mg, 49% yield).

Rf = 0.31 (ethyl acetate/petroleum ether 3/7)



$C_{12}H_{16}O_2$   
 $M = 192.26 \text{ g}\cdot\text{mol}^{-1}$

**$^1H$  NMR** (400 MHz,  $CDCl_3$ )  $\delta = 5.92$  (ddd,  $J = 17.1, 10.3, 6.7$  Hz, 1H; H-11),  $5.31$  (dt,  $J = 17.1, 1.1$  Hz, 1H; H-12a),  $5.23$  (dt,  $J = 10.3$  Hz, 1H; H-12b),  $5.21$  (m, 1H; H-9),  $3.00$  (ddd,  $J = 10.3, 7.9, 6.0$  Hz, 1H; H-10a),  $2.62$  (ddd,  $J = 14.4, 8.1, 4.7$  Hz, 1H; H-10b),  $2.29$  (t,  $J = 1.7$  Hz, 2H; H-1),  $2.22$  (s, 2H; H-5),  $1.10$  (s, 3H;  $CH_3$ ),  $1.09$  ppm (s, 3H;  $CH_3$ ).

**<sup>13</sup>C NMR**  $\delta = 195.0$  (C-4), 176.2 (C-2), 136.5 (C-11), 117.4 (C-12), 111.5 (C-3), 86.0 (C-9), 51.0 (C-5), 37.9 (C-1), 34.2 (C-6), 31.7 (C10), 28.9 (C-13/C-14), 28.8 ppm (C-13/C-14).

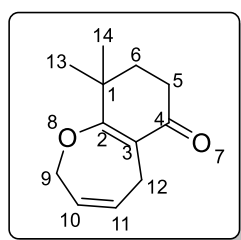
**IR** (neat):  $\tilde{\nu} = 2928, 2870, 1631, 1401, 1218, 1166, 1042, 926, 831$  cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>12</sub>H<sub>16</sub>O<sub>2</sub><sup>+</sup>: 192.1145 Found 192.1149.

### 9,9-dimethyl-5,7,8,9-tetrahydrobenzo[b]oxepin-6(2H)-one (III-134e)

According to general procedure A, the reaction was carried out with 4,4-dimethyl-1,3-cyclohexanedione (300 mg), Cs<sub>2</sub>CO<sub>3</sub> (847 mg) and trans-1,4- dibromo-2-butene (504 mg) in DMSO at 20°C. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:4 to 1:1) gave product **III-134e** as a light yellow oil (117 mg, 29% yield), along with product **III-135e** as brown oil (57 mg, 10% yield) and product **III-136e** as yellow oil (28 mg, 7% yield).

**R<sub>f</sub>** = 0.35 (ethyl acetate/petroleum ether 1/4).



C<sub>12</sub>H<sub>16</sub>O<sub>2</sub>  
M = 192.26 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR**  $\delta = 6.17$  (dt, J = 9.7, 6.2 Hz, 1H; H-11), 5.93 (dtt, J = 9.0, 6.6, 1.2 Hz, 1H; H-10), 4.62 (d, J = 6.6 Hz, 2H; H-9), 3.19 (dd, J = 6.2, 1.3 Hz, 2H; H-12), 2.28 (tt, J = 6.5, 1.5 Hz, 2H; H-5), 1.65 (t, J = 6.4 Hz, 2H; H-6), 1.02 ppm (s, 6H; 2CH<sub>3</sub>).

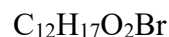
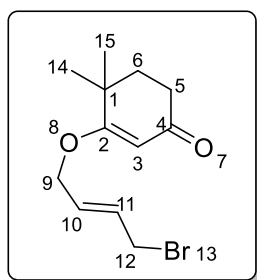
**<sup>13</sup>C NMR**  $\delta = 203.3$  (C-4), 172.4 (C-2), 137.5 (C-10), 126.3 (C-11), 111.4 (C-3), 65.6 (C-9), 39.7 (C-1), 33.9 (C-6), 27.7 (C-5), 25.1 (C-13 and C-14), 22.2 ppm (C-12).

**IR** (neat):  $\tilde{\nu} = 2926, 1642, 1598, 1453, 1376, 1302, 1224, 1198, 1002, 939, 844$  cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>12</sub>H<sub>16</sub>O<sub>2</sub><sup>+</sup>: 192.1145 Found 192.1148.

### (E)-3-((4-bromobut-2-en-1-yl)oxy)-4,4-dimethylcyclohex-2-en-1-one (III-135e)

**R<sub>f</sub>** = 0.25 (ethyl acetate/petroleum ether 5/5)



$$M = 273.17\text{g}\cdot\text{mol}^{-1}$$

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta = 6.09\text{--}5.98$  (m, 1H; H-11),  $5.96\text{--}5.86$  (m, 1H; H-10),  $5.24$  (s, 1H; H-3),  $4.38$  (d,  $J = 5.0$  Hz, 2H; H-9),  $3.97$  (dd,  $J = 7.3, 0.6$  Hz, 2H; H-12),  $2.45$  (t,  $J = 6.4$  Hz, 2H; H-5),  $1.81$  (t,  $J = 6.4$  Hz, 2H; H-6),  $1.11$  ppm (s, 6H; 2 $\text{CH}_3$ ).

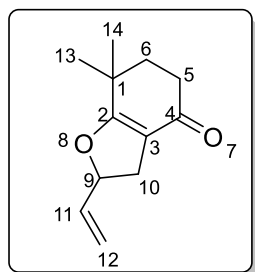
**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta = 204.5$  (C-4),  $175.1$  (C-2),  $130.5$  (C-11),  $128.3$  (C-10),  $101.7$  (C-3),  $67.6$  (C-9),  $40.6$  (C-1),  $35.1$  (C-5),  $31.3$  (C-6),  $26.3$  (C-12),  $24.6$  ppm (C-14 and C-15).

**IR** (neat):  $\tilde{\nu} = 2961, 2924, 2866, 1651, 1609, 1453, 1364, 1318, 1238, 1188, 967, 841\text{cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{12}\text{H}_{17}\text{O}_2$  ( $-\text{Br}$ ) $^+$ : 193.1229 Found 193.1224.

### 7,7-dimethyl-2-vinyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (III-136e)

**Rf** = 0.31 (ethyl acetate/petroleum ether 3/7).



$$M = 192.26\text{g}\cdot\text{mol}^{-1}$$

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta = 5.89$  (ddd,  $J = 17.0, 10.4, 6.4$  Hz, 1H; H-11),  $5.31$  (dt,  $J = 17.1$  Hz,  $1.1$  Hz, 1H; H-12a),  $5.22$  (dt,  $J = 10.4$  Hz, 1H, 1H; H-12b),  $5.18$  (m, 1H; H-9),  $3.00$  (dd,  $J = 14.4, 10.4$  Hz, 1H; H-10a),  $2.59$  (dd,  $J = 14.4, 7.2$  Hz, 1H; H-10b),  $2.40$  (t,  $J = 6.6$  Hz, 2H; H-5),  $1.84$  (t,  $J = 6.6$  Hz, 2H; H-6),  $1.23$  ppm (s, 6H; 2 $\text{CH}_3$ ).

**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta = 195.4$  (C-4),  $182.8$  (C-2),  $136.6$  (C-11),  $116.7$  (C-12),  $110.6$  (C-3),  $85.3$  (C-9),  $37.2$  (C-1),  $34.5$  (C-6),  $33.1$  (C-5),  $33.2$  (C-10),  $25.1$  ppm (C-13 and C-14).

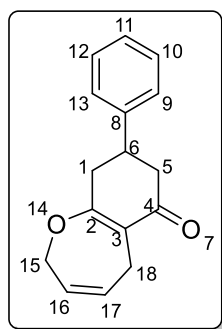
**IR** (neat):  $\tilde{\nu} = 3691, 3606, 2970, 2934, 2869, 1619, 1404, 1346, 1246, 1200, 1163, 1067\text{cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{12}\text{H}_{16}\text{O}_2$  $^+$ : 192.1145 Found 192.1148.

**8-phenyl-5,7,8,9-tetrahydrobenzo[b]oxepin-6(2H)-one (III-134f)**

According to general procedure A, the reaction was carried out with 5-phenyl-1,3-cyclohexanedione (200 mg), Cs<sub>2</sub>CO<sub>3</sub> (345 mg) and trans-1,4-dibromo-2-butene (272 mg) in DMSO at 20°C. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:4 to 1:1) gave the product **III-134f** as a white solid (yield 130 mg, 51%) and product **III-135f** as a yellow oil (12.5 mg, 4% yield).

**Rf** = 0.3 (ethyl acetate/petroleum ether 1/4)



C<sub>16</sub>H<sub>16</sub>O<sub>2</sub>  
M = 240.30 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR**  
(400 MHz, CDCl<sub>3</sub>)

$\delta$  = 7.32-7.23 (m, 2H; H-9 and H-13), 7.21-7.11 (m, 3H; H-10, H-11 and H-12), 6.23 (dt, J = 9.7, 6.3 Hz, 1H; H-17), 6.05-5.89 (m, 1H; H-16), 4.82 (dd, J = 12.6, 6.7 Hz, 1H; H-15a), 4.51 (dd, J = 12.7, 6.7 Hz, 1H; H-15b), 3.25 (d, J = 6.0 Hz, 2H; H-18), 3.23-3.13 (m, 1H; H-6), 2.63 (ddd, J = 16.2, 4.1, 1.8 Hz, 1H; H-5a), 2.59-2.41 ppm (m, 3H; H-5b, H-1a and H-1b).

**<sup>13</sup>C NMR**  
(101 MHz, CDCl<sub>3</sub>)

$\delta$  = 197.9 (C-4), 173.7 (C-2), 142.9 (C-8), 138.0 (C-17), 128.9 (C-9 and C-13), 127.1 (C-10 and C-12), 126.8 (C-11), 126.5 (C-16), 113.0 (C-3), 66.0 (C-15), 44.0 (C-5), 38.9 (C-1), 38.4 (C-6), 22.0 ppm (C-18).

**IR** (neat):

$\tilde{\nu}$  = 3031, 2884, 1644, 1598, 1379, 1282, 1258, 1211, 1038, 975, 955, 912 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>):

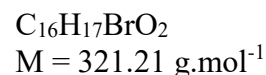
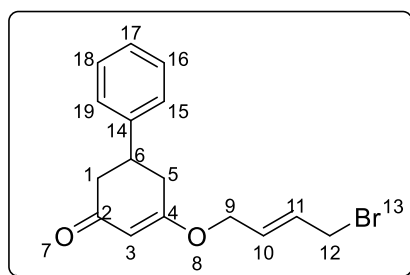
Calcd. for C<sub>16</sub>H<sub>16</sub>O<sub>2</sub><sup>+</sup>: 240.1145

Found 240.1143.

**Mp** = 89-91°C

**(E)-5-((4-bromobut-2-en-1-yl)oxy)-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (III-135f)**

**Rf** = 0.25 (ethyl acetate/petroleum ether 5/5)



**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.40\text{--}7.32$  (m, 2H; H-15 and H-19),  $7.30\text{--}7.21$  (m, 3H; H-16, H-17 and H-18),  $6.04$  (ddd,  $J = 8.6, 7.3, 6.1$  Hz, 1H; H-11),  $5.97\text{--}5.86$  (m, 1H; H-10),  $5.44$  (s, 1H; H-3),  $4.44$  (dd,  $J = 4.4, 2.3$  Hz, 2H; H-9),  $3.97$  (dd,  $J = 7.3, 0.6$  Hz, 2H; H-12),  $3.48\text{--}3.26$  (m, 1H; H-6),  $2.71\text{--}2.50$  ppm (m, H-4, H-1 and H-5).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta = 198.8$  (C-2),  $176.3$  (C-4),  $142.7$  (C-14),  $130.7$  (C-11),  $129.0$  (C-15 and C-19),  $128.0$  (C-16 and C-18),  $127.2$  (C-10),  $126.8$  (C-17),  $103.2$  (C-3),  $67.9$  (C-9),  $44.0$  (C-1),  $39.5$  (C-6),  $36.7$  (C-5),  $31.2$  ppm (C-12).

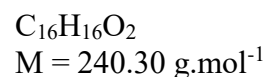
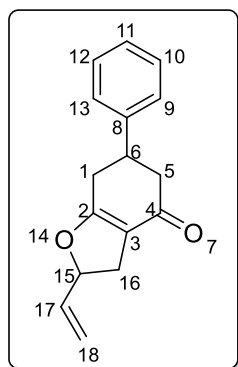
**IR** (neat):  $\tilde{\nu} = 2923, 1649, 1600, 1351, 1204, 1141, 969, 824, 761, 700, 585, 496$   $\text{cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{16}\text{H}_{17}\text{O}_2^+(-\text{Br})$ : 241.1229 Found 241.1224

### 6-phenyl-2-vinyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (III-136f)

According to general procedure B, the reaction was carried out with 5-phenyl-1,3-cyclohexanedione (37 mg),  $\text{Cs}_2\text{CO}_3$  (72 mg) and trans-1,4-dibromo-2-butene (47 mg) in DMSO at  $80^\circ\text{C}$ . Flash chromatography on silica gel (ethyl acetate/petroleum ether 3/7) gave the unseparated diastereoisomers **III-136f** as a yellow oil (38 mg, 0.72 mmol, 79% yield).

**R<sub>f</sub>** = 0.31 (ethyl acetate/petroleum ether 3/7)

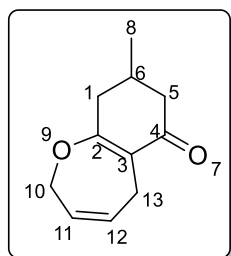


<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta$ = 7.40-7.32 (m, 2H; H-9 and H-13), 7.30-7.22 (m, 3H; H-10, H-11 and H-12), 6.04-5.89 (m, 1H; H-17), 5.35 (dddd, $J$ = 12.6, 3.9, 2.5, 1.1 Hz, 1H; H-18a), 5.30-5.20 (m, 2H; H-18b and H-15), 3.53-3.37 (m, 1H; H6), 3.15-3.00 (m, 1H; H-16a), 2.72-2.59 ppm (m, 5H; H-1, H-16b and H-15).	
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta$ = 194.0 (C-4), 176.4 (C-2), 142.7 (C-8), 136.3/136.2 (C-17), 128.9 (C-9 and C-13), 127.2 (C-11), 126.8 (C-10 and C-12), 117.8/117.5 (C-18), 86.4/86.2 (C-15), 44.0/43.9 (C-5), 40.4 (C-6), 31.8 (C-1) 31.6 ppm (C-16).	
<b>IR</b> (neat):	$\tilde{\nu}$ = 3028, 2933, 1624, 1398, 1245, 1203, 1106, 1043, 1005, 927, 824 cm <sup>-1</sup> .	
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd. for C <sub>16</sub> H <sub>16</sub> O <sub>2</sub> <sup>+</sup> : 240.1145	Found 240.1140.

### 8-methyl-5,7,8,9-tetrahydrobenzo[b]oxepin-6(2H)-one (**III-134g**)

According to general procedure A, the reaction was carried out with 5-methyl-1,3-cyclohexanedione (200 mg), Cs<sub>2</sub>CO<sub>3</sub> (518 mg) and trans-1,4-dibromo- 2-butene (406 mg) in DMSO at 20°C. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:4 to 2:3) gave the product **III-134g** as a light yellow oil (120 mg, 45% yield), along with product **III-135g** as a brown oil (31 mg, 8% yield).

**Rf** = 0.37 (ethyl acetate/petroleum ether 1/4)



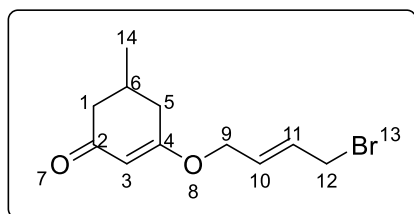
C<sub>11</sub>H<sub>14</sub>O<sub>2</sub>  
M = 178.23 g.mol<sup>-1</sup>

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta$ = 6.25 (dt, $J$ = 10.5, 6.2 Hz, 1H; H-12), 5.98 (dtd, $J$ = 9.1, 6.7, 0.9 Hz, 1H; H-11), 4.80 (dd, $J$ = 12.7, 6.7 Hz, 1H; H-10a), 4.55 (dd, $J$ = 12.7, 6.7 Hz, 1H; H-10b), 3.24 (d, $J$ = 6.1 Hz, 2H; H-13), 2.49–2.38 (m, 1H; H-5a), 2.36–2.25 (m, 1H; H-1a), 2.15–2.05 (m, 2H; H-6, H-1b), 2.00 (m, 2H; H-5b), 1.00 ppm (d, $J$ = 6.0 Hz, 3H; CH <sub>3</sub> ).	
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta$ = 198.8 (C-4), 174.1 (C-2), 137.9 (C-12), 126.4 (C-11), 112.8 (C-3), 65.8 (C-10), 45.4 (C-5), 39.6 (C-1), 27.9 (C-6), 21.9 (C-13), 20.9 ppm (C-8).	
<b>IR</b> (neat):	$\tilde{\nu}$ = 2955, 2874, 1644, 1597, 1376, 1284, 1212, 1052, 1035, 977, 914 cm <sup>-1</sup> .	

HRMS (EI<sup>+</sup>): Calcd. for C<sub>11</sub>H<sub>14</sub>O<sub>2</sub><sup>+</sup>: 178.0989 Found 178.0996.

**(E)-3-((4-bromobut-2-en-1-yl)oxy)-5-methylcyclohex-2-en-1-one (III-135g)**

R<sub>f</sub> = 0.25 (ethyl acetate/petroleum ether 5/5)



C<sub>11</sub>H<sub>15</sub>BrO<sub>2</sub>  
M = 259.14 g.mol<sup>-1</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 6.06-5.96 (m, 1H; H-11), 5.94-5.84 (m, 1H; H-10), 5.31 (d, J = 0.8 Hz, 1H; H-3), 4.37 (d, J = 5.4 Hz, 2H; H-9), 3.95 (dd, J = 7.3, 0.7 Hz, 2H; H-12), 2.47-2.41(m, 1H; H-5a) 2.41-2.37 (m, 1H; H-1a), 2.26-2.1 (m, 2H; H-6 and H-5b), 2.03 (m, 1H; H-1b), 1.06 ppm (d, J = 6.3 Hz, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 199.7 (C-2), 176.7 (C-4), 130.5 (C-11), 128.1 (C-10), 102.9 (C-3), 67.6 (C-9), 45.2 (C-1), 37.1 (C-5), 31.2 (C-12), 28.9 (C-6), 21.0 ppm (C-14).

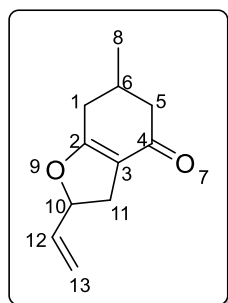
IR (neat):  $\tilde{\nu}$  = 2955, 2927, 2872, 1650, 1601, 1456, 1398, 1366, 1338, 1205, 1138, 995, 967, 936, 868, 822 cm<sup>-1</sup>.

HRMS (EI<sup>+</sup>): Calcd. for C<sub>11</sub>H<sub>15</sub>O<sub>2</sub><sup>+</sup>(-Br): 179.1072 Found 179.1067.

**6-methyl-2-vinyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one III-136g**

According to general procedure B, the reaction was carried out with 5-methyl-1,3-cyclohexanedione (25 mg), Cs<sub>2</sub>CO<sub>3</sub> (72 mg) and trans-1,4-dibromo-2-butene (47 mg) in DMSO at 80°C. Flash chromatography on silica gel (ethyl acetate/petroleum ether = 3:7) gave the following diastereoisomer products **III-136g** as a yellow oil (yield 25 mg, 71%).

R<sub>f</sub> = 0.31 (ethyl acetate/petroleum ether 3/7)



C<sub>11</sub>H<sub>14</sub>O<sub>2</sub>  
M = 178.23 g.mol<sup>-1</sup>

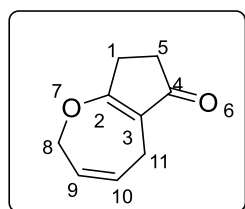


<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta = 5.91$ (dddd, $J = 17.1, 11.7, 10.3, 6.8$ Hz, 1H; H-12), $5.31$ (ddt, $J = 17.1, 6.0, 1.1$ Hz, 1H; H-13a), $5.26$ - $5.2$ (ddt, $J = 11.7, 6.0, 1.1$ Hz, 1H; H-13b), $5.2$ - $5.15$ (m, 1H; H-10) $3.06$ - $2.92$ (m, 1H; H-11a), $2.66$ - $2.53$ (m, 1H; H-11b), $2.53$ - $2.43$ (m, 1H; H-1a), $2.38$ (ddd, $J = 7.4, 4.8, 1.9$ Hz, 1H; H-5a), $2.34$ - $2.21$ (m, 1H; H-6), $2.18$ - $1.99$ (m, 2H; H-1b and H-5b), $1.10$ ppm (d, $J = 6.6$ Hz, 3H; CH <sub>3</sub> ).
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta = 195.2$ (C-4), $176.9$ (C-2), $136.4$ (C-12), $117.6/117.3$ (C-13), $112.7/112.6$ (C-3), $86.2/86.0$ (C-10), $45.1$ (C-5), $32.1$ (C-1), $31.8$ (C-11), $30.0$ (C-6), $21.2$ ppm (C-8).
<b>IR</b> (neat):	$\tilde{\nu} = 2928, 2873, 1628, 1400, 1209, 1136, 1049, 989, 928$ cm <sup>-1</sup> .
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd. for C <sub>11</sub> H <sub>14</sub> O <sub>2</sub> <sup>+</sup> : 178.0989                      Found 178.0999.

### 2,5,7,8-tetrahydro-6H-cyclopenta[b]oxepin-6-one (III-134h)

According to general procedure A, the reaction was carried out with 1,3-cyclopentanedione (200 mg, 2.04 mmol), Cs<sub>2</sub>CO<sub>3</sub> (717 mg, 2.2 mmol) and trans-1,4-dibromo-2-butene (450 mg, 2.1 mmol) in DMSO at 20°C. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:4 to 7:3) gave product **III-134h** as a light yellow solid (57 mg, 20% yield), along with product **III-135h** as a brown oil (80 mg, 17% yield).

**Rf** = 0.31 (ethyl acetate/petroleum ether 3/7)

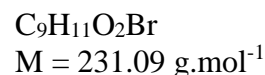
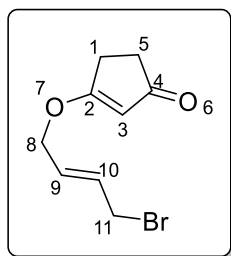


C<sub>9</sub>H<sub>10</sub>O<sub>2</sub>  
M = 150.18 g.mol<sup>-1</sup>

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta = 6.29$ (dt, $J = 10.1, 5.8$ Hz, 1H, H-10), $5.99$ (dtt, $J = 9.7, 7.1, 1.2$ Hz, 1H, H-9), $4.74$ (d, $J = 7.1$ Hz, 2H, H-8), $3.06$ (dd, $J = 5.8, 1.5$ Hz, 2H, H-11), $2.48$ (m, 2H, H-1), $2.39$ - $2.28$ ppm (m, 2H, H-5).
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta = 205.3$ (C-4), $185.7$ (C-2), $138.4$ (C-10), $125.6$ (C-9), $114.9$ (C-3), $66.8$ (C-8), $31.9$ (C-1), $27.9$ (C-5), $21.1$ ppm (C-11).
<b>IR</b> (neat):	$\tilde{\nu} = 2926, 1691, 1622, 1402, 1263, 1020, 928$ cm <sup>-1</sup> .
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd. for C <sub>9</sub> H <sub>10</sub> O <sub>2</sub> <sup>+</sup> : 150.0675                      Found 151.0676.

### (E)-3-((4-bromobut-2-en-1-yl)oxy)cyclopent-2-en-1-one (III-135h)

**Rf** = 0.15 (ethyl acetate/petroleum ether 5/5)



**$^1\text{H}$  NMR**  $\delta = 6.14 - 5.99$  (m, 1H; H-10), 5.91 (dt,  $J = 15.3, 5.6$  Hz, 1H; H-9), (400 MHz,  $\text{CDCl}_3$ ) 5.29 (s, 1H; H-3), 4.52 (d,  $J = 5.4$  Hz, 2H; H-8), 3.96 (d,  $J = 7.2$  Hz, 2H; H-11), 2.70 – 2.58 (m, 2H; H-1), 2.50 – 2.37 ppm (m, 2H; H-5).

**$^{13}\text{C}$  NMR**  $\delta = 205.9$  (C-4), 189.5 (C-2), 131.2 (C-3), 127.6 (C-10), 105.4 (C-9), (101 MHz,  $\text{CDCl}_3$ ) 70.8 (C-8), 34.2 (C-5), 30.9 (C-11), 28.6 ppm (C-1).

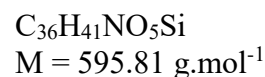
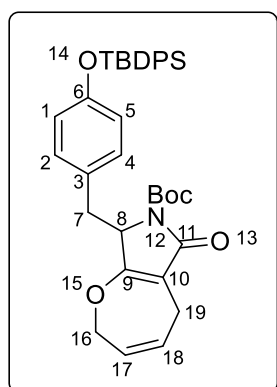
**IR** (neat):  $\tilde{\nu} = 3347, 2922, 1661, 1580, 1410, 1346, 1258, 1173, 1090, 971, 839$   $\text{cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_9\text{H}_{11}\text{O}_2\text{Br}^+$ : 231.0010 Found 231.0007.

### tert-butyl 8-(4-((tert-butyldiphenylsilyl) oxy) benzyl)-6-oxo-2,5,6,8-tetrahydro-7H-oxepino [2,3-c] pyrrole-7-carboxylate (**III-134i**)

According to general procedure A, the reaction was carried out with tetramic acid **III-104i**<sup>19</sup> (84 mg, 0.2 mmol),  $\text{Cs}_2\text{CO}_3$  (72 mg) and trans-1,4-dibromo-2-butene (47mg) in DMSO at rt. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:6 to 1:3) gave product **III-134i** as a light yellow solid (20 mg, 0.034 mmol, 17% yield) and product **III-135i** as a yellow oil (19 mg, 14% yield).

**Rf** = 0.3 (ethyl acetate/petroleum ether 2/8)

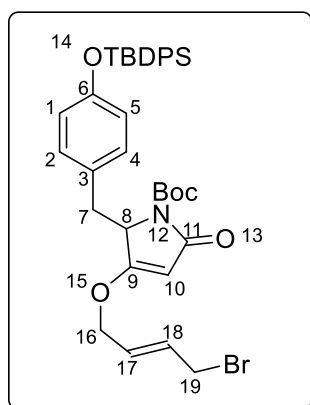


<sup>19</sup> This tetramic acid was available in the laboratory from previous synthetic works.

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	δ = 7.69 (m, 4H, H <sub>Ar</sub> -TBDPS), 7.47 – 7.29 (m, 6H, H <sub>Ar</sub> -TBDPS), 6.75 (d, J = 8.5 Hz, 2H, H-2 and H-4), 6.62 (d, J = 8.5 Hz, 4H, H-1 and H-5), 6.11 – 5.98 (m, 1H, H-18), 5.93 – 5.78 (m, 1H, H-17), 4.60 (dd, J = 12.6, 7.0 Hz, 1H, H-16a), 4.47 (dd, J = 12.6, 6.9 Hz, 1H, H-16b), 4.42 (m, 1H, H-8), 3.29 (dd, J = 14.0, 4.8 Hz, 1H, H-7a), 2.99 – 2.84 (m, 2H, H-7b and H-19a), 2.71 (dd, J = 19.8, 5.4 Hz, 1H, H-19b), 1.56 (s, 9H, H <sub>butyl</sub> -TBDPS), 1.08 ppm (s, 9H, H-Boc).
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	δ = 170.5, 168.9, 154.3, 149.5, 137.4, 135.4, 135.3, 132.9, 132.7, 130.6, 129.7, 129.6, 127.6, 127.5, 126.5, 125.0, 119.2, 105.6, 82.2, 77.2, 76.8, 76.5, 66.7, 58.9, 34.1, 28.1, 26.7, 26.3, 21.1, 19.3 ppm.
<b>IR</b> (neat):	$\tilde{\nu}$ = 2932, 2858, 1770, 1732, 1707, 1667, 1608, 1510, 1429, 1362, 1327, 1292, 1257, 1155, 1112, 1003, 918, 821, 777, 704 cm <sup>-1</sup> .
<b>HRMS</b> (ESI <sup>+</sup> ):	Calcd. for [C <sub>36</sub> H <sub>41</sub> NO <sub>2</sub> Si + H] <sup>+</sup> : 596.2827      Found 596.2827.

**tert-butyl(E)-3-((4-bromobut-2-en-1-yl)oxy)-2-(4-((tertbutyldiphenylsilyloxy)benzyl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (III-135i)**

R<sub>f</sub> = 0.35 (ethyl acetate/petroleum ether 6/4)



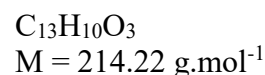
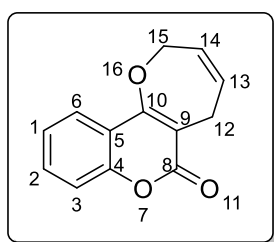
C<sub>36</sub>H<sub>42</sub>BrNO<sub>5</sub>Si  
M = 676.72 g.mol<sup>-1</sup>

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	δ = 7.68 (m, 4H, H <sub>Ar</sub> -TBDPS), 7.47 – 7.29 (m, 6H, H <sub>Ar</sub> -TBDPS), 6.71 (d, J = 8.5 Hz, 2H, H-2 and H-4), 6.62 (d, J = 8.5 Hz, 2H, H-1 and H-5), 5.92 (dt, J = 14.8, 7.3 Hz, 1H, H-18), 5.77 (dt, J = 15.3, 5.8 Hz, 1H, H-17), 4.72 (s, 1H, H-10), 4.59 (dd, J = 4.6, 3.2 Hz, 1H, H-8), 4.34 (dd, J = 12.7, 5.9 Hz, 1H, H-16a), 4.16 (dd, J = 12.9, 5.6 Hz, 1H, H-16b), 3.85 (d, J = 7.3 Hz, 2H, H-19), 3.32 (dd, J = 14.2, 4.8 Hz, 1H, H-7a), 2.97 (dd, J = 14.2, 3.1 Hz, 1H, H-7b), 1.57 (s, 9H), 1.08 ppm (s, 9H).
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	δ = 174.6, 168.6, 154.7, 149.5, 135.6, 135.5, 133.0, 132.9, 131.5, 130.4, 129.9, 129.8, 127.9, 127.7, 126.9, 126.6, 119.6, 96.0, 82.6, 77.3, 77.0, 76.7, 70.3, 60.4, 34.6, 30.6, 28.2, 26.9, 26.5, 19.4 ppm.
<b>IR</b> (neat):	$\tilde{\nu}$ = 2932, 2857, 2359, 2342, 1775, 1736, 1628, 1510, 1321, 1256, 1153, 968, 918, 821, 702 cm <sup>-1</sup> .
<b>HRMS</b> (ESI <sup>+</sup> ):	Calcd. for [C <sub>36</sub> H <sub>42</sub> BrNO <sub>5</sub> Si + H] <sup>+</sup> : 676.2088      Found 676.2083.

**2,5-dihydro-6H-oxepino[3,2-c]chromen-6-one (III-134j)**

According to general procedure, the reaction was carried out with 4-hydrocoumarin (300 mg), Cs<sub>2</sub>CO<sub>3</sub> (712 mg) and trans-1,4-dibromo-2-butene (428 mg) in DMSO at 20°C. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:9 to 1:4) gave product **III-134j** as a light yellow crystal (33 mg, 8% yield) and product **III-136j** as a light yellow crystal (48 mg, 12% yield):

R<sub>f</sub> = 0.5 (ethyl acetate/petroleum ether 3/7)



**<sup>1</sup>H NMR**  
(400 MHz, CDCl<sub>3</sub>)

$\delta$  = 7.79 (dd,  $J$  = 7.9, 1.5 Hz, 1H; H-3), 7.51 (ddd,  $J$  = 8.6, 7.4, 1.6 Hz, 1H; H-1), 7.28 (m,  $J$  = 12.8, 6.6, 1.9 Hz, 2H; H-6 and H-2), 6.36 (dt,  $J$  = 10.0, 6.0 Hz, 1H; H-13), 6.22-6.08 (m, 1H; H-14), 5.00 (d,  $J$  = 6.4 Hz, 2H; H-15), 3.65 ppm (d,  $J$  = 5.9 Hz, 2H; H-12).

**<sup>13</sup>C NMR**  
(101 MHz, CDCl<sub>3</sub>)

$\delta$  = 164.0 (C-8), 163.2 (C-10), 151.8 (C-4), 135.9 (C-13), 131.5 (C-6), 126.8 (C-14), 124.0 (C-2), 123.2 (C-1), 117.5 (C-5), 116.3 (C-3), 104.4 (C-9), 66.9 (C-15), 24.7 ppm (C-12).

**IR** (neat):

$\tilde{\nu}$  = 3042, 1693, 1608, 1570, 1488, 1455, 1396, 1380, 1307, 1277, 1198, 1157, 1107, 1047 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>):

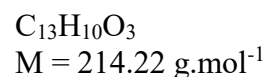
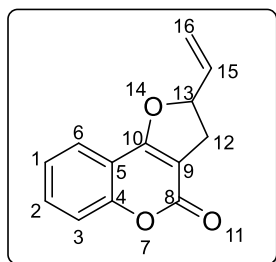
Calcd. for C<sub>13</sub>H<sub>10</sub>O<sub>3</sub><sup>+</sup>: 214.0625

Found 214.0624.

**Mp** = 80-82°C

**2-vinyl-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (III-136j)**

R<sub>f</sub> = 0.48 (ethyl acetate/petroleum ether 3/7)



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.66 (dd, *J* = 7.8, 1.6 Hz, 1H; H-3), 7.55 (ddd, *J* = 8.7, 7.4, 1.6 Hz, 1H; H-1), 7.36 (dd, *J* = 8.4, 0.6 Hz, 1H; H-6), 7.30 – 7.24 (m, 1H; H-2), 6.04 (ddd, *J* = 17.1, 10.4, 6.8 Hz, 1H; H-15), 5.53 (dtt, *J* = 9.9, 7.8, 1.0 Hz, 1H; H-13), 5.45 (dt, *J* = 17.1, 1.1 Hz, 1H; H-16a), 5.34 (dt, *J* = 10.4, 1.0 Hz, 1H; H-16b), 3.37 (dd, *J* = 15.2, 10.2 Hz, 1H; H-12a), 2.96 ppm (dd, *J* = 15.2, 7.6 Hz, 1H; H-12b).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 166.5 (C-8), 160.7 (C-10), 155.1 (C-4), 135.6 (C-15), 132.5 (C-6), 124.1 (C-2), 122.8 (C-1), 118.5 (C-3), 117.1 (C-16), 112.6 (C-5), 101.9 (C-9), 87.4 (C-13), 32.8 ppm (C-12).

**IR** (neat):  $\tilde{\nu}$  = 2927, 1718, 1643, 1608, 1499, 1410, 1271, 1206, 1158, 1094, 1025 cm<sup>-1</sup>.

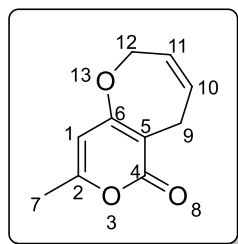
**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>13</sub>H<sub>10</sub>O<sub>3</sub><sup>+</sup>: 214.0625 Found 214.0636.

**Mp** = 105-106°C

### 8-methyl-2,5-dihydro-6H-pyrano[4,3-b] oxepin-6-one (III-134k)

According to general procedure A, the reaction was carried out with 4-hydroxy-6-methyl-2-pyrone (300 mg), Cs<sub>2</sub>CO<sub>3</sub> (932 mg) and trans-1,4-dibromo-2-butene (560 mg) in DMSO at 20°C. Flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:4) gave the product **III-134k** as a light yellow oil (20 mg, 5% yield) and product **III-136k** as a light yellow oil (48 mg, 12 % yield).

**R<sub>f</sub>** = 0.23 (ethyl acetate/petroleum ether 1/4)



C<sub>10</sub>H<sub>10</sub>O<sub>3</sub>  
M = 178.19 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.29 (dt, *J* = 9.8, 6.1 Hz, 1H; H-10), 6.02 (dtt, *J* = 9.2, 6.7, 1.2 Hz, 1H; H-11), 5.60 (d, *J* = 0.6 Hz, 1H; H-1), 4.75 (d, *J* = 6.7 Hz, 2H; H-12), 3.43 (d, *J* = 6.1 Hz, 2H; H-9), 2.12 (s, 3H; CH<sub>3</sub>).

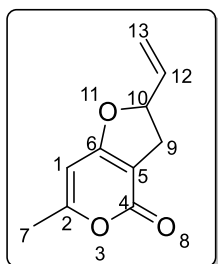
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 167.9 (C-4), 165.9 (C-6), 158.7 (C-2), 137.0 (C-10), 126.5 (C-11), 102.7 (C-1), 100.7 (C-5), 66.0 (C-12), 23.8 (C-9), 19.5 (C-7).

**IR** (neat):  $\tilde{\nu}$  = 2923, 1691, 1565, 1445, 1405, 1383, 1353, 1290, 1265, 1223, 1177, 1124, 1044, 1020 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>10</sub>H<sub>10</sub>O<sub>3</sub><sup>+</sup>: 178.0625 Found 178.0631.

## 6-methyl-2-vinyl-2,3-dihydro-4H-furo[3,2-c] pyran-4-one (III-136k)

Rf = 0.17 (ethyl acetate/petroleum ether 1/4)



$$\text{C}_{10}\text{H}_{10}\text{O}_3$$

$$M = 178.19 \text{ g}\cdot\text{mol}^{-1}$$

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.00-5.89 (m, 2H; H-12 and H-1), 5.39-5.29 (m, 2H; H-13a and H-10), 5.27 (dt,  $J = 10.3, 0.9$  Hz, 1H; H-13b), 3.19 (dd,  $J = 14.9, 10.1$  Hz, 1H; H-9a), 2.78 (dd,  $J = 14.9, 7.5$  Hz, 1H; H-9b), 2.24 ppm (d,  $J = 0.6$  Hz, 3H;  $\text{CH}_3$ ).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 171.2 (C-4), 165.4 (C-6), 162.2 (C-2), 135.7 (C-12), 118.2 (C-13), 99.1 (C-5), 95.8 (C-1), 86.8 (C-10), 31.7 (C-9), 20.5 ppm (C-7).

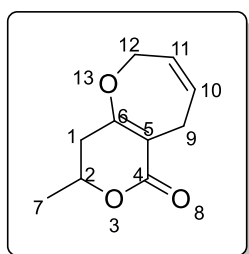
**IR** (neat):  $\tilde{\nu}$  = 2926, 1711, 1637, 1579, 1450, 1418, 1255, 1165, 1024  $\text{cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{10}\text{H}_{10}\text{O}_3^+$ : 178.0625 Found 178.0622.

## 8-methyl-2,5,8,9-tetrahydro-6H-pyrano[4,3-b]oxepin-6-one (III-134l)

According to general procedure A, the reaction was carried out with gerberin aglycone (200mg),  $\text{Cs}_2\text{CO}_3$  (605 mg) and trans-1,4-dibromo-2-butene (364 mg) in DMSO at 20°C. Flash chromatography on florosil gel (gradient of ethyl acetate/petroleum ether = 1:9 to 3:7) gave product **III-134l** as a yellow oil (72 mg, 26% yield) and product **III-136l** as a yellow oil (28 mg, 15% yield).

Rf = 0.5 (ethyl acetate/petroleum ether 3/7)



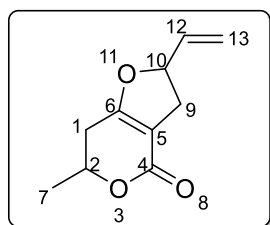
$$\text{C}_{10}\text{H}_{12}\text{O}_3$$

$$M = 180.20 \text{ g}\cdot\text{mol}^{-1}$$

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta$ = 6.31 (ddd, $J$ = 9.8, 7.3, 5.2 Hz, 1H; H-10), 6.09-5.98 (m, 1H; H-11), 4.87 (dd, $J$ = 12.6, 6.8 Hz, 1H; H-12a), 4.53 (dd, $J$ = 12.6, 6.9 Hz, 1H; H-12b), 4.43 (ddd, $J$ = 12.1, 6.2, 3.7 Hz, 1H; H-2), 3.51-3.39 (m, 1H; H-9a), 3.10 (dd, $J$ = 19.0, 7.3 Hz, 1H; H-9b), 2.47-2.36 (m, 1H; H-1a), 2.25-2.18 (m, 1H; H-1b), 1.37 ppm (d, $J$ = 6.3 Hz, 3H; CH <sub>3</sub> ).	
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta$ = 168.9 (C-4), 167.9 (C-6), 138.1 (C-10), 126.5 (C-11), 101.5 (C-5), 71.3 (C-2), 66.0 (C-12), 36.8 (C-1), 24.2 (C-9), 20.5 ppm (C-7).	
<b>IR</b> (neat):	$\tilde{\nu}$ = 2923, 2854, 1691, 1627, 1459, 1394, 1255, 1204, 1129, 1058, 944 cm <sup>-1</sup> .	
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd. for C <sub>10</sub> H <sub>12</sub> O <sub>3</sub> <sup>+</sup> : 180.0781	Found 180.0785.

### 6-methyl-2-vinyl-2,3,6,7-tetrahydro-4H-furo[3,2-c]pyran-4-one (III-136l)

R<sub>f</sub> = 0.25 (ethyl acetate/petroleum ether 3/7)



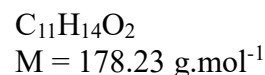
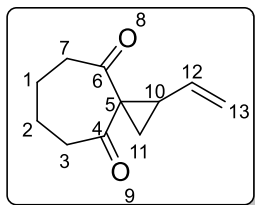
C<sub>10</sub>H<sub>12</sub>O<sub>3</sub>  
M = 180.20 g.mol<sup>-1</sup>

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta$ = 6.07-5.90 (m, 1H; H-12), 5.38 (ddt, $J$ = 17.0, 4.2, 1.0 Hz, 1H; H-13a), 5.34-5.27 (m, 2H; H-13b and H-10), 4.66-4.54 (m, 1H; H-2), 3.20-3.02 (m, 1H; H-9a), 2.82-2.62 (m, 1H; H-9b), 2.52-2.45 (m, 2H; H-11), 1.51 ppm (d, $J$ = 6.3 Hz, 3H; CH <sub>3</sub> ).	
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta$ = 171.4 (C-4), 165.7 (C-6), 136.0 (C-12), 118.1 (C-13), 101.6 (C-5), 86.9 (C-10), 73.2 (C-2), 32.4 (C-9), 30.9 (C-1), 20.9 ppm (C-7).	
<b>IR</b> (neat):	$\tilde{\nu}$ = 2923, 1707, 1659, 1401, 1260, 1223, 1120, 1054, 920 cm <sup>-1</sup> .	
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd. for C <sub>10</sub> H <sub>12</sub> O <sub>3</sub> <sup>+</sup> : 180.0781	Found 180.0778.

### 2,5,7,8,9,10-hexahydro-6H-cyclohepta[b]oxepin-6-one (III-149)

According to general procedure A, the reaction was carried out with 1,3-cycloheptanedione (126 mg), Cs<sub>2</sub>CO<sub>3</sub> (358 mg) and trans-1,4-dibromo-2-butene (214 mg) in DMSO at rt. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:6 to 7:3) gave product **III-149** as a light yellow oil (91 mg, 51% yield) and product **III-136n** as brown oil (30 mg, 17% yield):

R<sub>f</sub> = 0.38 (ethyl acetate/petroleum ether 8/2)



**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta = 5.38\text{--}5.24$  (m, 1H; H-12),  $5.31\text{--}5.28$  (m, 1H; H-13a)  $5.13\text{--}5.07$  (m, 1H; H-13b),  $2.75\text{--}2.65$  (m, 2H; H-3/H-7),  $2.65\text{--}2.56$  (m, 2H; H-3/H-7),  $2.56\text{--}2.47$  (m, 1H; H-10),  $2.00\text{--}1.88$  (m, 4H; H-1 and H-2),  $1.93\text{--}1.9$  (dd,  $J = 7.5\text{Hz}, 3.9\text{Hz}$ , 1H; H-11a)  $1.55$  ppm (dd,  $J = 8.7, 3.9$  Hz, 1H; H-11b).

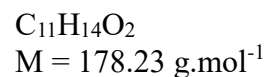
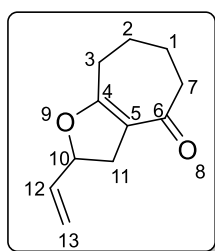
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta = 206.3$  and  $206.0$  (C-6, C-4),  $133.0$  (C-12),  $119.0$  (C-13),  $50.5$  (C-5),  $42.2$  (C-10),  $41.8$  (C-3/C-7),  $37.7$  (C-3/C-7),  $23.8$  (C-1/C-2),  $23.2$  (C11),  $22.4$  ppm (C-1/C-2).

**IR** (neat):  $\tilde{\nu} = 2939, 2868, 1677, 1451, 1332, 1302, 1271, 1219, 1196, 1118 \text{ cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{11}\text{H}_{14}\text{O}_2^+$ : 178.0999 Found 178.1001.

### 2-vinyl-2,3,5,6,7,8-hexahydro-4H-cyclohepta[b]furan-4-one (III-136n)

Rf = 0.38 (ethyl acetate/petroleum ether 7/3)



**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta = 5.89$  (ddd,  $J = 17.0, 10.4, 6.6$  Hz, 1H; H-12),  $5.27$  (dt,  $J = 17.1, 1.2$  Hz, 1H; H-13a),  $5.18$  (dt,  $J = 10.4, 1.1$  Hz, 1H; H-13b),  $5.04\text{--}4.94$  (m, 1H; H-10),  $3.15\text{--}3.02$  (m, 1H; H-11a),  $2.70$  (ddt,  $J = 14.8, 8.1, 1.7$  Hz, 1H; H-11b),  $2.61\text{--}2.51$  (m, 4H; H-3 and H-7),  $1.92\text{--}1.75$  ppm (m, 4H; H-1 and H-2).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta = 197.5$  (C-6),  $170.6$  (C-4),  $136.9$  (C-12),  $116.9$  (C-13),  $114.9$  (C-5),  $82.8$  (C-10),  $44.0$  (C-3/C-7),  $36.3$  (C-11),  $30.3$  (C-3/C-7),  $24.4$  (C-1/C-2),  $23.1$  ppm (C-1/C-2).

**IR** (neat):  $\tilde{\nu} = 2927, 2862, 1691, 1604, 1450, 1391, 1258, 1169, 1079 \text{ cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{11}\text{H}_{14}\text{O}_2^+$ : 178.0989 Found 178.0994.

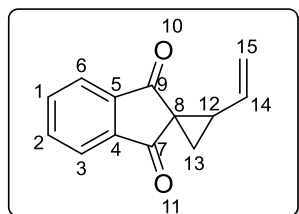
### 2-vinylspiro[cyclopropane-1,2'-indene]-1',3'-dione (III-148)

According to the general procedure A, the reaction was carried out with 1,3-indanedione



(100 mg),  $K_2CO_3$  (188 mg) and *trans*-1,4-dibromo-2-butene (146 mg) in DMF (6.8 mL) at rt. Flash chromatography on silica gel (diethyl ether/pentane = 1:4) gave product **III-148** as white solid (yield 95 mg, 71% yield):

**Rf** = 0.43 (Et<sub>2</sub>O/pentane = 1:4)



$C_{13}H_{10}O_2$   
 $M = 198.22 \text{ g}\cdot\text{mol}^{-1}$

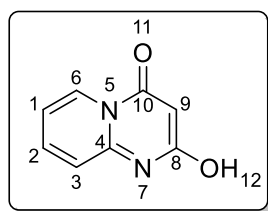
**<sup>1</sup>H NMR**  $\delta = 7.86$  (m, 4H; H<sub>ar</sub>), 6.02 (dt,  $J = 17.1, 10.0$  Hz, 1H; H-14), 5.28 (d,  $J = 17.1$  Hz, 1H; H-15a), 5.14 (d,  $J = 10.3$  Hz, 1H; H-15b), 2.81 (m, 1H; H-12), 2.13 (dd,  $J = 8.7, 4.1$  Hz, 1H; H-13a), 1.98 ppm (dd,  $J = 8.1, 4.0$  Hz, 1H; H-13b).

**<sup>13</sup>C NMR**  $\delta = 197.9, 197.1, 142.5, 141.8, 134.8, 134.7, 133.0, 122.5, 122.4, 118.5, 42.2, 40.2, 24.5$  ppm.

All analytical data matched those found in the literature.<sup>20</sup>

## 2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (III-104p)

A mixture of 2-aminopyridine (1.0 g, 1.0 equiv.) and freshly distilled dimethyl malonate (3 mL, 2.5 equiv.) was irradiated at 160°C under microwave conditions for 1 h. The title compound was obtained directly by filtration (1.1 g, 65% yield).



$C_8H_6N_2O_2$   
 $M = 162.15 \text{ g}\cdot\text{mol}^{-1}$

**<sup>1</sup>H NMR**  $\delta = 12.05$  (br s, 1H; H-12), 8.93 (d,  $J = 6.1$  Hz, 1H; H-6), 8.09 (t,  $J = 7.5$  Hz, 1H; H-2), 7.41 (d,  $J = 8.8$  Hz, 1H; H-3), 7.33 (dd,  $J = 7.5, 6.4$  Hz, 1H; H-1), 4.97 ppm (s, 1H; H-9).

**IR** (neat):  $\tilde{\nu} = 2923, 2854, 1689, 1460, 1377 \text{ cm}^{-1}$

**Mp** = 304 °C

All analytical data matched those found in the literature.<sup>21</sup>

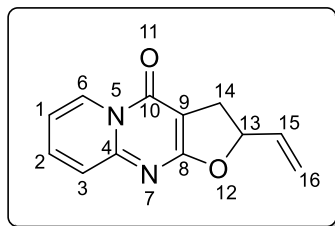
<sup>20</sup> F. Wei, C. L. Ren, D. Wang, L. Liu, *Chem. Eur. J.* **2015**, *21*, 2335 – 2338

<sup>21</sup> M. Abass, A. S. Mayas, *Heteroatom Chemistry* **2007**, *18*, 19-27

**2-vinyl-2,3-dihydro-4H-furo[2,3-d]pyrido[1,2-a]pyrimidin-4-one (III-150b)**

According to general procedure A, the reaction was carried out with 2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (60 mg), Cs<sub>2</sub>CO<sub>3</sub> (134 mg) and trans-1,4-dibromo-2-butene (89 mg) in DMF (3.7 mL) at rt. Flash chromatography on silica gel (EtOAc/PE = 7:3) gave the following products **III-150b** (4 mg, 5% yield) and **III-150c** (16 mg, 19% yield).

R<sub>f</sub> = 0.27 (EtOAc/PE 7:3)



C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>  
M = 214.22 g.mol<sup>-1</sup>

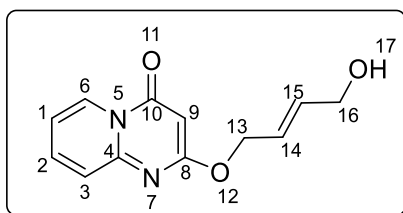
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 9.10 (d, J = 7.1 Hz, 1H; H-6), 7.75 (m, 1H; H-2), 7.63 – 7.49 (m, 1H; H-3), 7.13 (m, 1H; H-1), 6.03 (ddd, J = 16.9, 10.5, 6.2 Hz, 1H; H-15), 5.51 – 5.41 (m, 1H; H-16a), 5.39 (m, 1H; H-13), 5.29 (d, J = 10.4 Hz, 1H; H-16b), 3.49 (dd, J = 15.3, 9.7 Hz, 1H; H-14a), 3.06 ppm (dd, J = 15.3, 6.9 Hz, 1H; H-14b).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 171.7, 155.8, 152.4, 137.2, 136.3, 128.2, 125.4, 117.4, 114.8, 92.3, 83.1, 31.9 ppm.

**IR** (neat):  $\tilde{\nu}$  = 2922, 2851, 1691, 1638, 1570, 1524, 1450, 1353, 1232, 1167, 1015, 776 cm<sup>-1</sup>.

**(E)-2-((4-hydroxybut-2-en-1-yl)oxy)-4H-pyrido[1,2-a]pyrimidin-4-one (III-150c)**

R<sub>f</sub> = 0.38 (EtOAc/PE 7:3)



C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>  
M = 232.24 g.mol<sup>-1</sup>

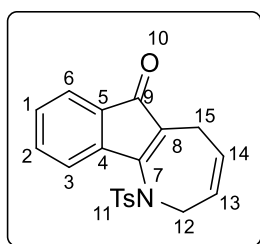
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 9.07 (d, J = 6.3 Hz, 1H; H-6), 8.09 (s, 1H; H-17), 7.77 (ddd, J = 8.6, 6.7, 1.6 Hz, 1H; H-2), 7.52 (m, 1H; H-3), 7.12 (m, 1H; H-1), 6.10-6.01 (m, 1H; H-15), 5.98 (dd, J = 13.4, 7.7 Hz, 1H; H-14), 5.83 (s, 1H; H-9), 4.91 (dd, J = 5.2, 1.1 Hz, 2H; H-13), 4.75-4.67 ppm (m, 2H; H-16).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 167.9, 160.6, 137.4, 129.4, 128.0, 127.0, 125.0, 114.7, 85.4, 77.34, 77.2, 77.0, 76.7, 66.0, 63.4, 60.2 ppm.

**1-tosyl-2,5-dihydroindeno[1,2-b]azepin-6(1H)-one (III-153)**

To a stirred solution of compound **III-148** (20 mg, 1.0 equiv.) in toluene (0.5 mL) were added tosylamide (18 mg, 1.05 equiv.) and  $\text{Ti}(\text{OEt})_4$  (25  $\mu\text{L}$ , 1.2 equiv.) at rt. The mixture was irradiated at 150 °C under microwave conditions for 30 min. The residue was extracted with EtOAc, dried over  $\text{Na}_2\text{SO}_4$ , evaporated in vacuo and purified by silica gel chromatography (PE/EtOAc = 85:15). The desired oxime sulfonate products **III-153** (6 mg, 17%) and **III-154** (8 mg, 16%) were obtained as red solids.

**R<sub>f</sub>** = 0.29 (PE/EtOAc 85:15)



$\text{C}_{20}\text{H}_{17}\text{NO}_3\text{S}$   
 $M = 351.42 \text{ g}\cdot\text{mol}^{-1}$

**<sup>1</sup>H NMR**  
 (400 MHz,  $\text{CDCl}_3$ )

$\delta = 7.69$  (d,  $J = 8.3$  Hz, 2H;  $\text{H}_{\text{Ar}}$ ),  $7.53$  (d,  $J = 7.1$  Hz, 1H;  $\text{H}_{\text{Ar}}$ ),  $7.46 - 7.32$  (m, 3H;  $\text{H}_{\text{Ar}}$ ),  $7.24$  (d,  $J = 8.0$  Hz, 2H;  $\text{H}_{\text{Ar}}$ ),  $5.44 - 5.34$  (m, 1H; H-14),  $5.34 - 5.20$  (m, 1H; H-13),  $4.26$  (dd,  $J = 4.7, 2.0$  Hz, 2H; H-12),  $2.68$  (dd,  $J = 4.3, 2.1$  Hz, 2H; H-15),  $2.42$  ppm (s, 3H;  $\text{CH}_3\text{-Ts}$ ).

**<sup>13</sup>C NMR**  
 (101 MHz,  $\text{CDCl}_3$ )

$\delta = 176.7, 156.9, 143.3, 136.4, 135.9, 134.0, 130.0, 128.8, 128.1, 126.1, 124.6, 122.6, 122.1, 48.5, 29.9, 25.1, 21.8, 14.2$  ppm.

**IR** (neat):

$\tilde{\nu} = 3691, 3606, 2927, 2251, 1711, 1602, 1459, 1363, 1168, 1092$   $\text{cm}^{-1}$ .

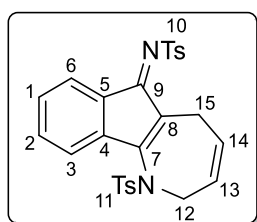
**HRMS** ( $\text{EI}^+$ ):

Calcd. for  $\text{C}_{19}\text{H}_{23}\text{NO}_5\text{S}_2^+$ : 351.0929      Found 351.0931.

**Mp** = 115-117°C

**(Z)-4-methyl-N-(1-tosyl-2,5-dihydroindeno[1,2-b]azepin-6(1H)-ylidene) benzenesulfonamide (III-154)**

**R<sub>f</sub>** = 0.13 (PE/EtOAc 85:15)



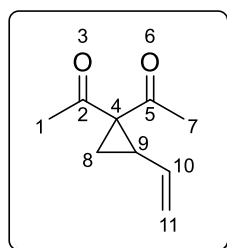
$\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_4\text{S}_2$   
 $M = 504.62 \text{ g}\cdot\text{mol}^{-1}$

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta$ = 8.42 (d, $J$ = 7.6 Hz, 1H; H-3), 7.91 (d, $J$ = 8.4 Hz, 2H; H <sub>ar</sub> -Ts), 7.71 (d, $J$ = 8.4 Hz, 2H; H <sub>ar</sub> -Ts), 7.48 (d, $J$ = 6.9 Hz, 1H; H-6), 7.41 (td, $J$ = 7.6, 1.0 Hz, 1H; H-2), 7.35-2.21 (m, 5H; H-1, H <sub>ar</sub> -Ts), 5.43 – 5.32 (m, 1H; H-14), 5.18 – 5.09 (m, 1H; H-13), 4.29 – 4.19 (m, 2H; H-12), 2.61 (s, 2H; H-15), 2.45 (s, 3H; CH <sub>3</sub> -Ts), 2.40 (s, 3H; CH <sub>3</sub> -Ts) ppm.	
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta$ = 174.3, 144.4, 143.9, 143.5, 142.8, 138.7, 136.6, 134.1, 129.8, 129.6, 128.8, 128.2, 127.2, 125.5, 124.5, 122.6, 48.4, 29.9, 25.9, 21.8 ppm.	
<b>IR</b> (neat):	$\tilde{\nu}$ = 3691, 3606, 3031, 2927, 2855, 1589, 1458, 1363, 1321, 1167, 1091 cm <sup>-1</sup> .	
<b>MS</b> (EI <sup>+</sup> ):	Calcd. for C <sub>27</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> Na <sup>+</sup> : 527.1070 C <sub>27</sub> H <sub>23</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub> <sup>-</sup> : 503.1105	Found [M+Na] <sup>+</sup> 527.0 [M-H] <sup>-</sup> 503.0
<b>Mp</b> = 180°C		

### 1,1'-(2-allylcyclopropane-1,1-diyl)bis(ethan-1-one) (III-158)

According to general procedure A, the reaction was carried out with acetylacetone (100 mg), Cs<sub>2</sub>CO<sub>3</sub> (326 mg) and trans-1,4-dibromo-2-butene (257 mg) in DMSO (10 mL) at rt. Flash chromatography on silica gel (Et<sub>2</sub>O/PE = 5:95) yield title product (84 mg, 55%) as a clear oil.

**R<sub>f</sub>** = 0.33 (Et<sub>2</sub>O/PE = 5:95)



C<sub>10</sub>H<sub>14</sub>O<sub>2</sub>  
M = 166.22 g.mol<sup>-1</sup>

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta$ = 5.30-5.26 (m, 2H; H-10, H-11a), 5.16-5.11 (m, 1H; H-11b), 2.61 (ddd, $J$ = 11.2, 6.5, 2.9 Hz, 1H; H-9), 2.25 (s, 3H; H-1/7), 2.15 (s, 3H; H-1/7), 1.82 (dd, $J$ = 7.3, 5.1 Hz, 1H; H-8a), 1.48 ppm (dd, $J$ = 8.8, 5.1 Hz, 1H; H-8b).
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta$ = 202.8, 202.5, 133.0, 119.0, 51.3, 32.5, 30.9, 27.0, 20.3 ppm.
<b>IR</b> (neat):	$\tilde{\nu}$ = 2923, 1708, 1671, 1596, 1382, 1361, 1224, 932, 626 cm <sup>-1</sup> .

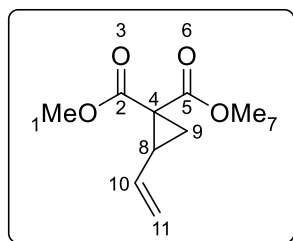
All analytical data matched those found in the literature.<sup>22</sup>

<sup>22</sup> R. K. Bowman, J. S. Johnson, *Org. Lett.* **2006**, *8*, 573–576.

**dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (III-159)**

Sodium (1.7 g, 2.0 equiv.) was added to methanol (29 mL) to obtain solution of sodium methoxide. After that, dimethyl malonate (8.66 mL, 2.05 equiv.) and a solution of *trans*-1,4-dibromo-2-butene (7.84 g, 1.0 equiv.) in methanol (29 mL) were added respectively to the flask containing sodium methoxide. The solution was refluxed for 6 hours. The resulted mixture was filtered and concentrated in vacuo. The colorless oil obtained was extracted with diethyl ether. The gathered organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude mixture was purified by flash silica chromatography eluted with petroleum ether/diethyl ether (9:1). The product **III-159** was obtained as colorless oil (4.2 g, 63% yield).

**R<sub>f</sub>** = 0.26 (PE/Et<sub>2</sub>O 9:1)



C<sub>9</sub>H<sub>12</sub>O<sub>4</sub>  
M = 184.19 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** δ = 5.41 (m, 1H; H-10), 5.27 (d, *J* = 8.0 Hz, 1H; H-11b), 5.13 (d, *J* = 8.0 Hz, 1H; H-11a), 3.75 (s, 6H; 2CH<sub>3</sub>), 2.56-2.62 (m, 1H; H-8), 1.72 (dd, *J* = 4.0, 8.0 Hz, 1H; H-9b), ppm 1.58 (dd, *J* = 4.0, 8.0 Hz, 1H; H-9a)

**<sup>13</sup>C NMR** δ = 167.8 (C-2/C-5), 170.0 (C-2/C-5), 133.0 (C-10), 118.7 (C-11), (101 MHz, CDCl<sub>3</sub>) 52.7 (C-1/C-7), 52.6 (C-1/C-7), 35.7 (C-4), 31.5 (C-8), 20.6 ppm (C-9).

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>9</sub>H<sub>12</sub>O<sub>4</sub><sup>+</sup>: 184.0736 Found 184.0731.

All analytical data matched those found in the literature.<sup>23</sup>

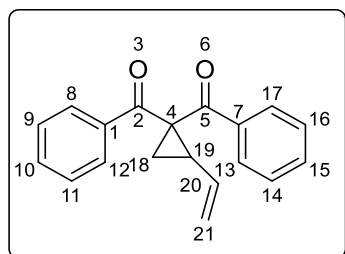
**(2-vinylcyclopropane-1,1-diyl)bis(phenylmethanone) (III-160a)**

According to general procedure A, the reaction was carried out with dibenzoylmethane (74 mg), Cs<sub>2</sub>CO<sub>3</sub> (108 mg) and *trans*-1,4-dibromo-2-butene (86 mg) in DMSO (3.3 mL) at rt.

<sup>23</sup> S. D. R. Christie, R. J. Davoile, M. R. J. Elsegood, R. Fryatt, R. C. F. Jones, G. J. Pritchard, *Chem. Commun.* **2004**, 0, 2474-2475.

Flash chromatography on silica gel (EtOAc/pentane = 5:95 to 1:9) yield product **III-160a** (37 mg, 40%) and product **III-160b** (14 mg, 15%).

R<sub>f</sub> = 0.42 (EtOAc/pentane 1:9)



C<sub>19</sub>H<sub>16</sub>O<sub>2</sub>  
M = 276.34 g.mol<sup>-1</sup>

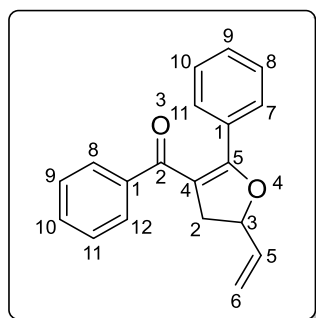
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.74-7.68 (m, 2H; H<sub>ar</sub>), 7.68-7.63 (m, 2H; H<sub>ar</sub>), 7.40-7.31 (m, 2H; H<sub>ar</sub>), 7.29-7.20 (m, 4H; H<sub>ar</sub>), 5.43-5.37 (m, 2H; H-20, H-21a), 5.09-5.03 (m, 1H; H-21b), 3.39-3.23 (m, 1H; H-19), 2.34 (dd, J = 7.3, 4.4 Hz, 1H; H-18a), 1.58 ppm (dd, J = 8.7, 4.4 Hz, 1H; H-18b).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 196.9, 196.2, 138.3, 137.8, 133.1, 133.1, 133.0, 128.8, 128.6, 128.6, 118.9, 47.9, 31.4, 21.5 ppm.

All analytical data matched those found in the literature.<sup>24</sup>

### phenyl(2-phenyl-5-vinyl-4,5-dihydrofuran-3-yl)methanone (III-160b)

R<sub>f</sub> = 0.17 (EtOAc/pentane 1:9)



C<sub>19</sub>H<sub>16</sub>O<sub>2</sub>  
M = 276.34 g.mol<sup>-1</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.47-7.40 (m, 2H; H<sub>ar</sub>), 7.25-7.14 (m, 4H; H<sub>ar</sub>), 7.11-7.00 (m, 4H; H<sub>ar</sub>), 6.11 (ddd, J = 17.0, 10.4, 6.4 Hz, 1H; H-5), 5.46 (dt, J = 17.1, 1.2 Hz, 1H; H-6a), 5.34-5.17 (m, 2H; H-6b, H-3), 3.45 (dd, J = 14.9, 9.9 Hz, 1H; H-2a), 3.14 ppm (dd, J = 14.9, 8.4 Hz, 1H; H-2b).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 193.8, 165.7, 139.2, 136.8, 131.3, 130.2, 129.6, 129.1, 127.8, 127.8, 117.4, 111.9, 82.7, 53.6, 38.9 ppm.

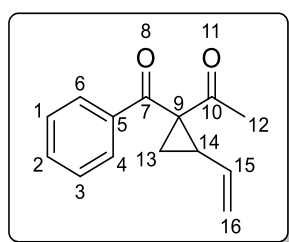
All analytical data matched those found in the literature.<sup>24</sup>

<sup>24</sup> Y. Xia, X. Liu, H. Zheng, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2015**, *54*, 227-230.

**1-(1-benzoyl-2-vinylcyclopropyl)ethan-1-one (III-161a)**

According to general procedure A, the reaction was carried out with benzoylacetone (100 mg), K<sub>2</sub>CO<sub>3</sub> (171 mg) and trans-1,4-dibromo-2-butene (133 mg) in DMF (6.2 mL) at rt. Flash chromatography on silica gel (diethylether/pentane= 1:9) yield diastereoisomers **III-161a** (77 mg, 58%) and product **III-161b** (22 mg, 15%).

R<sub>f</sub> = 0.3, 0.45 (Et<sub>2</sub>O/pentane 1:9)



C<sub>14</sub>H<sub>14</sub>O<sub>2</sub>  
M = 214.26 g.mol<sup>-1</sup>

Diastereoisomer 1

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 7.96 – 7.79 (m, 2H; H-4, H-6), 7.57 (t, J = 7.4 Hz, 1H; H-2), 7.46 (t, J = 7.7 Hz, 2H; H-1; H-4), 5.29 (dd, J = 16.9, 1.7 Hz, 1H; H-16a), 5.24 – 5.13 (m, 1H; H-15), 4.98 (dd, J = 10.0, 1.6 Hz, 1H; H-16b), 3.02 (dd, J = 16.0, 8.6 Hz, 1H; H-14), 2.03 (s, 3H; H-12), 1.92 (dd, J = 7.2, 4.4 Hz, 1H; H-13a), 1.49 ppm (dd, J = 8.7, 4.3 Hz, 1H; H-13b).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 202.9, 195.4, 137.4, 133.7, 133.6, 129.1, 129.1, 118.5, 48.7, 33.3, 29.8, 22.3 ppm.

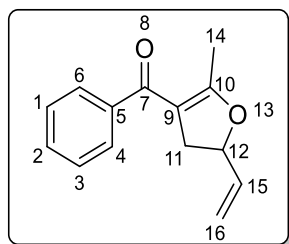
Diastereoisomer 2

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 7.95 – 7.83 (m, 2H; H-4, H-6), 7.58 (t, J = 7.4 Hz, 1H; H-2), 7.46 (t, J = 7.7 Hz, 2H; H-1, H-4), 5.51 (ddd, J = 17.2, 9.9, 8.9 Hz, 1H; H-15), 5.36 (dd, J = 17.1, 1.6 Hz, 1H; H-16a), 5.16 (dd, J = 10.1, 1.6 Hz, 1H; H-16b), 2.89 (dd, J = 16.3, 8.6 Hz, 1H; H-14), 2.10 (dd, J = 7.4, 4.5 Hz, 1H; H-13a), 1.95 (s, 3H; H-12), 1.46 ppm (dd, J = 8.7, 4.5 Hz, 1H; H-13b).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 202.0, 195.8, 137.1, 133.7, 132.9, 129.1, 128.9, 118.9, 49.6, 31.4, 31.0, 21.6 ppm.

All analytical data matched those found in the literature.<sup>25</sup>

<sup>25</sup> J. Zhang, Y. Tang, W. Wei, Y. Wu, Y. Li, J. Zhang, Y. Zheng, S. Xu, *Org. Lett.* **2017**, *19*, 3043–3046

**(2-methyl-5-vinyl-4,5-dihydrofuran-3-yl)(phenyl)methanone (III-161b)**Rf = 0.13 (Et<sub>2</sub>O/pentane 1:9)

C<sub>14</sub>H<sub>14</sub>O<sub>2</sub>  
M = 214.26 g.mol<sup>-1</sup>

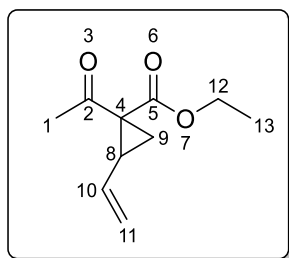
**<sup>1</sup>H NMR** δ = 7.60 – 7.53 (m, 2H; H-4, H-6), 7.51 – 7.37 (m, 3H; H-1, H-2, H-3), 5.98 (ddd, J = 17.0, 10.4, 6.6 Hz, 1H; H-15), 5.34 (dt, J = 17.1, 1.1 Hz, 1H; H-16a), 5.25 (d, J = 10.4 Hz, 1H; H-16b), 5.15 – 5.03 (m, 1H; H-12), 3.35 – 3.16 (m, 1H; H-11a), 2.90 (ddd, J = 14.4, 8.3, 1.5 Hz, 1H; H-11b), 1.84 ppm (t, J = 1.4 Hz, 3H; H-14).

**<sup>13</sup>C NMR** δ = 193.4, 168.8, 141.2, 136.9, 131.3, 128.5, 128.1, 117.4, 112.6, 83.1, 77.3, 37.3, 30.6, 15.7 ppm.

All analytical data matched those found in the literature.<sup>25</sup>**ethyl 1-acetyl-2-vinylcyclopropane-1-carboxylate (III-162)**

According to general procedure A, the reaction was carried out with ethyl acetoacetate (130 mg), Cs<sub>2</sub>CO<sub>3</sub> (325 mg) and trans-1,4-dibromo-2-butene (257 mg) in DMSO (10 mL) at rt. Flash chromatography on silica gel (EtOAc/PE = 5:95) yield afford a mixture of diastereomers as a clear oil (58 mg, 32% and 47 mg 26%).

Rf = 0.33, 0.23 (EtOAc/PE 5:95)



C<sub>10</sub>H<sub>14</sub>O<sub>3</sub>  
M = 182.22 g.mol<sup>-1</sup>

Diastereoisomer 1

**<sup>1</sup>H NMR** δ = 5.29-2.25 (m, 2H; H-10, H-11a), 5.15 – 5.07 (m, 1H; H-11b), 4.32 – 4.07 (m, 2H; H-12), 2.66 – 2.54 (m, 1H; H-8), 2.31 (s, 3H; H-13), 1.83 (dd, J = 7.5, 4.6 Hz, 1H; H-9a), 1.52 (dd, J = 8.8, 4.6 Hz, 1H; H-9b), 1.28 ppm (t, J = 7.1 Hz, 3H; H-13).



<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta = 202.2, 169.0, 133.2, 119.0, 61.6, 43.4, 34.4, 29.7, 23.2, 14.4$ ppm.	
<b>IR</b> (neat):	$\tilde{\nu} = 3691, 2986, 2930, 1700, 1371, 1269, 1217, 1183, 1122, 1030$ cm <sup>-1</sup> .	
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd for C <sub>10</sub> H <sub>14</sub> O <sub>3</sub> <sup>+</sup> : 182.0943	Found 182.0936.

Diastereoisomer 2

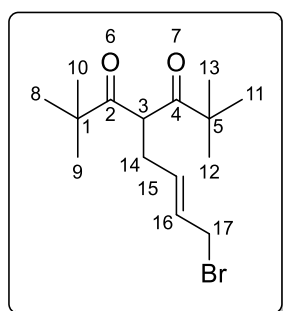
<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta = \delta 5.49$ (ddd, $J = 17.1, 10.2, 8.6$ Hz, 1H; H-10), $5.28$ (ddd, $J = 17.0, 1.5, 0.5$ Hz, 1H; H-11a), $5.19 - 5.04$ (m, 1H; H-11b), $4.29 - 4.17$ (m, 2H; H-12), $2.59$ (dd, $J = 16.7, 8.5$ Hz, 1H; H-8), $2.39$ (s, $J = 2.7$ Hz, 3H; H-1), $1.74$ (dd, $J = 7.7, 4.4$ Hz, 1H; H-9a), $1.56$ (dd, $J = 8.9, 4.4$ Hz, 1H; H-9b), $1.28$ ppm (t, $J = 7.2$ Hz, 3H; H-13).	
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta = 202.2, 169.0, 133.2, 119.0, 77.4, 61.6, 43.4, 34.4, 29.8, 23.2, 14.4$ ppm.	
<b>IR</b> (neat):	$\tilde{\nu} = 3691, 2985, 2928, 1722, 1695, 1372, 1314, 1257, 1190, 1123, 1022$ cm <sup>-1</sup> .	
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd. for C <sub>10</sub> H <sub>14</sub> O <sub>3</sub> <sup>+</sup> : 182.0943	Found 182.0936.

All analytical data matched those found in the literature.<sup>31</sup>

**(Z)-5-(((E)-4-bromobut-2-en-1-yl)oxy)-2,2,6,6-tetramethylhept-4-en-3-one (III-163)**

According to general procedure A, the reaction was carried out with heptanedione (159 mg), Cs<sub>2</sub>CO<sub>3</sub> (280 mg) and trans-1,4-dibromo-2-butene (220 mg) in DMSO (9 mL) at rt. Flash chromatography on silica gel (EtOAc/PE = 1:9 to 1:1) yield title product (37 mg, 14%) as a yellow oil.

R<sub>f</sub> = 0.16 (EtOAc/PE 1:1)



C<sub>15</sub>H<sub>25</sub>BrO<sub>2</sub>  
M = 317.27 g.mol<sup>-1</sup>

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta = 5.62$ (dd, $J = 13.3, 7.6$ Hz, 1H; H-16), $5.52 - 5.33$ (m, 1H; H-15), $4.41$ (t, $J = 6.5$ Hz, 1H; H-3), $3.98$ (d, $J = 5.5$ Hz, 2H; H-14), $2.57 - 2.40$ (m, 2H; H-17), $1.10$ ppm (s, 18H; 2H <sub>tBu</sub> ).	
<b><sup>13</sup>C NMR</b>	$\delta = 209.9$ (C2, C4), $131.9$ (C-16), $128.6$ (C-15), $63.1$ (C-14), $55.1$ (C-	

(101 MHz, CDCl<sub>3</sub>) 3), 44.5 (C-1, C-5), 32.4 (C-17), 27.3 (C<sub>tBu</sub>) ppm.

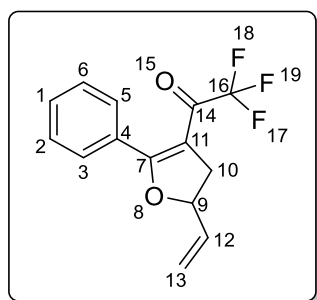
**IR** (neat):  $\tilde{\nu}$  = 3614, 2969, 2873, 1719, 1690, 1478, 1368, 1055 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>15</sub>H<sub>25</sub>BrO<sub>2</sub><sup>+</sup>: 316.1038 Found 179.1153.

### 2,2,2-trifluoro-1-(2-phenyl-5-vinyl-4,5-dihydrofuran-3-yl)ethan-1-one (III-164a)

According to general procedure A, the reaction was carried out with trifluoro-phenylbutadione (100 mg, 1.0 equiv.), TBAF (1 M, 0.46 mL, 1.0 equiv.), HMPA (320 μL, 4 equiv.) and trans-1,4-dibromo-2-butene (98 mg, 1.1 equiv.) in THF (0.65 mL) at rt. Flash chromatography on silica gel (Et<sub>2</sub>O/PE = 5:95 to 1:9) yield product **III-164a** (18 mg, 15%) and product **III-164b** (10 mg, 7%).

**Rf** = 0.60 (Et<sub>2</sub>O/PE = 2:8)



C<sub>14</sub>H<sub>11</sub>F<sub>3</sub>O<sub>2</sub>  
M = 268.24 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.88 – 7.76 (m, 2H; H-2, H-6), 7.57 – 7.48 (m, 1H; H-1), 7.48 – 7.33 (m, 2H; H-3, H-5), 6.04 (ddd, *J* = 17.1, 10.3, 6.7 Hz, 1H; H-12), 5.44 (dt, *J* = 17.1, 1.0 Hz, 1H; H-13a), 5.38 – 5.28 (m, 2H; H-13b, H-9), 3.47 (ddd, *J* = 14.6, 10.3, 0.8 Hz, 1H; H-10a), 3.10 ppm (ddd, *J* = 14.6, 8.5, 0.7 Hz, 1H; H-10b).

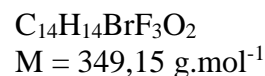
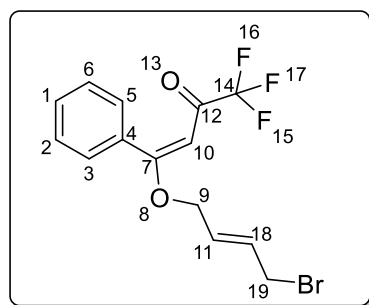
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 175.5, 175.2, 173.5, 135.5, 132.1, 129.6, 128.9, 127.9, 118.4, 115.4, 104.7, 84.3, 77.4, 77.0, 76.7, 35.3 ppm.

**IR** (neat):  $\tilde{\nu}$  = 3308, 2921, 1661, 1597, 1581, 1450, 1172, 1086, 991, 935, 713, 686 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>14</sub>H<sub>11</sub>F<sub>3</sub>O<sub>2</sub><sup>+</sup>: 268.0711 Found 268.0706.

### (E)-4-((4-bromobut-2-en-1-yl)oxy)-1,1,1-trifluoro-4-phenylbutan-2-one (III-164b)

**Rf** = 0.57 (Et<sub>2</sub>O/PE = 2:8)



**$^1\text{H NMR}$**   $\delta = 8.02 - 7.87$  (m, 2H; H-2, H-6),  $7.68 - 7.57$  (m, 1H; H-1),  $7.56 - 7.45$  (m, 2H; H-3, H-5),  $6.59$  (s, 1H; H-10),  $5.89$  (dtt,  $J = 14.3, 7.0, 1.2$  Hz, 1H; H-18),  $5.78$  (dt,  $J = 15.3, 5.6$  Hz, 1H; H-11),  $4.63$  (d,  $J = 5.4$  Hz, 2H; H-9),  $3.83$  ppm (dd,  $J = 7.3, 0.7$  Hz, 2H; H-19).

**$^{13}\text{C NMR}$**   $\delta = 189.7, 152.1-151.1$  (m,  $\text{CF}_3$ ),  $137.6, 134.3, 131.5, 129.4, 129.3, 129.2, 128.6, 105.9, 105.8, 74.1, 31.3, 30.8$  ppm.

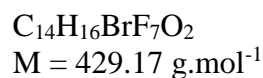
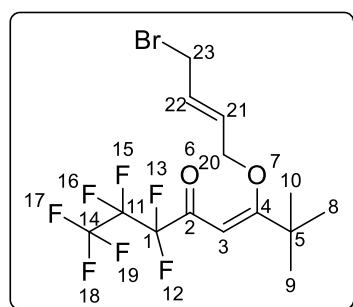
**IR** (neat):  $\tilde{\nu} = 3673, 2987, 2901, 1394, 1250, 1066, 892 \text{ cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $C_{14}H_{14}F_3O_2^+$ : 269.0784 Found 269.8672.

**(Z)-6-(((E)-4-bromobut-2-en-1-yl)oxy)-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloct-5-en-4-one (III-165)**

According to general procedure A, the reaction was carried out with 2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedione (100 mg, 1.0 equiv.), TBAF (1 M, 0.68 mL, 2.0 equiv.), HMPA (235  $\mu\text{L}$ , 4.0 equiv.) and trans-1,4-dibromo-2-butene (138 mg, 2.0 equiv.) in THF (2.2 mL) at rt. Flash chromatography on silica gel ( $\text{Et}_2\text{O}/\text{PE} = 2:97$  to 1:9) yield title product (25 mg, 17%) as yellow oil.

**Rf** = 0.45 ( $\text{Et}_2\text{O}/\text{PE} = 5:95$ )



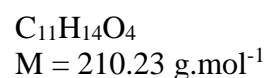
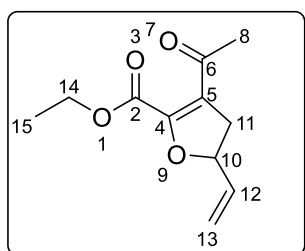
**$^1\text{H NMR}$**   $\delta = 6.26$  (s, 1H; H-3),  $6.03-5.93$  (m, 1H; H-22),  $5.91-5.80$  (m, 1H; H-21),  $4.54$  (d,  $J = 5.5$  Hz, 2H; H-20),  $4.00-3.88$  (m, 2H; H-23),  $1.18$  ppm (s, 9H; H-8, H-9, H-10).

**IR** (neat):  $\tilde{\nu} = 2968, 1754, 1695, 1627, 1348, 1224, 1123, 966, 736 \text{ cm}^{-1}$ .

**ethyl 3-acetyl-5-vinyl-4,5-dihydrofuran-2-carboxylate (III-168)**

According to general procedure A, the reaction was carried out with ethyl-dioxoalate (316 mg, 3 mmol), Cs<sub>2</sub>CO<sub>3</sub> (717 mg) and trans-1,4-dibromo-2-butene (470 mg) in DMSO at 20°C. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:9 to 2:8) gave product **III-168** as a light yellow oil (50 mg, 12% yield) and **III-169** as a light yellow oil (100 mg, 24% yield).

**Rf** = 0.13 (ethyl acetate/petroleum ether 1/9)



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 5.92 (ddd, J = 17.0, 10.4, 6.6 Hz, 1H, H-12), 5.33 (dt, J = 17.1, 1.0 Hz, 1H, H-13a), 5.24 (dd, J = 10.4, 0.8 Hz, 1H, H-13b), 5.20-5.06 (m, 1H, H-10), 4.34 (d, J = 7.1 Hz, 2H, H-11), 3.16 (dd, J = 15.8, 10.6 Hz, 1H, H-14a), 2.80 (dd, J = 15.8, 8.5 Hz, 1H, H-14b), 2.29 (s, 3H, H-8), 1.35 ppm (t, J = 7.1 Hz, 3H, H-15).

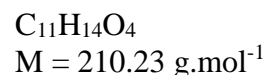
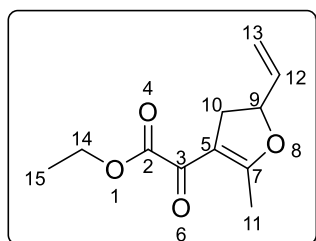
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 194.14 (C-6), 160.8 (C-2), 152.6 (C-4), 135.6 (C-12), 119.0 (C-5), 118.0 (C-13), 84.0 (C-10), 62.6 (C-14), 36.5 (C-11), 29.2 (C-8), 14.0 ppm (C-15).

**IR** (neat):  $\tilde{\nu}$  = 2923, 1738, 1651, 1614, 1371, 1279, 1237, 1163, 1087, 1024, 931, 855, 773 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>11</sub>H<sub>14</sub>O<sub>4</sub><sup>+</sup>: 210.0887 Found 210.0886.

**5,7,8,9-tetrahydrobenzo[b]oxepin-6(2H)-one (III-169)**

**Rf** = 0.2 (ethyl acetate/petroleum ether 1/9)

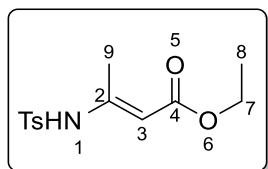


<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta = 5.89$ (ddd, $J = 17.1, 10.4, 6.7$ Hz, 1H, H-12), $5.29$ (dt, $J = 17.1, 1.1$ Hz, 1H, H-13a), $5.21$ (dt, $J = 10.4, 1.0$ Hz, 1H, H-13b), $5.15$ - $5.06$ (m, 1H, H-9), $4.28$ (q, $J = 7.1$ Hz, 2H, H-10), $3.28$ - $3.14$ (m, 1H, H-14a), $2.81$ (ddd, $J = 14.5, 8.0, 1.3$ Hz, 1H, H-14b), $2.18$ (t, $J = 1.2$ Hz, 3H, H-11), $1.33$ ppm (t, $J = 7.2$ Hz, 3H, H-15).	
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta = 181.3$ (C-3), $174.2$ (C-7), $164.6$ (C-2), $136.0$ (C-12), $117.7$ (C-13), $109.5$ (C-7), $84.4$ (C-9), $61.9$ (C-14), $34.8$ (C-10), $15.1$ (C-11), $14.1$ ppm (C-15).	
<b>IR</b> (neat):	$\tilde{\nu} = 2983, 2926, 1731, 1599, 1576, 1381, 1274, 1209, 1119, 1017, 940, 837, 762$ cm <sup>-1</sup> .	
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd. for C <sub>10</sub> H <sub>13</sub> O <sub>2</sub> <sup>+</sup> : 210.0887	Found 210.0888.

### ethyl (E)-3-((4-methylphenyl)sulfonamido)but-2-enoate (III-171)

To a stirred solution of ethyl acetoacetate (200 mg, 0.2 mL, 1.0 equiv.) in toluene (3 mL) were added tosylamide (791 mg, 3.0 equiv.) and distilled Ti(OEt)<sub>4</sub> (646  $\mu$ L, 2.0 equiv.) at rt. Then the mixture was irradiated at 150 °C under microwave conditions for 1 h. The residue was extracted with EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated in vacuo and purified by silica gel chromatography (PE/EtOAc = 95:5) to afford the title compound (111 mg, 26%) as colorless oil.

R<sub>f</sub> = 0.30 (PE/EtOAc = 95:5)



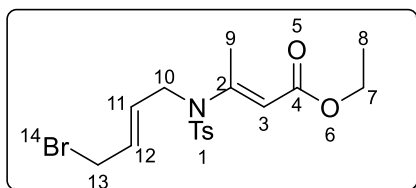
C<sub>13</sub>H<sub>17</sub>NO<sub>4</sub>S  
M = 283.34 g.mol<sup>-1</sup>

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta = 11.15$ (s, 1H; H-1), $7.77$ (d, $J = 8.3$ Hz, 2H; H <sub>ar</sub> -Ts), $7.32$ (d, $J = 8.1$ Hz, 2H; H <sub>ar</sub> -Ts), $4.89$ (d, $J = 0.8$ Hz, 1H; H-3), $4.15$ (q, $J = 7.1$ Hz, 2H; H-7), $2.42$ (s, 3H; CH <sub>3</sub> -Ts), $2.02$ (d, $J = 0.6$ Hz, 3H; H-9), $1.26$ ppm (t, $J = 7.1$ Hz, 3H; H-8).	
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta = 169.2$ (C-4), $152.8$ (C-2), $144.4$ (C-T <sub>Sar</sub> ), $137.7$ (C-T <sub>Sar</sub> ), $130.1$ (C-T <sub>Sar</sub> ), $127.3$ (C-T <sub>Sar</sub> ), $96.5$ (C-3), $60.2$ (C-7), $21.7$ (C-T <sub>SCH3</sub> ), $19.8$ (C-9), $14.3$ (C-8) ppm.	
<b>IR</b> (neat):	$\tilde{\nu} = 3691, 3145, 2985, 1162, 1668, 1626, 1423, 1353, 1179, 1092, 1056, 1020, 977$ cm <sup>-1</sup> .	
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd. for C <sub>13</sub> H <sub>17</sub> NO <sub>4</sub> S <sup>+</sup> : 283.0873	Found 283.0871.

**ethyl (E)-3-((N-((E)-4-bromobut-2-en-1-yl)-4-methylphenyl)sulfonamido)but-2-enoate (III-172b)**

According to the general procedure A, the reaction was carried out with compound **III-177** (70 mg), Cs<sub>2</sub>CO<sub>3</sub> (95 mg) and trans-1,4-dibromo-2-butene (68 mg) in DMSO (2.6 mL). Flash chromatography on silica gel (EtOAc/PE = 1:9) yield the product **III-172a** (7 mg, 6%) and the product **III-172b** (36 mg, 41%).

**R<sub>f</sub>** = 0.75 (EtOAc/PE = 1:4)



C<sub>17</sub>H<sub>22</sub>BrNO<sub>4</sub>S  
M = 416.33 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 7.67 (d, *J* = 8.3 Hz, 2H; H<sub>ar</sub>-Ts), 7.31 (d, *J* = 8.2 Hz, 2H; H<sub>ar</sub>-Ts), 5.96 – 5.78 (m, 1H; H-12), 5.77 – 5.62 (m, 1H; H-11), 5.68 (d, *J* = 0.8 Hz, 1H; H-3), 4.20 – 4.06 (m, 4H; H-7, H-10), 3.90 (d, *J* = 7.3 Hz, 2H; H-13), 2.44 (s, 3H; CH<sub>3</sub>-Ts), 2.20 (d, *J* = 1.0 Hz, 3H; H-9), 1.27 ppm (t, *J* = 7.1 Hz, 3H; H-8).

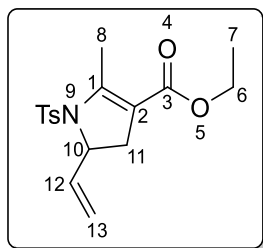
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 166.2 (C-4), 152.6 (C-2), 144.3 (C-T<sub>Sar</sub>), 136.1 (C-T<sub>Sar</sub>), 130.7 (C-12), 130.0 (2C-T<sub>Sar</sub>), 129.4 (C-11), 127.6 (2C-T<sub>Sar</sub>), 117.0 (C-3), 60.3 (C-10), 49.8 (C-7), 31.3 (C-13), 21.7 (C-T<sub>SCH3</sub>), 18.7 (C-9), 14.4 (C-8) ppm.

**IR** (neat):  $\tilde{\nu}$  = 3691, 3391, 2984, 2928, 1714, 1638, 1600, 1356, 1338, 1164, 1093, 1041 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>17</sub>H<sub>22</sub>BrNO<sub>4</sub>S<sup>+</sup>: 415.0448 Found 415.0444.

**ethyl 2-methyl-1-tosyl-5-vinyl-4,5-dihydro-1H-pyrrole-3-carboxylate (III-172a)**

**R<sub>f</sub>** = 0.68 (EtOAc/PE = 1:4)



C<sub>17</sub>H<sub>21</sub>NO<sub>4</sub>S  
M = 335.42 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta = 7.73 - 7.66$  (m, 2H; H<sub>ar</sub>-Ts), 7.31 (d,  $J = 8.0$  Hz, 2H; H<sub>ar</sub>-Ts), 5.88 (ddd,  $J = 16.9, 10.2, 6.6$  Hz, 1H; H-12), 5.42 – 5.27 (m, 1H; H-13a), 5.18 (dd,  $J = 10.3, 1.1$  Hz, 1H; H-13b), 4.72 (ddd,  $J = 10.2, 5.6, 3.3$  Hz, 1H; H-10), 4.20-3.98 (m, 2H; H-6), 2.83 (ddq,  $J = 14.8, 10.6, 2.0$  Hz, 1H; H-11a), 2.46 (t,  $J = 1.9$  Hz, 3H; H-8), 2.43 (s, 3H; CH<sub>3</sub>-Ts), 2.40-2.38 (m, 1H; H-11b), 1.24 ppm (t,  $J = 7.2$  Hz, 3H; H-7).

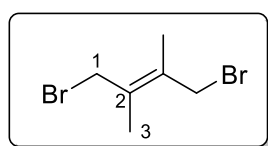
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta = 165.8$  (C-3), 144.3 (C-1), 137.7 (C-T<sub>Sar</sub>), 136.8 (C-12), 130.1 (C-T<sub>Sar</sub>), 127.3 (C-T<sub>Sar</sub>), 116.0 (C-13), 110.9 (C-T<sub>Sar</sub>), 63.1 (C-10), 60.1 (C-6), 34.7 (C-11), 21.7 (C-T<sub>SCH3</sub>), 14.4 ppm (C-7, C-8).

**IR** (neat):  $\tilde{\nu} = 2985, 2930, 1694, 1634, 1357, 1247, 1168, 1096, 986$  cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>17</sub>H<sub>21</sub>NO<sub>4</sub>S<sup>+</sup>: 335.1191 Found 335.1195.

### (E)-1,4-dibromo-2,3-dimethylbut-2-ene (III-144)

A solution of 2,3-dimethylbutadiene (7 mL, 62 mmol, 1.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (44 mL) was placed in a bath cooled to -78 °C and allowed to stir for 30 minutes. A solution of bromine (3.1 mL, 62 mmol, 1.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (18 mL) was added dropwise via addition funnel over 1h. The pale yellow heterogeneous mixture was allowed to stir for 2 hours after the complete addition of bromine at -78 °C upon which the golden yellow mixture was removed from the cooling bath and concentrated via rotary evaporation. (The pressure of the rotary evaporator was reduced to no lower than 100 mbar to prevent sublimation and the flask was submerged into an ice water bath). After complete evacuation of CH<sub>2</sub>Cl<sub>2</sub>, the golden yellow solution was allowed to stand at 23 °C in the dark upon which the colorless solid crystallized out of solution. Cooling in a freezer chilled to -20 °C aids full recovery of the crystalline solid. The mother liquor was decanted to afford the title compound as a colorless crystalline solid (13.3 g, 55 mmol, 89% yield).



C<sub>6</sub>H<sub>10</sub>Br<sub>2</sub>  
M = 241.95 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta = 4.00$  (s, 4H; H-1), 1.88 ppm (s, 6H; H-3).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta = 131.9, 35.0, 17.2$  ppm.

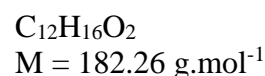
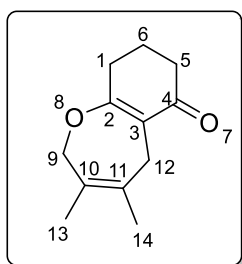
All analytical data matched those found in the literature.<sup>26</sup>

<sup>26</sup> A. M. Camelio, T. C. Johnson, D. Siegel, *J. Am. Chem. Soc.* **2015**, *137*, 11864–11867.

**3,4-dimethyl-5,7,8,9-tetrahydrobenzo[b]oxepin-6(2H)-one (III-145)**

According to general procedure A, the reaction was carried out with 1,3-cyclohexanedione (224 mg, 2 mmol), Cs<sub>2</sub>CO<sub>3</sub> (717 mg) and dibromobutene **III-144** (532 mg) in DMSO at 20°C. Flash chromatography on silica gel (gradient of ethyl acetate/petroleum ether = 1:9 to 3:7) gave product **III-145** as a light yellow oil (45 mg, 12% yield) and product **III-146** as a light yellow oil (125 mg, 33% yield).

R<sub>f</sub> = 0.17 (ethyl acetate/petroleum ether 1/9)



**<sup>1</sup>H NMR** δ = 4.62 (s, 2H, H-9), 3.20 (s, 2H, H-12), 2.35 – 2.23 (m, 4H, H-1 and H-5), 1.88 – 1.80 (m, 2H, H-6), 1.78 (dd, J = 2.2, 1.1 Hz, 3H, H-14), 1.75 ppm (s, 3H, H-13).

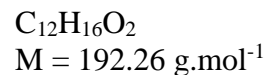
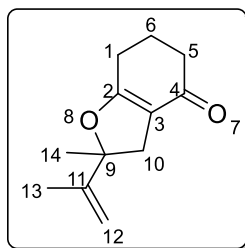
**<sup>13</sup>C NMR** δ = 198.6 (C-4), 174.1 (C-2), 139.2 (C-10), 126.5 (C-11), 113.1 (C-3), 72.1 (C-9), 37.1 (C-5), 31.0 (C-1), 28.1 (C-6), 20.6 (C-12), 20.5 (C-14), 18.2 ppm (C-13).

**IR** (neat):  $\tilde{\nu}$  = 2936, 1642, 1594, 1434, 1389, 1296, 1259, 1186, 1125, 1066, 1011, 968, 906, 863, 727, 595, 454 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>10</sub>H<sub>13</sub>O<sub>2</sub><sup>+</sup>: 192.1145 Found 192.1147.

**2-methyl-2-(prop-1-en-2-yl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (III-146)**

R<sub>f</sub> = 0.25 (ethyl acetate/petroleum ether 3/7)



**<sup>1</sup>H NMR** δ = 4.98 (s, 1H, H-12a), 4.83 (s, 1H, H-12b), 2.83 (d, J = 14.4 Hz, 1H, H-10a), 2.62 (d, J = 14.4 Hz, 1H, H-10b), 2.44 (t, J = 6.2 Hz, 2H, H-1), 2.39-2.29 (m, 2H, H-5), 2.12-1.94 (m, 2H, H-6), 1.76 (s, 3H, H-13), 1.49 ppm (s, 3H, H-14).

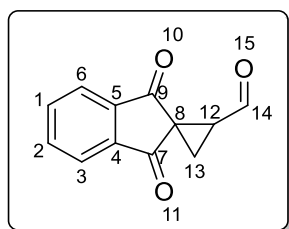


<b><math>^{13}\text{C}</math> NMR</b> (101 MHz, $\text{CDCl}_3$ )	$\delta = 195.9$ (C-4), $176.2$ (C-2), $146.8$ (C-11), $112.7$ (C-3), $110.2$ (C-12), $93.5$ (C-9), $37.6$ (C-10), $36.5$ (C-5), $26.3$ (C-14), $24.2$ (C-1), $21.9$ (C-6), $18.6$ ppm (C-13).
<b>IR</b> (neat):	$\tilde{\nu} = 2941, 2871, 1626, 1398, 1370, 1249, 1184, 1127, 1051, 999, 901, 853, 758, 728, 613$ $\text{cm}^{-1}$ .
<b>HRMS</b> ( $\text{EI}^+$ ):	Calcd. for $\text{C}_{10}\text{H}_{13}\text{O}_2^+$ : 192.1145                      Found 192.1147.

### 1',3'-dioxo-1',3'-dihydrospiro[cyclopropane-1,2'-indene]-2-carbaldehyde (III-151)

To a solution of compound **III-148** (100 mg, 1.0 equiv.) in DCM (2.5 mL) at  $-78^\circ\text{C}$  was applied a flow of ozone for 1 h 30 min. The solution was then quenched by the addition of  $\text{Me}_2\text{S}$  (18  $\mu\text{L}$ , 1.0 equiv.). This was allowed to warm to rt while stirring. Then the reaction was washed with water and extracted with DCM. After drying over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo, the title compound **III-151** was furnished as a light yellow solid (85 mg, 85%).

**Rf** = 0.25 (PE/EtOAc 4:1)



$\text{C}_{12}\text{H}_8\text{O}_3$   
 $M = 200.19$   $\text{g}\cdot\text{mol}^{-1}$

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta = 9.57$  (d,  $J = 6.8$  Hz, 1H; H-14),  $8.04 - 7.93$  (m, 2H; H-2, H-6),  $7.91 - 7.75$  (m, 2H; H-1, H-3),  $2.79$  (ddd,  $J = 8.6, 7.5, 6.9$  Hz, 1H; H-12),  $2.47$  (dd,  $J = 7.5, 4.5$  Hz, 1H; H-13a),  $2.23$  ppm (dd,  $J = 8.7, 4.5$  Hz, 1H; H-13b).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta = 196.5, 196.2, 195.0, 142.0, 141.8, 135.7, 135.7, 123.2, 123.1, 41.5, 41.0, 21.1$  ppm.

**IR** (neat):  $\tilde{\nu} = 2857, 1713, 1597, 1348, 1282, 1215, 1157, 1080, 1009$   $\text{cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd for  $\text{C}_{12}\text{H}_8\text{O}_3^+$ : 200.0468                      Found 200.0462.

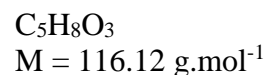
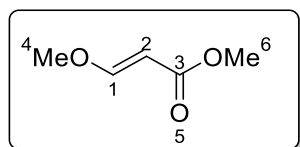
**Mp** =  $116^\circ\text{C}$

### methyl (E)-3-methoxyacrylate (III-110)

Methyl propiolate (1.1 mL 1.0 equiv.) was added dropwise to a stirred solution of triethylamine (1.6 mL, 1.0 equiv.) and MeOH (0.48 mL, 1.0 equiv.) in  $\text{Et}_2\text{O}$  (15 mL) at  $0^\circ\text{C}$ . The resulting reaction mixture was stirred at rt for 2h, then carefully acidified with HCl 1M

and extracted with Et<sub>2</sub>O. The combined organic phases were washed with saturated NaHCO<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue was purified by flash chromatography with a gradient solvent system pentane/Et<sub>2</sub>O (10:1 to 4:1) and afforded compound **II-109** a colorless liquid (1.2 g, 88% yield).

**R<sub>f</sub>** = 0.44 (pentane/ Et<sub>2</sub>O 7:3)



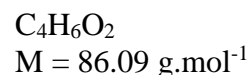
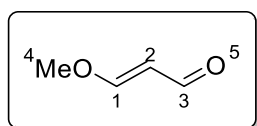
**<sup>1</sup>H NMR** δ = 7.64 (d, J=12.6Hz, 1H; H-1), 5.20 (d, J=12.6Hz, 1H; H-2), 3.71 (400 MHz, CDCl<sub>3</sub>) (s, 3H; H-4/6), 3.70 (s, 3H; H-4/6) ppm.

All analytical data matched those found in the literature.<sup>27</sup>

### (E)-3-methoxyacrylaldehyde (**III-108**)

To a solution of methyl (E)-3-methoxyacrylate **III-110** (0.46 mL, 1.0 equiv.) in DCM (15 mL) was added dropwise a solution of DIBALH in toluene (6.5 mL, 1.5 M, 2.25 equiv.) during 10 min at -78°C. After 1h stirring, the reaction was quenched with Rochelle salts, stirring for further 90 min. The liquid layer was separated from the precipitate and extracted with DCM. After dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuo, the crude mixture was passed through a small pad of silica to eliminate toluene, eluting with pentane/Et<sub>2</sub>O (100% to 1:1). The resulted product was concentrated and dissolved in DCM (15 mL). After added MnO<sub>2</sub> (4.7 g), 17 equiv.), the reaction was kept stirring for 16h. The furnished reaction mixture was filtered through Celite® and washed with Et<sub>2</sub>O/pentane (1:1) to yield a colorless oil as title compound (80 mg, 22%).

**R<sub>f</sub>** = 0.3 (Et<sub>2</sub>O/pentane 1:1)



**<sup>1</sup>H NMR** δ = 9.31 (s, 1H; H-3), 7.61 (d, J = 12.6 Hz, 1H; H-2), 5.56 ppm (d, J = 12.6 Hz, 1H; H-1).

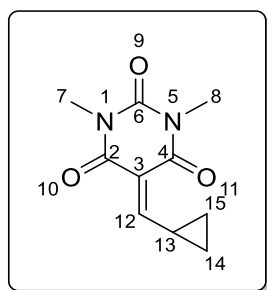
All analytical data matched those found in the literature.<sup>28</sup>

<sup>27</sup> J. Wang, H. Wang, H. Ren, *Synthetic Communications* **2010**, *40*, 980-983.

**5-(cyclopropylmethylene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (III-111a)**

To a stirred solution of cyclopropanecarbaldehyde (21  $\mu$ L, 1.0 equiv.) and 1,3-dimethylbarbituric acid (53 mg, 1.2 equiv.) in toluene (1.5 mL 0.2 M) was added L-proline (4 mg, 0.1 equiv.), then the resulting solution was stirring at rt and monitoring by TLC analysis. After 16 h, the reaction mixture was filtered to give a light yellow solid which was purified by flash chromatography (cyclohexane/EtOAc = 4:1) to give the title compound (48 mg, 78% yield).

**Rf** = 0.24 (cyclohexane/EtOAc 4:1)



$C_{10}H_{12}N_2O_3$   
 $M = 208.22 \text{ g}\cdot\text{mol}^{-1}$

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.20$  (d,  $J = 11.9$  Hz, 1H; H-12), 3.61 – 3.41 (m, 1H; H-13), 3.36 (s, 3H; H-7/8), 3.35 (s, 3H; H-7/8), 1.49 – 1.32 (m, 2H; H-14/15), 1.14 – 1.00 ppm (m, 2H; H-14/15).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta = 174.13, 161.94, 151.63, 118.01, 28.75, 28.16, 16.40, 14.16$  ppm.

**IR** (neat):  $\tilde{\nu} = 2956, 2923, 1736, 1659, 1575, 1443, 1415, 1306, 1257, 1152, 1087, 1054, 952, 899, 858, 748 \text{ cm}^{-1}$

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $^+$ : 208.0848 Found 208.0842.

**Mp** = 155°C

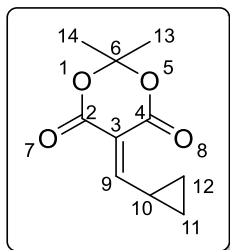
**5-(cyclopropylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (III-111b)**

To a stirred solution of cyclopropanecarbaldehyde (21  $\mu$ L, 1.0 equiv.) and Meldrum's acid (49 mg, 1.2 equiv.) in toluene (1.5 mL 0.2M) was added L-proline (4 mg, 0.1 equiv.), then the resulting solution was stirred at rt, monitoring by TLC. After 16 h, the reaction mixture

<sup>28</sup> Y. V. Quang, D. Marais, L. V. Quang, F. Le Goffic, *Tetrahedron Letters* **1983**, *24*, 5209-5210.

was filtered to give a light yellow solid which was purified by flash chromatography (cyclohexane/EtOAc = 5:1) to give compound **III-111b** (48 mg, 85% yield).

**R<sub>f</sub>** = 0.19 (cyclohexane/EtOAc 5:1)



$C_{10}H_{12}O_4$   
 $M = 196.20 \text{ g}\cdot\text{mol}^{-1}$

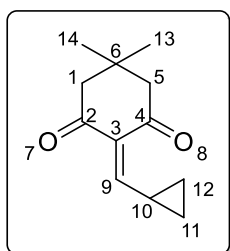
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.19 (d, *J* = 11.9 Hz, 1H; H-9), 3.21 (m, 1H; H-10), 1.74 (s, 6H; H-13, H-14), 1.50 – 1.42 (m, 2H; H-11/12), 1.12 – 1.06 ppm (m, 2H; H-11/12).

All analytical data matched those found in the literature.<sup>29</sup>

### 2-(cyclopropylmethylene)-5,5-dimethylcyclohexane-1,3-dione (**III-111c**)

To a stirred solution of cyclopropanecarbaldehyde (40  $\mu$ L, 0.54 mmol, 1.2 equiv.) and 5,5-dimethyl-1,3-cyclohexanedione (50 mg, 1.0 equiv.) in toluene (5 mL 0.1M) was added L-proline (5 mg, 0.1 equiv.), then the resulting solution was stirred at rt, monitoring by TLC. After 16 h, the reaction mixture was filtered to give a light yellow solid which was purified by flash chromatography (cyclohexane/EtOAc = 5:1 to 4:1) to give compound **III-111c** (64 mg, 88% yield).

**R<sub>f</sub>** = 0.19 (cyclohexane/EtOAc 5:1)



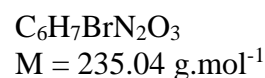
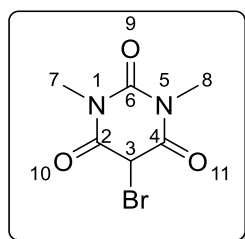
$C_{12}H_{16}O_2$   
 $M = 196.26 \text{ g}\cdot\text{mol}^{-1}$

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.76 (d, *J* = 11.8 Hz, 1H; H-9), 3.30 – 3.11 (m, 1H; H-10), 2.51 (s, 2H; H-1/5), 2.47 (s, 2H; H-1/5), 1.34-1.29 (m, 2H; H-11/12), 0.97-0.93 (m, 2H; H-11/12), 1.06 ppm (s, 6H; H-13 and H-14).

<sup>29</sup> K. Liu, W. Rao, H. Parikh, Q. bin, L. T. L. Guo, S. Grant, G. E. Kellogg, S. Zhang, European Journal of Medicinal Chemistry 47, 2012, 125-137.

**5-bromo-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (III-114)**

1,3-Dimethylbarbituric acid (200 mg, 1.0 equiv.) was dissolved in NaOH solution (2 mL, 0.5 M), the resulting solution was kept at 0-3 °C while Br<sub>2</sub> (65 μL, 1.0 equiv.) was added slowly. The mixture was stirred at 25 °C for further 2 h. The resulting precipitate was filtered and washed with water. The product was dried under vacuum to afford a pink crystalline solid (301 mg, 83%).



**<sup>1</sup>H NMR**  $\delta = 4.66$  (s, 1H; H-3), 3.34 ppm (s, 6H; H-7, H-8).  
(400 MHz, CDCl<sub>3</sub>)

**<sup>13</sup>C NMR**  $\delta = 167.9, 150.6, 48.9, 29.4$  ppm.  
(101 MHz, CDCl<sub>3</sub>)

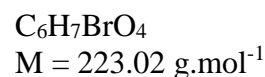
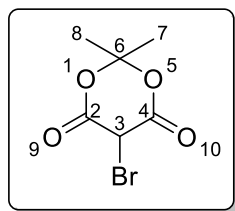
**IR** (neat):  $\tilde{\nu} = 2923, 2853, 1671, 1447, 1380, 1294, 1091, 988, 753$  cm<sup>-1</sup>.

All analytical data matched those found in the literature.<sup>30</sup>

**5-bromo-2,2-dimethyl-1,3-dioxane-4,6-dione (III-116)**

2,2-Dimethyl-[1,3]dioxane-4,6-dione (300 mg, 1.0 equiv.) was dissolved with a 1M NaOH solution (0.8 mL). Bromine (106 μL, 174 mmol) was added at 0 °C over 10 min. The white precipitate was formed immediately and then filtered off. The solid was washed with cold water and dried under vacuum to give 5-bromo-2,2-dimethyl-[1,3]dioxane-4,6-dione (**III-116**) (320 mg, 69%) as a white solid.

<sup>30</sup> K. Sweidan, A. Al-Sheikhb, B. Sweilehc, M. Sunjukd, N. Kuhn, *Letters in Organic Chemistry* **2009**, *6*, 1-3.



**$^1\text{H NMR}$**   $\delta = 5.12$  (s, 1H), 1.93 (s, 3H), 1.83 ppm (s, 3H).  
(400 MHz,  $\text{CDCl}_3$ )

**IR** (neat):  $\tilde{\nu} = 3003, 2916, 1748, 1396, 1385, 1286, 1199, 1010, 867 \text{ cm}^{-1}$

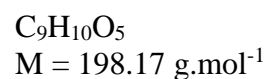
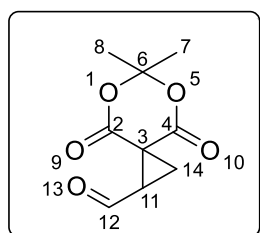
**Mp** = 53-54°C

All analytical data matched those found in the literature.<sup>31</sup>

### 6,6-dimethyl-4,8-dioxo-5,7-dioxaspiro[2.5]octane-1-carbaldehyde (III-117)

To a solution of acrolein (296  $\mu\text{L}$ , 5.0 equiv.) in DMF (2 mL) was added monobromide **III-116** (200 mg, 1.0 equiv.), followed by  $\text{K}_2\text{CO}_3$  (244 mg, 2.0 equiv.). The heterogeneous mixture was stirred vigorously until the reaction was deemed to be complete by TLC analysis. Glacial AcOH was added and the solution was then diluted with EtOAc and water. The organic layer was separated and then the aqueous layer was extracted five times with EtOAc. The combined organic layers were washed with water and brine, dried over  $\text{MgSO}_4$  and concentrated in vacuo. The title compound was purified by flash chromatography with a gradient solvent system cyclohexane/EtOAc (4:1 to 7:3) to afford an oily product (77 mg, 44% yield).

**Rf** = 0.17 (cyclohexane/EtOAc 7:3)



**$^1\text{H NMR}$**   $\delta = 9.43$  (d,  $J = 5.6 \text{ Hz}$ , 1H; H-12), 2.85 (ddd,  $J = 9.2, 8.3, 5.6 \text{ Hz}$ , 1H; H-11), 2.66 (dd,  $J = 8.3, 4.6 \text{ Hz}$ , 1H; H-14a), 2.44 (dd,  $J = 9.2, 4.6 \text{ Hz}$ , 1H; H-14b), 1.82 (d,  $J = 0.5 \text{ Hz}$ , 3H; H-H/7/8), 1.79 ppm (d,  $J = 0.5 \text{ Hz}$ , 3H; H-7/8).

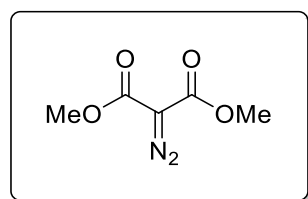
<sup>31</sup> S. Perreault, C. Spino, *Org. Lett.* **2006**, *8*, 4385-4388.

<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta$ = 195.1, 165.8, 165.1, 116.3, 106.3, 41.5, 28.0, 28.8, 23.8 ppm.	
<b>IR</b> (neat):	$\tilde{\nu}$ = 3448, 1741, 1322, 1283, 1201, 1046, 968, 759, 664 cm <sup>-1</sup> .	
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd. for C <sub>9</sub> H <sub>10</sub> O <sub>5</sub> <sup>+</sup> : 198.0528	Found 183.0294.

### dimethyl 2-diazomalonate (III-122)

Dimethylmalonate (0.43 mL, 1.0 equiv.), triethylamine (1.3 mL, 1.1 equiv.) and 4-acetamidobenzenesulfonyl azide (1.4 g, 1.5 equiv.) were dissolved in acetonitrile (15 mL) at 0°C. The solution was stirred at room temperature for 3 hours and then filtered on cotton. The obtained solution was concentrated under reduced pressure and purified by column chromatography (pentane/EtOAc 8:2) afforded title compound as yellow oil (587 mg, 100% yield).

**R<sub>f</sub>** = 0.32 (Pentane/Et<sub>2</sub>O 1:1).



C<sub>5</sub>H<sub>6</sub>N<sub>2</sub>O<sub>4</sub>  
M = 158.11 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR**  $\delta$  = 3.87 ppm (s, 1H, OCH<sub>3</sub>).  
(400 MHz, CDCl<sub>3</sub>)

**<sup>13</sup>C NMR**  $\delta$  = 161.2, 52.4 ppm.  
(101 MHz, CDCl<sub>3</sub>)

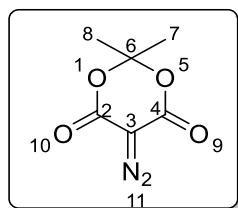
All analytical data matched those found in the literature.<sup>32</sup>

### 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione (III-123)

To a solution of MsCl (59  $\mu$ L, 1.1 equiv.) in MeCN (6 mL) was added NaN<sub>3</sub> (54 mg, 1.2 equiv.) at rt, then stirring for 3h. The resulting mixture was added to a solution of Meldrum's acid (100 mg) and Et<sub>3</sub>N (187  $\mu$ L, 2 equiv.) at 0°C. After 1h stirring, the solvent of the reaction was evaporated and purified through a pad of silica eluting with EtOAc/Et<sub>2</sub>O 5:95). The title compound was obtained as a white solid (143 mg, 61% yield).

<sup>32</sup> F. de Nanteuil, E. Serrano, D. Perrotta, J. Waser, *J. Am. Chem. Soc.* **2014**, *136*, 6239–6242.

R<sub>f</sub> = 0.8 (EtOAc/Et<sub>2</sub>O 5:95)



C<sub>6</sub>H<sub>6</sub>N<sub>2</sub>O<sub>4</sub>  
M = 170.12 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** δ = 3.32 ppm (s, 6H; 2CH<sub>3</sub>).  
(400 MHz, DMSO-d<sub>6</sub>)

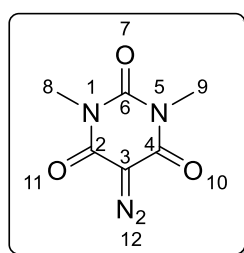
**IR** (neat):  $\tilde{\nu}$  = 3201, 3084, 2845, 2428, 2281, 1788, 1727, 1452, 1402, 1253, 1030, 802, 752 cm<sup>-1</sup>.

All analytical data matched those found in the literature.<sup>33</sup>

### 5-diazo-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (III-124)

To a solution of MsCl (109 μL, 1.1 equiv.) in MeCN (3 mL) was added NaN<sub>3</sub> (100 mg, 1.2 equiv.) at rt, then stirring for 3h. The resulting mixture was added to a solution of 1,3-dimethyl-barbituric acid (200 mg) and Et<sub>3</sub>N (345 μL, 2 equiv.) at 0°C. After 1h stirring, the solvent of the reaction was evaporated and purified through a pad of silica eluting with EtOAc. The title compound was obtained as a yellow solid (232 mg, 99% yield).

R<sub>f</sub> = 0.19 (EtOAc/cyclohexane 1:4)



C<sub>6</sub>H<sub>6</sub>N<sub>4</sub>O<sub>3</sub>  
M = 182.14 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** δ = 3.35 ppm (s, 6H; H-8 and H-9).  
(400 MHz, DMSO-d<sub>6</sub>)

**IR** (neat):  $\tilde{\nu}$  = 3333, 3264, 2156, 1658, 1576, 1379, 1309, 1140, 988, 880, 773, 685 cm<sup>-1</sup>.

All analytical data matched those found in the literature.<sup>33</sup>

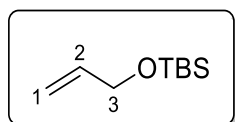
<sup>33</sup> D. B. Ramachary, V. V. Narayana, K. Ramakumar, *Tetrahedron Lett.* **2008**, 49, 2704–2709.



**(allyloxy)(tert-butyl)dimethylsilane (III-127)**

To a solution of TBSCl (300 mg, 1.0 equiv.) in dry THF (5 mL) was added imidazole (327 mg, 2.4 equiv.) under argon. The solution was stirred for 5 min before prop-2-en-1-ol (207  $\mu$ L, 1.5 equiv.) was added. The reaction mixture was filtered through a plug of layered Celite<sup>®</sup> and silica gel, eluting with pentane. The resulted colorless filtrate was concentrated in vacuo and then dissolved in Et<sub>2</sub>O. The solution was then treated with saturated NH<sub>4</sub>Cl solution and extracted with Et<sub>2</sub>O. After washed with brine and dried over MgSO<sub>4</sub>, the oiliness title compound was obtained by evaporation under vacuum (112 mg, 33%).

Rf = 0.42 (EtOAc/pentane 5:95)



C<sub>9</sub>H<sub>20</sub>OSi  
M = 172.34 g.mol<sup>-1</sup>

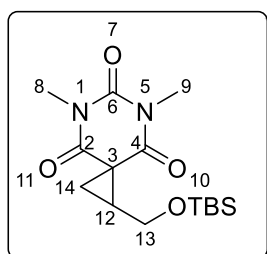
<sup>1</sup>H NMR  
(400 MHz, CDCl<sub>3</sub>)

$\delta$  = 5.92 (ddt, J = 17.1, 10.4, 4.6 Hz, 1H; H-2), 5.27 (dq, J = 17.1, 1.9 Hz, 1H; H-1a), 5.08 (dq, J = 10.4, 1.7 Hz, 1H; H-1b), 4.18 (dt, J = 4.5, 1.8 Hz, 2H; H-3), 0.92 (s, 9H; H<sub>tBu</sub>-TBS), 0.08 ppm (s, 6H; H<sub>CH<sub>3</sub></sub>-TBS).

**1-(((tert-butyl)dimethylsilyloxy)methyl)-5,7-dimethyl-5,7-diazaspiro[2.5]octane-4,6,8-trione (III-125b)**

To a solution of **III-127** (19 mg, 2.0 equiv.) and Rh<sub>2</sub>(TPA)<sub>4</sub> (7.9 mg, 0.01 equiv.) was added dropwise compound **III-124** in CDCl<sub>3</sub> (0.3 mL). Then the mixture was stirring at 50°C for 16h. The resulted mixture was concentrated and purified directly by flash chromatography with a gradient solvent system cyclohexane/EtOAc (95:5 to 80:20), which yield an oily product (2.7 mg, 15%).

Rf = 0.33 (cyclohexane/EtOAc 4:1)



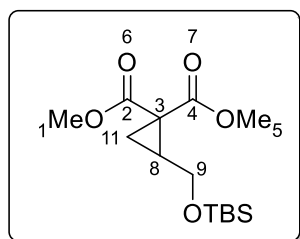
C<sub>15</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>Si  
M = 326.47 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.02 (dd, *J* = 11.5, 5.0 Hz, 1H; H-13a), 3.75 (dd, *J* = 11.5, 9.6 Hz, 1H; H-13b), 3.32 (d, *J* = 5.0 Hz, 6H; H-8, H-9), 2.54-2.39 (m, 1H; H-12), 2.21-2.11 (m, 1H; H-14a), 2.00 (dd, *J* = 8.8, 3.8 Hz, 1H; H-14b), 0.82 (s, 9H; H<sub>tBu</sub>-TBS), 0.01 ppm (s, 3H; H<sub>CH3</sub>-TBS), -0.01 ppm (s, 3H; H<sub>CH3</sub>-TBS).

**dimethyl 2-(((tert-butyl)dimethylsilyloxy)methyl)cyclopropane-1,1-dicarboxylate (III-125a)**

To a solution of **III-127** (11 mg, 1.0 equiv.) and Rh<sub>2</sub>(OAc)<sub>4</sub> (1.4 mg, 0.05 equiv.) was added dropwise dimethyl diazomalonate **III-122** (11 mg, 1.1 equiv.) in CDCl<sub>3</sub> at rt. Then the mixture was stirred at 50°C for 16h. The resulted mixture was concentrated and purified directly by flash chromatography with a gradient solvent system cyclohexane/EtOAc (95:5 to 80:20), which yielded a oily product (9 mg, 43%).

**R<sub>f</sub>** = 0.6 (cyclohexane/EtOAc 7:3)



C<sub>14</sub>H<sub>26</sub>O<sub>5</sub>Si  
M = 302.44 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 3.76-3.71(m, 1H; H-9a), 3.74 (s, 3H; H-1/5), 3.72 (d, *J* = 1.7 Hz, 3H; H-1/5), 3.67 (dd, *J* = 11.1, 6.2 Hz, 1H; H-9b), 2.26 – 2.02 (m, 1H; H-8), 1.56 (dd, *J* = 7.6, 4.6 Hz, 1H; H-11a), 1.39 (dd, *J* = 9.2, 4.6 Hz, 1H; H-11b), 0.86 (s, 9H; H<sub>tBu</sub>-TBS), 0.02 ppm (s, 6H; H<sub>CH3</sub>-TBS).

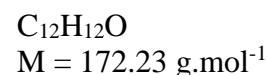
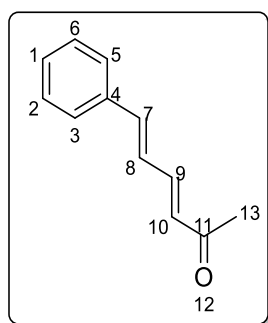
## 1.4. Chapter IV: Total synthesis of oxepin-based natural products

### 1.4.1 Total synthesis of radulanins

#### (3E,5E)-6-phenylhexa-3,5-dien-2-one (IV-20)

A solution of NaOH (8 mL, 3 mol/L, 1.0 equiv.) was slowly added to a flask containing acetone (30 mL, 20 equiv.) and *trans*-cinnamaldehyde (4 g, 0.03 mol, 1.0 equiv.) at 0°C under argon. The reaction was stirred at 0°C for 1h and monitored by TLC. When the reaction was completed, an aqueous 10% HCl solution was added to adjust pH to 2-3. Then acetone was evaporated at maximum under reduced pressure and the remaining aqueous phase was extracted with diethyl ether. The gathered organic layers were dried and evaporated under reduced pressure. The crude mixture was purified by flash chromatography with EtOAc/petroleum ether (5/95 to 10/90) and the obtained solid could be further purified by recrystallization in absolute ethanol, filtered and washed with iced distilled water to get desired compound **IV-20** as a yellow solid (2.6g, 0.02 mol, 75% yield).

**R<sub>f</sub>** = 0.34 (EtOAc/petroleum ether : 1/9)



**<sup>1</sup>H NMR**                    δ = 7.45 (dd, J = 8.2, 1.3 Hz, 2H, H-3 and H-5), 7.37-7.22 (m, 4H, H-1, H-2, H-6, H-7), 6.88 (m, 2H; H-8 and H-9), 6.23 (d, J = 15.5 Hz, 1H, H-10), 2.29 ppm (s, 3H, CH<sub>3</sub>).

**<sup>13</sup>C NMR**                    δ = 198.4, 143.5, 141.3, 136.0, 130.5, 129.3, 128.9, 127.3, 126.7, 77.5, 77.2, 76.8, 27.4 ppm.

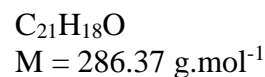
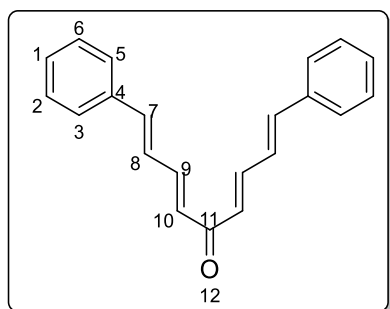
All data matched those found in the literature.<sup>34</sup>

#### (1E,3E,6E,8E)-1,9-diphenylnona-1,3,6,8-tetraen-5-one (IV-21)

<sup>34</sup> R. L. Nongkhilaw, R. Nongrum, B. Myrboh, *J. Chem. Soc., Perkin Trans.* **2001**, *1*, 1300-1303.

This yellow solid byproduct was produced at the same time of aldolization step as byproduct.

R<sub>f</sub> = 0.18 (20 % petroleum ether in n-hexane)



<sup>1</sup>H NMR  $\delta = 7.56\text{-}7.27$  (m, 12H, H-Ar and H-7),  $7.05\text{-}6.83$  (m, 4H, H-8 and H-9),  $6.57$  ppm (d,  $J = 15.2$  Hz, 2H, H-10).

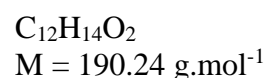
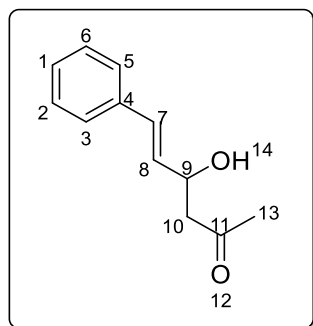
<sup>13</sup>C NMR  $\delta = 188.9, 143.0, 141.5, 136.2, 129.1, 129, 128.8, 127.3, 127.0$  ppm. (101 MHz, CDCl<sub>3</sub>)

All data matched those found in the literature.<sup>35</sup>

#### (E)-4-hydroxy-6-phenylhex-5-en-2-one (IV-22)

This yellow liquid byproduct was produced at the same time of aldolization step as byproduct.

R<sub>f</sub> = 0.14 (EtOAc/ Petroleum ether: 1/9)



<sup>1</sup>H NMR  $\delta = 7.46\text{-}7.16$  (m, 5H, H-Ar),  $6.64$  (d,  $J = 15.9$  Hz, 1H, H-7),  $6.20$  (dd,  $J = 15.9, 6.1$  Hz, 1H, H-8),  $4.76$  (q,  $J = 5.6$  Hz, 1H, H-9),  $3.13$  (s, 1H, OH),  $2.76$  (d,  $J = 6.0$  Hz, 2H, H-10),  $2.21$  ppm (s, 3H, CH<sub>3</sub>).

<sup>13</sup>C NMR  $\delta = 209.1, 136.6, 130.6, 130.2, 128.7, 127.9, 126.6, 68.6, 50.1, 31.0$

<sup>35</sup> a) I. M. Ferreira, E. B. Meira, I. G. Rosset, A. L. M. Porto., *Journal of Molecular Catalysis B: Enzymatic* **2015**, 115, 59-65; b) G. Liang, S. Yang, L. Jiang, Y. Zhao, L. Shao, J. Xiao, F. Ye, Y., X. Li, *Chem. Pharm. Bull.* **2008**, 56, 2, 162-167.

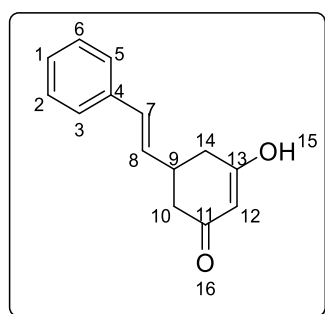
(101 MHz, CDCl<sub>3</sub>) ppm.

All data matched those found in the literature<sup>36</sup>

### (E)-3-hydroxy-5-styrylcyclohex-2-en-1-one (IV-23)

A 1 M solution of sodium methoxide (6 mL, 1,1 equiv.) was freshly prepared by dissolving sodium metal in dry methanol under argon. Then distilled dimethyl malonate (729  $\mu$ L, 1,1 equiv.) was added. The reaction mixture was stirred under ambient temperature for 20 min and then transferred to a flask containing ketone **IV-20** (1 g, 5.8 mmol, 1.0 equiv.) in 50 mL dry methanol. The reaction mixture was allowed to reflux for 12h. The resulting mixture was then concentrated under vacuum, resulting the crude ester as a dark red/brown solid. This crude product was placed directly in 20 mL distilled water, and an aqueous solution of 4mL potassium hydroxide (10 M) was added. The reaction mixture was refluxed for 2 h. The brown solid formed during the reflux was removed by filtration and an aqueous solution of hydrochloric acid (10 M) was added to the resulting solution of the crude carboxylic acid salt until pH=2. After refluxing for 2h, the flask was cooled to ambient temperature and then placed in an ice bath for 30 minutes. The resulting yellow solid was collected by filtration, washed with DCM, and purified by recrystallization to obtain a white solid as title compound **IV-23** (630 mg, 3 mmol, 52% yield).

R<sub>f</sub> = 0.15 (100% EtOAc)



C<sub>14</sub>H<sub>14</sub>O<sub>2</sub>  
M = 214.26 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, DMSO)  $\delta$  = 11.17 (s, 1H, OH), 7.40 (d, J = 7.5 Hz, 2H, H-3 and H-5), 7.32 (t, J = 7.6 Hz, 2H, H-2 and H-6), 7.22 (t, J = 7.2 Hz, 1H, H-1), 6.46 (d, J = 16.1 Hz, 1H, H-7), 6.32 (dd, J = 16.0, 6.7 Hz, 1H, H-8), 5.25 (s, 1H, H-12), 3.00-2.83 (m, 1H, H-9), 2.48-2.23 ppm (m, 4H, H-10 and H-14).

<sup>36</sup> I. Simpura, V. Nevalainen, *Tetrahedron* **2003**, 59, 7535–7546.

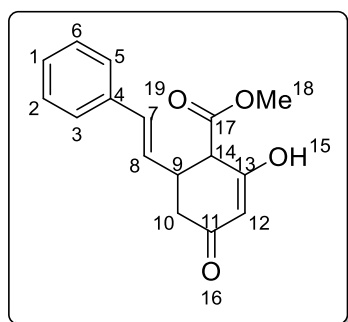
**$^{13}\text{C}$  NMR**  $\delta$  = 175.4, 144.4, 136.8, 132.5, 129.0, 128.6, 127.3, 126.1, 103.6, (101 MHz, DMSO) 36.4 ppm.

All data matched those found in the literature<sup>37</sup>

### methyl (E)-2-hydroxy-4-oxo-6-styrylcyclohex-2-ene-1-carboxylate (IV-24)

A 1M solution of sodium methoxide (18 mL, 1.1 equiv.) was freshly prepared by dissolving sodium metal in dry methanol under argon. Then distilled dimethyl malonate (2.9 mL, 1.1 equiv.) was added. The reaction mixture was stirred under ambient temperature for 20 min and then transferred to a flask containing ketone **IV-20** (2.9 g, 16.8 mmol, 1.0 equiv.) in 150 mL dry methanol. The reaction mixture was allowed to reflux for 12h. The resulting mixture was then adjusted to pH=5 and concentrated under reduced pressure to remove methanol. Then aqueous was extracted with EtOAc three times. After concentrated the organic phase, the resulting mixture was washed with diethyl ether and then recrystallized in MeOH/Et<sub>2</sub>O to get a white solid as title compound (1.8 g, 6.7 mmol, 40% yield).

**Rf** = 0.3 (petroleum ether/EtOAc: 5/5)



$\text{C}_{16}\text{H}_{16}\text{O}_4$   
 $M = 272.30 \text{ g}\cdot\text{mol}^{-1}$

**$^1\text{H}$  NMR**  $\delta$  = 11.56 (s, 1H, OH), 7.43-7.28 (m, 4H, H-2, H-3, H-5 and H-6), 7.27 -7.17 (m, 1H, H-1), 6.47 (d,  $J = 15.9$  Hz, 1H, H-7), 6.20 (dd,  $J = 15.9, 8.1$  Hz, 1H, H-8), 5.29 (s, 1H, H-12), 3.58 (s, 3H, H-18), 3.44 (d,  $J = 11.4$  Hz, 1H, H-14), 3.22-3.03 (m, 1H, H-10a), 2.66-2.54 (m, 1H, H-9), 2.42 ppm (dd,  $J = 17.2, 4.8$  Hz, 1H, H-10b).

**$^{13}\text{C}$  NMR**  $\delta$  = 170.7 (C-11 and C-17), 136.7 (C-13), 131.1 (C-12), 130.1 (C-1), 128.9 (C-3 and C-5), 127.8 (C-2 and C-6), 126.4 (C-4), 103.8 (C-8), 102.9 (C-7), 52.1/51.8 (C-18), 48.8 (C-14), 38.2 (C-10), 36.6 ppm (C-9).

**IR** (neat):  $\tilde{\nu} = 3676, 2955, 2893, 1732, 1611, 1590, 1520, 1341, 1309, 1234,$

<sup>37</sup> M. F. Mechelke, A. A. Dumke, S. E. Wgwerth, *Journal of undergraduate chemistry research* **2013**, *12*, 47-50.

1176, 1152, 1093, 965  $\text{cm}^{-1}$ .HRMS (EI<sup>+</sup>):Calcd for  $\text{C}_{10}\text{H}_{13}\text{O}_2^+$ : 272.1043

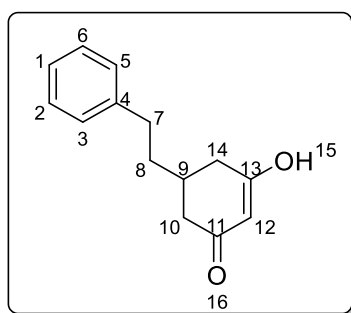
Found 272.1037.

Mp= 175°C

**3-hydroxy-5-phenethylcyclohex-2-en-1-one (IV-25)**

The flask containing a mixture of compound **IV-23** (190 mg, 0.89 mmol, 1.0 equiv.) and 10% Pd/C (2 mg, 2 mol %) in MeOH (15 mL) was placed under a hydrogen flux (generator) for 40 min. The reaction mixture was then filtered through Celite, and the solvent was removed in vacuo to give title compound **IV-25** (yield 190 mg, 0.089 mmol, 100%).

Rf = 0.15 (100% EtOAc)



$\text{C}_{14}\text{H}_{16}\text{O}_2$   
 $M = 216.28 \text{ g}\cdot\text{mol}^{-1}$

<sup>1</sup>H NMR  
(400 MHz, DMSO)

$\delta = 7.38\text{-}7.08$  (m, 5H; H-Ar), 5.17 (s, 1H; H-12), 3.47 (br s, 1H; OH), 2.59 (pseudo t,  $J = 7.8$  Hz, 2H; H-7), 2.30 (dd,  $J = 16.6, 4.1$  Hz, 2H; H-10/H-14), 2.07 (dd,  $J = 16.3, 11.3$  Hz, 2H; H-10/H-14), 2.01-1.87 (m, 1H; H-9), 1.74 – 1.53 ppm (m, 2H; H-8).

<sup>13</sup>C NMR  
(101 MHz, DMSO)

$\delta = 189.7$  (C-11 and C-13), 141.9 (C-4), 128.3 (C-3 and C-5), 128.2 (C-2 and C-6), 125.7 (C-1), 103.4 (C-12), 39.0 (C-10 and C-14), 36.7 (C-8), 32.9 (C-9), 32.2 ppm (C-7).

IR (neat):

$\tilde{\nu} = 3668, 3024, 2921, 2856, 1718, 1582, 1454, 1394, 1311, 1220, 1143, 1047 \text{ cm}^{-1}$ .

HRMS (EI<sup>+</sup>):Calcd for  $\text{C}_{10}\text{H}_{13}\text{O}_2^+$ : 216.1145

Found 216.1143.

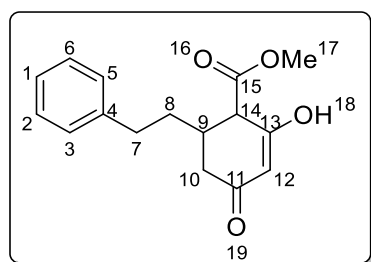
Mp= 137°C

**methyl 2-hydroxy-4-oxo-6-phenethylcyclohex-2-ene-1-carboxylate (IV-26)**

The flask containing a mixture of compound **IV-24** (1.1 g, 4 mmol, 1.0 equiv.) and 10% Pd/C (110 mg, 2 mol %) in MeOH (51 mL) was placed under hydrogen flux (generator) for 40 min. The reaction mixture was then filtered through Celite®, and the solvent was

removed in vacuo to give title compound **IV-26** (yield 1.08 g, 3.9 mmol, 98%).

**Rf** = 0.3 (petroleum ether/EtOAc: 5/5)



$C_{16}H_{18}O_4$   
 $M = 274.32 \text{ g}\cdot\text{mol}^{-1}$

**$^1\text{H NMR}$**   $\delta = 7.29\text{-}7.20$  (m, 2H, H-3 and H-5),  $7.20\text{-}7.10$  (m, 3H, H-2, H-6 and H-1),  $5.05$  (s, 1H, H-12),  $3.69$  (s, 3H, H-17),  $3.25$  (d,  $J = 10.7$  Hz, 1H, H-14),  $2.76\text{-}2.66$  (m, 1H, H-10a),  $2.61$  (dd,  $J = 17.1, 4.5$  Hz, 1H, H-7a),  $2.56\text{-}2.49$  (m, 1H, H-9),  $2.47\text{-}2.37$  (m, 1H, H-10b),  $2.29$  (dd,  $J = 17.1, 10.5$  Hz, 1H, H-7b),  $1.75\text{-}1.55$  ppm (m, 2H, H-8).

**$^{13}\text{C NMR}$**   $\delta = 193.3$  (C-11),  $185.4$  (C-15),  $172.9$  (C-13),  $142.8$  (C-4),  $129.5$  (C-Ar),  $127.1$  (C-1),  $104.0$  (C-12),  $58.5/52.7$  (C-17),  $38.4$  (C-14),  $37.3$  (C-10),  $36.8$  (C-8),  $35.3$  (C-9),  $33.9$  ppm (C-7).

**IR** (neat):  $\tilde{\nu} = 3181, 2920, 2851, 1737, 1594, 1454, 1316, 1226, 1154, 1029 \text{ cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd for  $C_{16}H_{18}O_4^+$ : 274.1200 Found 274.1197.

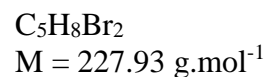
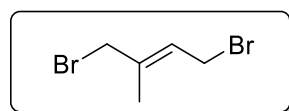
**Mp** =  $175^\circ\text{C}$

### (E)-1,4-dibromo-2-methylbut-2-ene (III-139)

To a solution of 60 mmol of isoprene and 6 mmol  $\text{K}_2\text{CO}_3$  in 30 mL of n-hexane was dropwise added dropwise 30 mmol of bromine at a temperature range from  $-50^\circ\text{C}$  to  $-30^\circ\text{C}$ . The resulting reaction solution was stirred for 2.5 hours at  $-30^\circ\text{C}$ . Then the reaction was hydrolyzed with water, followed by extraction with  $\text{Et}_2\text{O}$ . The resulting organic layer was washed sequentially with a diluted aqueous solution of sodium thiosulfate, a diluted aqueous solution of sodium hydrogencarbonate and brine. After drying over anhydrous sodium sulfate, the filtered solution was evaporated under vacuum (not under 100 mbar) to give a crude 1,4-dibromo-2-methyl-2-butene. Purification by flash chromatography column with  $\text{Et}_2\text{O}$ /pentane (1/99) yielded title compound as a yellow oil (yield 5.2g, 76%).

**Rf** = 0.25 ( $\text{Et}_2\text{O}$ /pentane 1/99)





**$^1\text{H}$  NMR**  $\delta = 5.91$  (t,  $J = 8.3$  Hz, 1H), 3.99 (d,  $J = 8.8$  Hz, 2H), 3.97 (s, 2H), 1.88 (400 MHz,  $\text{CDCl}_3$ ) ppm (d,  $J = 0.9$  Hz, 3H).

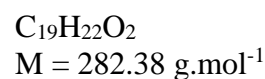
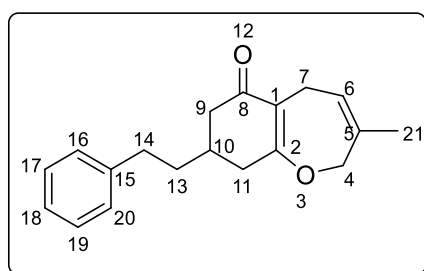
**$^{13}\text{C}$  NMR**  $\delta = 138.3, 125.8, 39.6, 28.0, 14.9$  ppm. (101 MHz,  $\text{CDCl}_3$ )

All data matched those found in the literature<sup>38</sup>

### 3-methyl-8-phenethyl-5,7,8,9-tetrahydrobenzo[b]oxepin-6(2H)-one (III-140c)

$\text{Cs}_2\text{CO}_3$  (184 mg, 1.1 equiv.) was added to a solution of compound **IV-25** (100 mg, 0.46 mmol, 1.0 equiv.) in 2.7 mL DMSO at rt and stirring for 20 min, then a solution of dibromobutene **III-139** (129 mg, 1.1 equiv.) in 2 mL DMSO was added to the mixture at 20°C, kept stirring at 20°C for another 12 h. The reaction was diluted with diethyl ether and quenched with water at 0°C. Washed the organic layer 3 times with brine and then extracted the aqueous phases 3 times with diethyl ether. The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure at 0°C. The residue was then purified by flash chromatography on silica gel (gradient of  $\text{Et}_2\text{O}$ /petroleum ether = 5:95 to 1:9) gave dihydrooxepine **III-140c** as a light yellow oil (yield 50 mg, 0.19 mmol, 40%), and as a 3:1 mixture of regioisomers in favor of **III-140c**.

**Rf** = 0.41 ( $\text{Et}_2\text{O}$  /petroleum ether: 2/8)



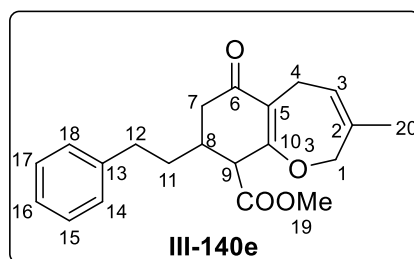
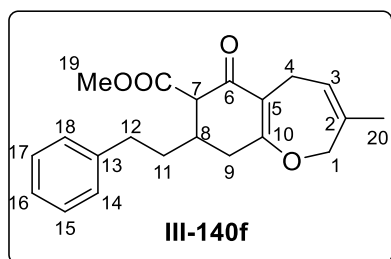
<sup>38</sup> a) V. L. Heasley, C. L. Frye, R. T. Gore, P. S. Wilday, *J. Org. Chem.* **1968**, *33*, 2342-2345; b) C. A. Falcioni, K. Tissot-Crosset, H. Reyneri and A. Alexakis, *Adv. Synth. Catal.* **2008**, *350*, 1090-1100.

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta$ = 7.25-7.17 (m, 2H, H-16 and H-20), 7.14-7.04 (m, 3H, H-17, H-18 and H-19), 5.84 (broad t, $J$ = 6.3 Hz, 1H, H-6), 4.78 (d, $J$ = 12.3 Hz, 1H, H-4a), 4.37 (dd, $J$ = 12.3, 0.6 Hz, 1H, H-4b), 3.07 (d, $J$ = 6.4 Hz, 2H, H-7), 2.62-2.52 (m, 2H, H-14), 2.48 (ddd, $J$ = 9.4, 4.6, 2.8 Hz, 1H, H-9a), 2.30 (dd, $J$ = 17.0, 4.0 Hz, 1H, H-11a), 2.1-1.98 (m, 2H, H-11b and H-9b), 1.96-1.90 (m, 1H, H-10), 1.75 (d, $J$ = 1.4 Hz, 3H, CH <sub>3</sub> ), 1.59 ppm (dd, $J$ = 15.4, 6.9 Hz, 2H, H-13).	
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta$ = 198.43 (C-8), 173.72 (C-2), 141.83 (C-15), 134.99 (C-5), 130.48 (C-6), 128.58 (C-20 and C-16), 128.42 (C-17 and C-20), 126.07 (C-18), 113.6 (C-1), 70.47 (C-4), 43.46 (C-9), 37.61 (C-11), 37.32 (C-13), 32.80 (C-14), 32.12 (C-10), 21.32 ppm (C-7).	
<b>IR</b> (neat):	$\tilde{\nu}$ = 3025, 2923, 2854, 1646, 1603, 1496, 1454, 1390, 1285, 1260, 1226, 1197, 1045, 979 cm <sup>-1</sup> .	
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd for C <sub>10</sub> H <sub>13</sub> O <sub>2</sub> <sup>+</sup> : 282.1615	Found 282.1620.

**methyl 3-methyl-6-oxo-8-phenethyl-2,5,6,7,8,9-hexahydrobenzo[b]oxepine-7-carboxylate (III-140f) and methyl 3-methyl-6-oxo-8-phenethyl-2,5,6,7,8,9-hexahydrobenzo[b]oxepine-9-carboxylate (III-140e)**

Cs<sub>2</sub>CO<sub>3</sub> (502 mg, 1.1 equiv) was added to a solution of compound **IV-26** (300 mg, 1.1 mmol, 1.0 equiv) in 7 mL DMSO and stirring for 20 min, then a solution of dibromobutene **III-139** (319 mg, 1.1 equiv.) in 7 mL DMSO was added to the mixture at 20°C, kept stirring at 20°C for another 12 h. The reaction was diluted with diethyl ether and quenched with water at 0°C. The organic layer was washed three times with brine and then the aqueous phases were extracted three times with diethyl ether. The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure at 0°C. The residue was then purified by flash chromatography on silica gel (gradient of Et<sub>2</sub>O/petroleum ether = 5/95 to 1/9) giving product **III-140f** as a light yellow oil (yield 60 mg, 0.18 mmol, 16%), and its regioisomer **III-140e** as a light yellow oil (yield 60 mg, 0.18 mmol, 16%), in a 1:1 ratio.

**R<sub>f</sub>** = 0.4 (EtOAc/PE 1:4)



C<sub>21</sub>H<sub>24</sub>O<sub>4</sub>  
M = 340.42 g.mol<sup>-1</sup>

**Regioisomer III-140f**

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta = 7.36-7.25$ (m, 2H; H <sub>Ar</sub> ), $7.24-7.12$ (m, 3H; H <sub>Ar</sub> ), $5.94-5.88$ (m, 1H; H-3), $4.86$ (d, $J = 12.3$ Hz, 1H; H-1a), $4.56-4.47$ (m, 1H; H-1b), $3.77$ (s, 3H; H-19), $3.30-3.04$ (m, 2H; H-9/11), $2.81-2.64$ (m, 2H; H-9/11), $2.62-2.51$ (m, 2H; H-7 and H-4a), $2.48-2.31$ (m, 1H; H-4b), $2.26-2.15$ (m, 1H; H-11a), $1.85$ (s, 3H, H-20), $1.61$ (m, 1H; H-11b), $1.01-0.84$ ppm (m, 1H; H-8).
<b>IR</b> (neat):	$\tilde{\nu} = 2922, 2852, 1740, 1645, 1599, 1496, 1454, 1434, 1392, 1311, 1222, 1202, 1153, 973, 746, 700$ cm <sup>-1</sup>
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd for C <sub>10</sub> H <sub>13</sub> O <sub>2</sub> <sup>+</sup> : 340.1675                      Found 340.1684.

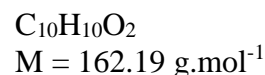
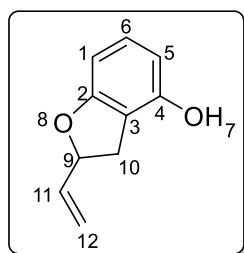
**Regioisomer III-140e**

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta = 7.36-7.25$ (m, 2H; H <sub>Ar</sub> ), $7.24-7.12$ (m, 3H; H <sub>Ar</sub> ), $5.76$ (m, 1H; H-3), $4.77$ (dd, $J = 12.0, 6.5$ Hz, 1H; H-1a), $4.69-4.59$ (m, 1H; H-1b), $3.76$ (s, 3H; H-19), $3.30-3.04$ (m, 2H; H-9/11), $2.81 - 2.64$ (m, 2H; H-9/11), $2.62 - 2.51$ (m, 2H; H-7 and H-4a), $2.48 - 2.31$ (m, 1H; H-4b), $2.26 - 2.15$ (m, 1H; H-11a), $1.85$ (s, 3H, H-20), $1.61$ (m, 1H; H-11b), $1.01 - 0.84$ ppm (m, 1H; H-8).
<b>IR</b> (neat):	$\tilde{\nu} = 3442, 2951, 1737, 1650, 1602, 1454, 1436, 1382, 1249, 1158$ cm <sup>-1</sup> .
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd for C <sub>10</sub> H <sub>13</sub> O <sub>2</sub> <sup>+</sup> : 340.1675                      Found 340.1666.

**2-vinyl-2,3-dihydrobenzofuran-4-ol (IV-27)**

2,5-Dihydrooxepine **III-134c** (40 mg, 0.22 mmol, 1.0 equiv.), I<sub>2</sub> (12 mg, 20 mol%), DMSO (20  $\mu$ l, 1.0 equiv), CH<sub>3</sub>NO<sub>2</sub> (0.8 mL) were added to a sealed tube with a magnetic bar. The mixture was stirred at 100 °C for 3 h. After cooling down to room temperature, the solution was diluted with ethyl acetate (10 mL) and washed with a 0.1 M Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous solution (5 mL), extracted with ethyl acetate (3 $\times$ 5 mL), and evaporated under vacuum. The crude reaction mixture was purified by column chromatography on silica gel with petroleum ether / ethyl acetate (10:1 to 4:1) to get phenol product IV-27 as yellow liquid (yield 12 mg, 0.07 mmol, 32%).

**Rf** = 0.75 (petroleum ether / ethyl acetate: 4/1)



**$^1\text{H}$  NMR**  $\delta = 6.99$  (t,  $J = 8.0$  Hz, 1H, H-6), 6.46 – 6.40 (dd,  $J = 7.8$ Hz, 0.5Hz, 1H, H-1), 6.31 (dd,  $J = 8.1, 0.5$  Hz, 1H, H-5), 6.03 (ddd,  $J = 17.1, 10.4, 6.7$  Hz, 1H, H-11), 5.39 (dt,  $J = 17.1, 1.1$  Hz, 1H, H-12a), 5.31 – 5.17 (m, 2H, H-12b and H-9), 4.74 (s, 1H, OH), 3.34 (dd,  $J = 15.2, 9.4$  Hz, 1H, H-10a), 2.92 ppm (td,  $J = 14.8, 7.0$  Hz, 1H, H-10b).

**$^{13}\text{C}$  NMR**  $\delta = 161.3$  (C-2), 152.6 (C-4), 137.3 (C-11), 129.4 (C-6), 117.1 (C-12), 112.2 (C-3), 107.9 (C-5), 102.6 (C-1), 84.1 (C-8), 33.0 ppm (C-10).

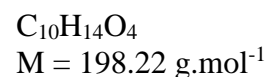
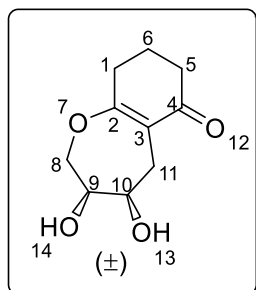
**IR** (neat):  $\tilde{\nu} = 3387, 2920, 2851, 1605, 1463, 1319, 1271, 1231, 1026, 931 \text{ cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{10}\text{H}_{13}\text{O}_2^+$ : 162.0676 Found 162.0680.

### (3S,4R)-3,4-dihydroxy-3,4,5,7,8,9-hexahydrobenzo[b]oxepin-6(2H)-one (III-137)

To a solution of **III-134c** (50 mg, 0.3 mol, 1.0 equiv.) in acetone/water (3:1 v/v, 3 mL) was added NMO (47 mg, 1.3 equiv.), followed by a 4% osmium tetroxide water solution (16  $\mu\text{L}$ , 5 mol %) at  $0^\circ\text{C}$ . The reaction was stirred at rt and complete after 20 mins, then the solution was filtered through Celite®. After concentration in vacuo, the crude product was chromatographed on silica gel, eluted with 100% EtOAc to 1% methanol in EtOAc, to afford white crystal **III-137** (yield 50 mg, 0.26 mmol, 85%). Crystals for X-ray crystallography were obtained from  $\text{CHCl}_3$ .

**R<sub>f</sub>** = 0.31 (1% methanol in EtOAc)



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.23 (dd, *J* = 11.9, 4.3 Hz, 1H, H-8a), 4.09 (m, 1H, H-9), 3.97 (m, 2H, H10 and H-8b), 3.55 (brs, 1H, OH), 3.43 (brs, 1H, OH), 2.80 (ddt, *J* = 16.2, 10.1, 1.9 Hz, 1H, H-11a), 2.60 (dd, *J* = 16.1, 2.0 Hz, 1H, H-11b), 2.47-2.27 (m, 4H, H-1 and H-5), 2.00-1.75 ppm (m, 2H, H-6).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 200.2 (C-4), 177.0 (C-2), 115.1 (C-3), 72.3 (C-8), 69.9 (C-9), 69.2 (C-10), 36.8 (C-5), 30.4 (C-1), 26.0 (C-11), 20.2 ppm (C-6).

**IR** (neat):  $\tilde{\nu}$  = 3362, 2956, 2922, 2853, 1605, 1462, 1378, 1248, 1189, 1065, 1008, 498 cm<sup>-1</sup>.

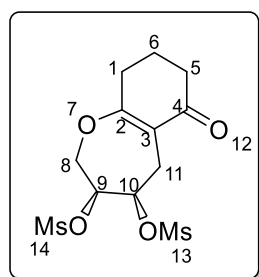
**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>10</sub>H<sub>13</sub>O<sub>2</sub><sup>+</sup>: 198.0888 Found 198.0893.

**Mp** = 85-87°C

**(3*S*,4*R*)-6-oxo-2,3,4,5,6,7,8,9-octahydrobenzo[*b*]oxepine-3,4-diyl dimethanesulfonate (IV-30)**

To a solution of diol **III-137** (30 mg, 0.15 mmol, 1.0 equiv.) in 1.5 mL pyridine was added MsCl (58  $\mu$ L, 5.0 equiv.). The reaction mixture turned from yellow to brown and was then stirred at rt overnight. When no more starting material remained, the reaction was diluted with EtOAc and washed with 1N HCl, sat NaHCO<sub>3</sub> and brine. After dried over MgSO<sub>4</sub>, the organic layer was concentrated in vacuo to furnish the title compound without further purification (yield 49 mg, 0.14 mmol, 93%).

**Rf** = 0.65 (100% EtOAc)



C<sub>12</sub>H<sub>18</sub>O<sub>8</sub>S<sub>2</sub>  
M = 354.39 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 5.13 – 5.05 (m, 1H, H-9), 4.98 (ddd, *J* = 10.3, 3.3, 2.1 Hz, 1H, H-10), 4.27 (dd, *J* = 12.8, 4.1 Hz, 1H, H-8a), 4.11 (dd, *J* = 12.8, 7.9 Hz, 1H, H-8b), 3.16 (s, 3H, CH<sub>3</sub>), 3.11 (m, 1H, H-11a), 3.07 (s, 3H, CH<sub>3</sub>), 2.75 (ddq, *J* = 15.9, 2.6, 1.4 Hz, 1H, H-11b), 2.46 (m, 2H, H-5), 2.41 – 2.33 (m, 2H, H-1), 1.99 – 1.86 ppm (m, 2H, H-6).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 198.3, 177.0, 115.9, 76.7, 75.9, 69.2, 39.1, 38.7, 36.5, 30.2, 23.8, 19.9 ppm.

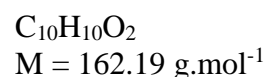
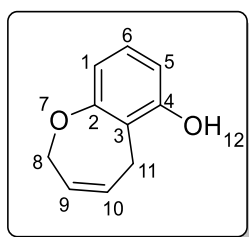
**IR** (neat):  $\tilde{\nu}$  = 3368, 2922, 1715, 1616, 1394, 1353, 1174, 1017, 952, 704 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>10</sub>H<sub>13</sub>O<sub>2</sub><sup>+</sup>: 354.0443 Found 149.0958.

**2,5-dihydrobenzo[b]oxepin-6-ol (IV-28)**

To a solution of dimesylate **IV-30** (49 mg, 0.14 mmol, 1.0 equiv) in 3.4 mL DMSO at rt was added 0.66 mL TBAF 1M in THF (4.0 equiv.) dropwise over 5 min. Then the reaction was stirred for further 30 min. The reaction was quenched by adding saturated  $\text{NH}_4\text{Cl}$  solution and extracted with EtOAc. The combined organic phase was washed with water and brine, dried over  $\text{MgSO}_4$  and concentrated in vacuo. Purification by flash chromatography column with cyclohexane/EtOAc (9/1) furnished desired product **IV-28** as white crystals (yield 18 mg, 0.12 mmol, 85%), suitable for X-ray crystallography.

**Rf** = 0.5 (cyclohexane/EtOAc 8/2)



**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.01 (t,  $J$  = 8.0 Hz, 1H, H-6), 6.68 (d,  $J$  = 7.9 Hz, 1H, H-5), 6.54 (d,  $J$  = 8.1 Hz, 1H, H-1), 5.86 (dtt,  $J$  = 13.3, 5.3, 2.2 Hz, 1H, H-9), 5.50 (dtd,  $J$  = 9.7, 2.7, 1.3 Hz, 1H, H-10), 4.91 (s, 1H, OH), 4.59 (m, 2H, H-8), 3.54 ppm (dd,  $J$  = 5.2, 2.0 Hz, 2H, H-11).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 160.4 (C-4), 152.7 (C-2), 127.8 (C-10), 127.4 (C-6), 126.0 (C-9), 123.2 (C-5), 114.2 (C-1), 111.60 (C-3), 71.5 (C-8), 22.8 ppm (C-11).

**IR** (neat):  $\tilde{\nu}$  = 3360, 3022, 2922, 2851, 1587, 1465, 1285, 1268, 1197, 1057, 1024, 948, 794, 725, 633, 497  $\text{cm}^{-1}$ .

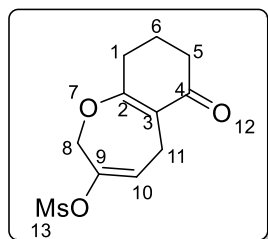
**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{10}\text{H}_{13}\text{O}_2^+$ : 162.0676 Found 162.0681.

**Mp** =  $>210^\circ\text{C}$  (decompose)

**6-oxo-2,5,6,7,8,9-hexahydrobenzo[b]oxepin-3-yl methanesulfonate (IV-31)**

To a solution of dimesylate **IV-30** (30 mg, 0.08 mmol, 1.0 equiv.) in 0.8 mL THF at rt was added DBU (31  $\mu\text{L}$ , 2.5 equiv.) dropwise. Then the reaction was stirred overnight at  $80^\circ\text{C}$ . Quenched the reaction by adding saturated  $\text{NH}_4\text{Cl}$  and extracted with EtOAc. The combined organic phases were washed with water and brine, dried over  $\text{MgSO}_4$  and concentrated in vacuo. Purification by flash chromatography column with cyclohexane/EtOAc (5/5) furnished desired product **IV-31** (yield 6 mg, 0.02 mmol, 29%).

**Rf** = 0.3 (cyclohexane/EtOAc :5/5)



$C_{11}H_{14}O_5S$   
 $M = 258.29 \text{ g}\cdot\text{mol}^{-1}$

**$^1\text{H NMR}$**   $\delta = 5.34$  (d,  $J = 3.1$  Hz, 1H, H-8a ),  $5.24$  (dd,  $J = 10.7, 7.5$  Hz, 1H, H-10),  $5.18$  (d,  $J = 3.2$  Hz, 1H, H-8b),  $3.15$  (s, 3H,  $\text{CH}_3$ ),  $3.04$  (ddt,  $J = 14.7, 10.6, 2.0$  Hz, 1H, H-11a),  $2.88$  (ddt,  $J = 14.8, 7.4, 2.0$  Hz, 1H, H-11b),  $2.46$  (tt,  $J = 6.4, 2.0$  Hz, 2H, H-5),  $2.36$  (dd,  $J = 7.2, 5.9$  Hz, 2H, H-1),  $2.06$  ppm (p,  $J = 6.5$  Hz, 2H, H-6).

**$^{13}\text{C NMR}$**   $\delta = 195.36$  (C-4),  $176.55$  (C-2),  $151.13$  (C-9),  $113.10$  (C-3),  $104.51$  (C-10),  $82.69$  (C-8),  $38.43$  (C-5),  $36.56$  (C-1),  $30.05$  (C-13),  $23.91$  (C-6),  $21.76$  ppm (C-11).

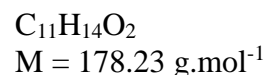
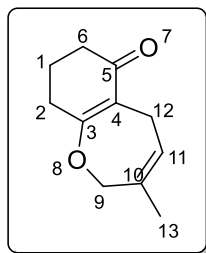
**IR** (neat):  $\tilde{\nu} = 2922, 2852, 1630, 1463, 1353, 1275, 1170, 1066, 750 \text{ cm}^{-1}$ .

**Mp** =  $155^\circ\text{C}$

### 3-methyl-5,7,8,9-tetrahydrobenzo[b]oxepin-6(2H)-one (III-140b)

$\text{Cs}_2\text{CO}_3$  (1.57 g, 1.1 equiv.) was added to a solution of cyclohexadione (448 mg, 3.8 mmol, 1.0 equiv.) in 30 mL DMSO and the mixture was stirred for 20 min, then a solution of dibromobutene **III-139** (1.15 g, 1.2 equiv.) in DMSO (10 mL) was added to the mixture at  $20^\circ\text{C}$ , kept stirring at rt for another 5h. The reaction was diluted with diethyl ether and quenched with water at  $0^\circ\text{C}$ . The organic layer was washed three times with brine and then the aqueous phases were extracted three times with diethyl ether. The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (gradient of  $\text{Et}_2\text{O}$  /petroleum ether = 1:9 to 2:8) giving oily product **III-140b** (yield 182 mg, 1 mmol, 26%) as a 3:1 mixture with its 11-methyl isomer, along with dihydrofuran as byproduct (yield 275 mg, 1.5 mmol, 39%).

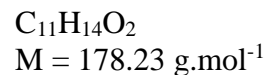
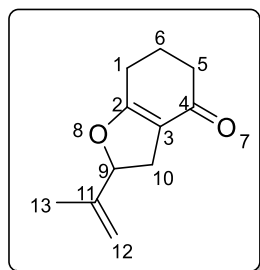
**Rf** = 0.5 (EtOAc /petroleum ether: 2/8)



<b><math>^1\text{H}</math> NMR</b> (400 MHz, $\text{CDCl}_3$ )	$\delta = \delta$ 5.90 – 5.82 (m, 1H, H-11), 4.61 (s, 2H, H-9), 3.11 (dd, $J = 6.3, 1.1$ Hz, 2H, H-12), 2.33 – 2.22 (m, 4H, H2 and H-6), 1.83 (dd, $J = 13.0, 6.6$ Hz, 2H, H-1), 1.78 ppm (d, $J = 1.54$ Hz, 3H, $\text{CH}_3$ ).
<b><math>^{13}\text{C}</math> NMR</b> (101 MHz, $\text{CDCl}_3$ )	$\delta = \delta$ 198.6 (C-5), 174.2 (C-3), 135.0 (C-10), 130.3 (C-11), 113.8 (C-4), 70.3 (C-9), 37.0 (C-6), 31.1 (C-2), 21.9 (C-13), 21.3 (C-12), 20.5 ppm (C-1).
<b>IR</b> (neat):	$\tilde{\nu} = 3361, 2925, 2854, 1626, 1591, 1403, 1252, 1224, 1188, 1138, 1019 \text{ cm}^{-1}$ .
<b>HRMS</b> ( $\text{EI}^+$ ):	Calcd. for $\text{C}_{10}\text{H}_{13}\text{O}_2^+$ : 178.0989                      Found 178.0091.

### 2-(prop-1-en-2-yl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one

**R<sub>f</sub>** = 0.26 (ethyl acetate/petroleum ether 3/7)



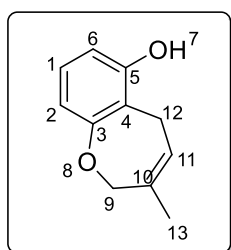
<b><math>^1\text{H}</math> NMR</b> (400 MHz, $\text{CDCl}_3$ )	$\delta =$ 5.13 (dd, $J = 10.5, 8.1$ Hz, 1H, H-9), 4.97 (d, $J = 0.6$ Hz, 1H, H-12a), 4.89-4.83 (m, 1H, H-12b), 2.93 (ddt, $J = 14.3, 10.6, 1.7$ Hz, 1H, H-10b), 2.65-2.54 (m, 1H, H-10a), 2.46-2.38 (m, 2H, H-1), 2.36-2.26 (m, 2H, H-5), 2.06 – 1.95 (m, 2H, H-6), 1.68 ppm (d, $J = 1.0$ Hz, 3H, H-13).
<b><math>^{13}\text{C}</math> NMR</b> (101 MHz, $\text{CDCl}_3$ )	$\delta =$ 195.5 (C-4), 177.4 (C-2), 142.9 (C-11), 113.1 (C-3), 112.6 (C-12), 88.0 (C-9), 30.7 (C-5), 24.1 (C-10), 23.9 (C-1), 21.7 (C-6), 17.0 ppm (C-13).
<b>IR</b> (neat):	$\tilde{\nu} = 2943, 2869, 1630, 1630, 1401, 1229, 1181, 1061, 908 \text{ cm}^{-1}$ .
<b>HRMS</b> ( $\text{EI}^+$ ):	Calcd. for $\text{C}_{10}\text{H}_{13}\text{O}_2^+$ : 178.0989                      Found 178.0989.



**3-methyl-2,5-dihydrobenzo[b]oxepin-6-ol (IV-36)**

To a solution of **III-140b** (40 mg, 0.2 mmol, 1.0 equiv.) in acetone/water (3:1 v/v, 3 mL) was added NMO (34 mg, 1.3 equiv.), followed by 4% osmium tetroxide water solution (70  $\mu\text{L}$ , 5 mol%) at 0°C. The reaction was stirred at rt and complete after 1h, then the solution was filtered over a small pad of silica, eluting with 100% EtOAc to get the diol product. Then this crude diol was solubilized in 1.6 mL pyridine and added MsCl (64  $\mu\text{L}$ , 5.0 equiv.), stirring at rt overnight. When no more starting material remained, the reaction was diluted with EtOAc and washed with 1N HCl, sat  $\text{NaHCO}_3$  and brine. After drying over  $\text{MgSO}_4$ , the organic layer was concentrated in vacuo to furnish the mesylate intermediate. The obtained dimesylate was then put into 0.8 mL DMSO at rt and 0.32 mL TBAF 1M in THF (4.0 equiv.) was added dropwise, stirring for further 2 h. The reaction was quenched by adding saturated  $\text{NH}_4\text{Cl}$  and extracted with EtOAc. The combined organic phase was washed with water and brine, dried over  $\text{MgSO}_4$  and concentrated in vacuo. Purification by flash chromatography column with cyclohexane/EtOAc (9/1) furnished desired product **IV-36** (5 mg, 0.03 mmol, 14% overall yield).

**Rf** = 0.25 (cyclohexane/EtOAc: 9/1)



$\text{C}_{11}\text{H}_{12}\text{O}_2$   
 $M = 176.22 \text{ g}\cdot\text{mol}^{-1}$

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.01$  (t,  $J = 8.0$  Hz, 1H, H-1), 6.68 (dd,  $J = 8.0, 1.1$  Hz, 1H, H-6), 6.55 (dd,  $J = 8.1, 1.1$  Hz, 1H, H-2), 5.62 (m, 1H, H-11), 4.73 (s, 1H, OH), 4.42 (m, 2H, H-9), 3.44 (m, 2H, H-12), 1.58 ppm (d,  $J = 1.9$  Hz, 3H,  $\text{CH}_3$ ).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta = 160.2$  (C-5), 152.3 (C-3), 134.3 (C-10), 127.3 (C-1), 123.6 (C-6), 120.5 (C-11), 114.0 (C-4), 111.6 (C-2), 74.4 (C-9), 21.8 (C-12), 20.2 ppm (C-13).

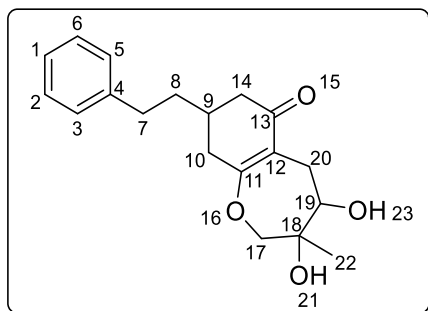
**IR** (neat):  $\tilde{\nu} = 3359, 2922, 2850, 1705, 1592, 1466, 1334, 1284, 1203, 1052, 1000, 938, 907, 778, 732 \text{ cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{10}\text{H}_{13}\text{O}_2^+$ : 176.0832 Found 176.0829.

**3,4-dihydroxy-3-methyl-8-phenethyl-3,4,5,7,8,9-hexahydrobenzo[b]oxepin-6(2H)-one (IV-39)**

$\text{Cs}_2\text{CO}_3$  (342 mg, 1.1 equiv.) was added to a solution of compound **IV-25** (186 mg, 0.86 mmol, 1.0 equiv.) in 5 mL DMSO and the mixture was stirred for 20 min, then a solution of dibromobutene **III-139** (240 mg, 1.1 equiv.) in 3.7 mL DMSO was added to the mixture at 20°C, kept stirring at 20°C for another 12h. The reaction was diluted with diethyl ether and quenched with water at 0°C. The organic layer was washed three times with brine and the aqueous phases extracted three times with diethyl ether. The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure at 0°C. The obtained crude mixture was subjected in acetone/water (3:1 v/v, 16 ml), and NMO (254 mg, 1.3 equiv.), a 4% osmium tetroxide water solution (56  $\mu\text{L}$ , 5 mol%) were added at 0°C. The reaction was completed in 1h. Then the solution was filtered through Celite®. After concentration in vacuo, the crude product was chromatographed on silica gel, eluting with PE/EtOAc (6:4), to afford diastereoisomers **IV-39** as yellow amorphous solid (yield 192 mg, 0.6 mmol, 71%).

Rf = 0.15 (PE/EtOAc 6:4)



$\text{C}_{19}\text{H}_{24}\text{O}_4$   
 $M = 316.40 \text{ g}\cdot\text{mol}^{-1}$

**$^1\text{H NMR}$**   $\delta = 7.28$  (m, 2H;  $\text{H}_{\text{Ar}}$ ),  $7.24$ - $7.07$  (m, 3H;  $\text{H}_{\text{Ar}}$ ),  $4.31$ - $4.20$  (m, 1H; H-17a),  $4.02$  (br s, 1H; H-23),  $3.98$  (s, 1H; H-21),  $3.73$ - $3.55$  (m, 1H; H-17b),  $3.16$  (s, 3H),  $2.73$ - $2.41$  (m, 6H; H-7, H-10, H-14),  $2.27$ - $1.85$  (m, 2H; H-8),  $2.04$  (s, 3H; H-22),  $1.77$ - $1.63$  (m, 2H; H-20),  $0.95$ - $0.98$  ppm (m, 1H; H-9).

**$^{13}\text{C NMR}$**   $\delta = 199.4$ ,  $175.7$ ,  $141.6$ ,  $128.5$ ,  $128.3$ ,  $126.1$ ,  $114.4/113.3$ ,  $78.1/76.7$ ,  $74.6/74.5$ ,  $73.6/73.2$ ,  $72.4/72.2$ ,  $43.1/42.9$ ,  $42.7$ ,  $37.2/36.8$ ,  $36.7/36.5$ ,  $33.1/32.9$ ,  $32.7/31.9$ ,  $27.0/26.7$ ,  $24.3/23.8$  ppm.

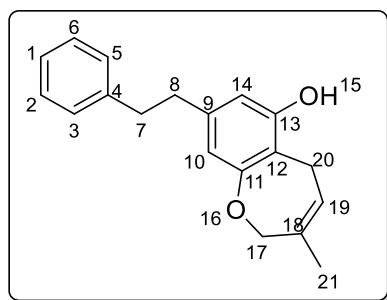
**IR** (neat):  $\tilde{\nu} = 2922$ ,  $2853$ ,  $1463$ ,  $1377$ ,  $1284$ ,  $1131 \text{ cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{10}\text{H}_{13}\text{O}_2^+$ : 316.1675 Found 316.1684.

**3-methyl-8-phenethyl-2,5-dihydrobenzo[b]oxepin-6-ol (Radulanin A IV-1)**

To a solution of **IV-39** (160 mg, 0.5 mmol, 1 equiv.) in 5 mL pyridine was added MsCl (194  $\mu$ L, 5equiv.), The reaction was stirred at rt overnight. When no more starting material remained, it was diluted with EtOAc and washed with 1N HCl, sat. NaHCO<sub>3</sub> and brine. After drying over MgSO<sub>4</sub>, the organic layer was concentrated in vacuo to furnish the dimesylate compound. The obtained dimesylate was put in 5 mL DMSO at rt and 2.5mL TBAF 1M in THF (5 equiv.) were added dropwise, stirring for further 2h. The reaction was quenched by adding a saturated solution of NH<sub>4</sub>Cl and then extracted with EtOAc. The combined organic phases werewashed with water and brine, dried over MgSO<sub>4</sub> and concentrated in vacuo. Purification by flash chromatography column with cyclohexane/EtOAc (9/1) furnished desired product radulanin A (**IV-1**) as a colorless oil (yield 21 mg, 0.075 mmol, 14%).

**Rf** = 0.3 (cyclohexane/EtOAc: 9/1)



C<sub>19</sub>H<sub>20</sub>O<sub>2</sub>  
M = 280.37 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR**  
(400 MHz, CDCl<sub>3</sub>)

$\delta$  = 7.33 –7.08 (m, 5H, H-Ar), 6.54 (d, J = 1.7 Hz, 1H, H-14), 6.38 (d, J = 1.6 Hz, 1H, H-10), 5.61 (tt, J = 5.7, 2.9 Hz, 1H, H-19), 4.65 (s, 1H, OH), 4.40 (dq, J = 2.6, 1.4 Hz, 2H, H-17), 3.40 (dq, J = 5.8, 1.9 Hz, 2H, H-20), 2.88 (ddd, J = 10.3, 6.5, 2.2 Hz, 2H, H-8), 2.85 – 2.76 (m, 2H, H-7), 1.54 ppm (d, J=1.04Hz, 3H, CH<sub>3</sub>).

**<sup>13</sup>C NMR**  
(101 MHz, CDCl<sub>3</sub>)

$\delta$  = 160.0 (C-11), 152.1 (C-13), 141.8 (C-9), 141.6 (C-4), 134.3 (C-18), 128.6 (C-2 and C-6), 128.5 (C-3 and C-5), 126.1 (C-1), 120.7 (C-19), 114.0 (C-12), 111.6 (C-10 and C-14), 74.4 (C-17), 37.7 (C-8), 37.6 (C-7), 21.8 (C-20), 20.3 ppm (C-21).

**IR** (neat):

$\tilde{\nu}$  = 3364, 2923, 2854, 2322, 1619, 1587, 1496, 1449, 1307, 1269, 1206, 1069 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>):

Calcd. for C<sub>10</sub>H<sub>13</sub>O<sub>2</sub><sup>+</sup>: 280.1457

Found 280.1450.

Comparison with the literature (in CDCl<sub>3</sub>):<sup>39</sup>

<sup>39</sup> a) Y. Asakawa, M. Toyota, T. Takemoto, *Specialia* **1978**, 971-972; b) M. Stefinovic, V. Snieckus, *J. Org. Chem* **1998**, *63*, 2808-2809.

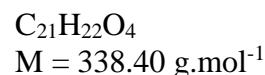
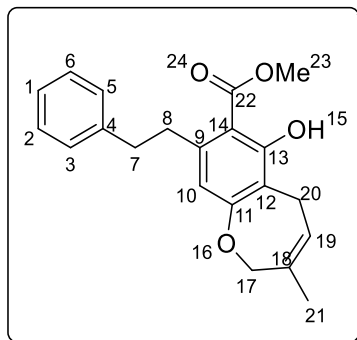
<b>H</b>	<b>Reference Radulanin A (<math>\delta</math> ppm)</b>	<b>Synthesized (<math>\delta</math> ppm)</b>
21	1.54 (s)	1.54 (d, J=1.04Hz)
7	2.8-2.7 (m)	2.85 – 2.76 (m)
8		2.88 (ddd, J = 10.3, 6.5, 2.2 Hz)
20	3.4 (d)	3.40 (dq, J = 5.8, 1.9 Hz)
17	4.4 (brs)	4.40 (dq, J = 2.6, 1.4 Hz)
OH	4.8 (brs)	4.65 (brs)
19	5.6 (m)	5.61 (tt, J = 5.7, 2.9 Hz)
10	6.37 (d)	6.38 (d, J = 1.6 Hz)
14	6.53 (d)	6.54 (d, J = 1.7 Hz),
1, 2, 3, 5, 6	7.32-7.16 (m)	7.33 –7.08 (m)
<b>C</b>	<b>Reference Radulanin A (<math>\delta</math> ppm)</b>	<b>Synthesized (<math>\delta</math> ppm)</b>
21	19.9	20.3
20	21.5	21.8
7	37.3	37.6
8		37.7
17	74.1	74.4
10, 14	111.5	111.6
12	113.0	114.0
19	120.6	120.7
1	120.8	121.1
3, 5	125.7	128.5
2, 6	128.21	128.6
18	133.6	134.4
4	141.0	141.6
9	141.5	141.8
13	152.6	152.1
11	159.6	160.0

**methyl 6-hydroxy-3-methyl-8-phenethyl-2,5-dihydrobenzo[b]oxepine-7-carboxylate (IV-37a)**

To a stirring solution of dihydrooxepine **III-140f** (50 mg, 0.15 mmol, 1.0 equiv.) in THF (0.8 mL) was added NaH (7 mg, 1.2 equiv.) at 0°C and the reaction was kept agitated for 30 min. Then a solution of PhSeBr (45 mg, 1.3 equiv.) in THF (0.7 mL) was added dropwise at 0°C following by stirring for further 1h. Quenched with saturated NH<sub>4</sub>Cl solution and extracted with Et<sub>2</sub>O. The gathered organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, the solvent was evaporated under vacuum. The crude mixture was purified with a small pad of silica, eluting with 20% EtOAc in petroleum ether. The obtained yellow oil was solubilized in DCM (0.5 mL) and a 30% solution of H<sub>2</sub>O<sub>2</sub> (21  $\mu$ L, 2.0 equiv.) in 0.5 mL DCM was added at 0°C. After stirring 1h at this temperature, the reaction was quenched using a saturated aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and warmed up to rt. Then the mixture was exytracted with Et<sub>2</sub>O, the combined organic phases were washed with water and brine, dried

over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Purification by flash chromatography column with petroleum ether/DCM (4/1) furnished product **IV-37a** as yellow oil (yield 15 mg, 0.04 mmol, 30% for two steps).

**Rf** = 0.33 (petroleum ether/DCM 4/1)



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 11.89 (s, 1H, OH), 7.30 (m, 2H, H-3 and H-5), 7.24 – 7.15 (m, 3H, H-1, H-2 and H-6), 6.41 (s, 1H, H-10), 5.69 (td, J = 5.6, 1.4 Hz, 1H, H-19), 4.47 (s, 2H, H-17), 3.97 (s, 3H, H-23), 3.50 (dd, J = 5.5, 1.3 Hz, 2H, H-20), 3.19 – 3.04 (m, 2H, H-8), 2.83 (dd, J = 9.8, 6.7 Hz, 2H, H-7), 1.62 ppm (s, 3H, H-21).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ = 172.7 (C-22), 162.8 (C-11), 161.2 (C-13), 144.3 (C-9), 142.1 (C-4), 134.2 (C-18), 128.6 (C-2 and C-6), 128.5 (C-3 and C-5), 126.1 (C-1), 122.4 (C-19), 120.2 (C-12), 115.7 (C-10), 107.4 (C-14), 73.3 (C-17), 52.4 (C-23) 38.9 (C-8), 38.5 (C-7), 21.8 (C-20), 20.7 ppm (C-21).

**IR** (neat):  $\tilde{\nu}$  = 2924, 2855, 1653, 1612, 1576, 1441, 1404, 1294, 1255, 1200, 1153, 1023, 747, 700, 497 cm<sup>-1</sup>.

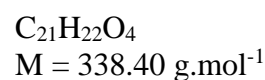
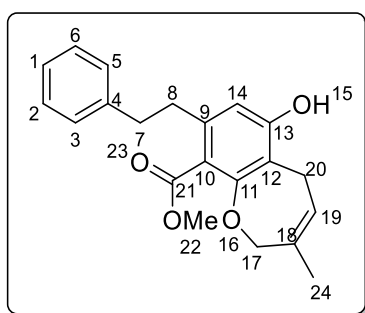
**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>10</sub>H<sub>13</sub>O<sub>2</sub><sup>+</sup>: 338.1513 Found 338.1514.

#### **methyl 6-hydroxy-3-methyl-8-phenethyl-2,5-dihydrobenzo[b]oxepine-9-carboxylate (IV-37b)**

To a solution of **III-140e** (100 mg, 0.3 mmol 1 equiv.) in acetone/water (3:1 v/v, 4 ml) was added NMO (44 mg, 1.3 equiv.), followed by a 4% osmium tetroxide water solution (20 μL, 5 mol%) at 0°C. The reaction was stirring at rt and complete after 1h, then the solution was filtered a small pad of silica, eluting with 100% EtOAc to diol product. Then this crude diol was solubilized in 1.5mL pyridine and MsCl (100 μL, 5 equiv.) was added, stirring at rt overnight. When no more starting material remained, the solution was diluted with EtOAc and washed with 1N HCl, sat NaHCO<sub>3</sub> and brine. After drying over Na<sub>2</sub>SO<sub>4</sub>, the organic layer was concentrated in vacuo to furnish the dimesylate intermediate. The

product was put in 3 mL DMSO at rt and 1.5 mL TBAF 1M in THF (5 equiv.) was added dropwise, while stirring for further 2h. The reaction was quenched by adding a saturated  $\text{NH}_4\text{Cl}$  solution and extracted with EtOAc. The combined organic phase was washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. Purification by flash chromatography with petroleum/EtOAc (8/2) furnished desired product **IV-37b** as white solid (yield 14 mg, 0.042 mmol, 14%).

**Rf** = 0.28 (Petroleum/EtOAc 8/2)



**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.29 (m, 2H, H-3 and H-5), 7.23 – 7.13 (m, 3H, H-1, H-2, H-6), 6.36 (s, 1H, H-14), 5.58 (ddd,  $J$  = 7.1, 3.9, 1.5 Hz, 1H, H-19), 4.96 (brs, 1H, OH), 4.47 (d,  $J$  = 0.7 Hz, 2H, H-17), 3.90 (s, 3H, H-22), 3.40 – 3.33 (m, 2H, H-20), 2.84 (br s, 4H, H-8 and H-7), 1.54 ppm (d,  $J$  = 0.9 Hz, 3H, H-24).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 168.6 (C-21), 157.2 (C-11), 153.2 (C-13), 141.6 (C-9), 139.1 (C-4), 134.4 (C-18), 128.6 (C-2 and C-6), 128.6 (C-3 and C-5), 126.2 (C-1), 122.0 (C-12), 120.5 (C-10), 119.8 (C-19), 112.4 (C-14), 74.3 (C-17), 52.3 (C-22), 37.8 (C-8), 35.8 (C-7), 21.7 (C-20), 20.1 ppm (C-24).

**IR** (neat):  $\tilde{\nu}$  = 3383, 2925, 2857, 1705, 1605, 1427, 1285, 1198, 1148, 1079, 1008, 750, 701  $\text{cm}^{-1}$ .

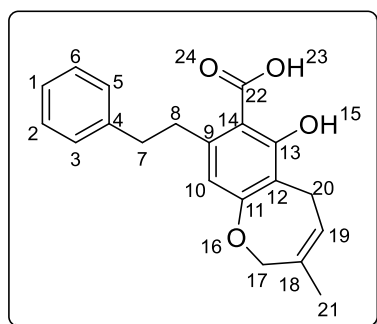
**HRMS** (EI<sup>+</sup>): Calcd. for  $\text{C}_{10}\text{H}_{13}\text{O}_2^+$ : 338.1513 Found 338.1509.

### 6-hydroxy-3-methyl-8-phenethyl-2,5-dihydrobenzo[b]oxepine-7-carboxylic acid (radulanin H IV-3)

To a stirred solution of radulanin H methyl ester **IV-37a** (10 mg, 0.03 mmol, 1.0 equiv.) in THF/MeOH (1:1) (2 mL) was added LiOH (1.44 mg, 0.06 mmol 2.0 equiv.) in water at rt and stirring was continued for 12 h at 50°C. The reaction mixture was quenched with aqueous HCl and extracted with EtOAc. The combined extracts were washed with brine and the residue upon workup was chromatographed on silica gel with EtOAc/petroleum ether/DCM (3:5:2) as eluent to give radulanin H (6.7 mg, 0.02 mmol, 70%) as colorless

crystals.

R<sub>f</sub> = 0.34 (EtOAc/petroleum ether/DCM 3:5:2)



C<sub>20</sub>H<sub>20</sub>O<sub>4</sub>  
M = 324.38 g.mol<sup>-1</sup>

<sup>1</sup>H NMR δ = 11.82 (brs, 1H), 7.33 – 7.27 (m, 2H), 7.22-7.18 (m, 3H), 6.41 (s, 1H), 5.71 (t, J = 6.4 Hz, 1H), 4.49 (s, 2H), 3.51 (d, J = 4.3 Hz, 2H), 3.20 (dt, J = 9.8, 6.7 Hz, 2H), 2.88 (dt, J = 9.7, 6.6 Hz, 2H), 1.63 ppm (s, 3H).

Comparison with the literature (in CDCl<sub>3</sub>):<sup>40</sup>

H	Reference Radulanin H (δ ppm)	Synthesized (δ ppm)
21	1.64 (s)	1.63 (s)
7	2.89 (t, J = 7.6 Hz),	2.88 (dt, J = 9.7, 6.6 Hz)
8	3.22 (t, J = 7.6 Hz)	3.20 (dt, J = 9.8, 6.7 Hz)
20	3.52 (d, J = 4.4 Hz)	3.51 (d, J = 4.3 Hz)
17	4.50 (s)	4.49 (s)
OH		
19	5.72 (t, J = 4.4 Hz)	5.71 (m)
10	6.41 (s)	6.41 (s)
1, 2, 6	7.18–7.21 (m)	7.22-7.18 (m), 7.33 – 7.27 (m),
3, 5	7.27–7.31 (m)	11.82 (brs)
23(COOH)	11.70 (brs);	1.63 (s)

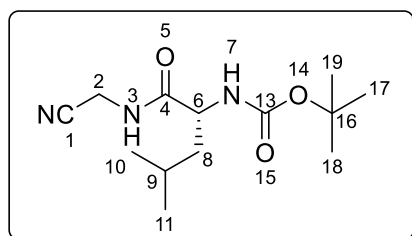
<sup>40</sup> M. Yoshida, K. Nakatani, K. Shishido, *Tetrahedron* **2009**, 65, 5702-5708.

## 1.4.2. Total synthesis of janoxepin and cinereain

**tert-butyl (S)-(1-((cyanomethyl)amino)-4-methyl-1-oxopentan-2-yl) carbamate (IV-91a)**

A solution of *N*-Boc-D-leucine (1.5 g, 6.5 mmol, 1.0 equiv.) in THF (24 mL, 0.3 M) was cooled to  $-25\text{ }^{\circ}\text{C}$  ( $\text{CO}_2$ /acetone bath). *N*-methylmorpholine (0.78 mL, 1.1 equiv.) and *iso*-butylchloroformate (0.974 g, 1.1 equiv.) were added successively and a white precipitate formed immediately. After stirring for 15 min, solutions of aminoacetonitrile bisulfate (1.1 g, 1.1 equiv.) in water (5 M) followed by 1 M aqueous NaOH (0.363 g, 1.4 equiv.) were added at  $0\text{ }^{\circ}\text{C}$ . The reaction mixture was warmed to room temperature and stirred for 18 h. After concentration in vacuo to remove THF, the resulting aqueous solution was extracted with EtOAc. The combined organic phase was washed with water, sat.  $\text{NaHCO}_3$  (aq.), brine, dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo to yield a colourless oil, which solidified under vacuum. The crude product was suspended in petroleum ether and the title compound **IV-91a** was isolated by filtration as colourless needles (1.6 g, 6.2 mmol, 95% yield).

R<sub>f</sub> = 0.4 (PE/EtOAc 1:1)



$\text{C}_{13}\text{H}_{23}\text{N}_3\text{O}_3$   
 $M = 269.35\text{ g}\cdot\text{mol}^{-1}$

**$^1\text{H NMR}$**   $\delta = 7.52$  (br s, 1 H; H-3),  $5.13$  (s, 1 H; H-7),  $4.16$ - $4.14$  (m, 1 H; H-6),  $4.08$  (d,  $J = 5.5$  Hz, 2 H; H-2),  $1.56$ - $1.49$  (m, 1 H; H-9),  $1.47$ - $1.55$  (m, 2 H; H-8),  $1.38$  (s, 9 H; H<sub>Boc</sub>),  $0.88$  (d,  $J = 6.0$  Hz, 3 H; H-10/11),  $0.86$  ppm (d,  $J = 6.0$  Hz, 3 H; H-10/11).

**$^{13}\text{C NMR}$**   $\delta = 173.2$  (C-4),  $156.0$  (C-13),  $115.8$  (C-1),  $79.8$  (C-6),  $40.7$  (C-2),  $28.2$  (C-17, C-18, C-19),  $27.7$  (C-16),  $27.2$  (C-8),  $24.6$  (C-9),  $21.6$  (C-10/11),  $22.8$  ppm (C-10/11).

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_{13}\text{H}_{23}\text{N}_3\text{O}_3^+$ : 269.1739 Found 269.1734.

All analytical data matched those found in the literature<sup>41</sup>

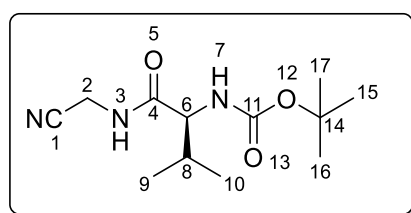
<sup>41</sup> R. G. Doveston, R. Steendam, S. Jones, R.J. K. Taylor, *Org. Lett.* **2012**, *14*, 1122-1125.



**tert-butyl (S)-(1-((cyanomethyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (VI-91b)**

A solution of *N*-Boc-*L*-valine (15 g, 69 mmol, 1.0 equiv.) in THF (230 mL, 0.3 M) was cooled to  $-25\text{ }^{\circ}\text{C}$  ( $\text{N}_2$ /acetone bath). *N*-methylmorpholine (8.3 mL, 1.1 equiv.) and *iso*-butylchloroformate (7.38 mL, 1.1 equiv.) were added successively and a white precipitate formed immediately. After stirring for 15 min, solutions of aminoacetonitrile bisulfate (11.7 g, 1.1 equiv.) in water (15 mL, 5 M) followed by 1 M aqueous NaOH (100 mL, 1.4 equiv.) were added at  $0\text{ }^{\circ}\text{C}$ . The reaction mixture was warmed to room temperature and stirred for 18 h. After concentration in vacuo to remove THF, the resulting aqueous solution was extracted with EtOAc. The combined organic phases were washed with water, sat.  $\text{NaHCO}_3$  (aq.), brine, dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo to yield a colourless oil, which solidified under vacuum. The crude product was suspended in petroleum ether and the title compound isolated by filtration as colourless needles (14.6 g, 57 mmol, 83% yield).

**R<sub>f</sub>** = 0.40 (PE/EtOAc 3:2)



$\text{C}_{12}\text{H}_{21}\text{N}_3\text{O}_3$   
 $M = 255.32\text{ g}\cdot\text{mol}^{-1}$

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.43$  (s, 1H; H-3),  $5.26$  (s, 1H; H-7),  $4.20$  (dd,  $J = 17.4, 5.8$  Hz, 1H; H-2a),  $4.11$  (dd,  $J = 17.4, 5.7$  Hz, 1H; H-2b),  $4.04$ - $3.89$  (m, 1H, H-6),  $2.15$ - $2.05$  (m, 1H; H-8),  $1.45$  (s, 9H;  $\text{H}_{\text{Boc}}$ ),  $0.96$  ppm (dd,  $J = 8.0, 7.1$  Hz, 6H; H-9, H-10).

**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta = 172.9$  (C-4),  $156.4$  (C-11),  $116.1$  (C-1),  $80.4$  (C-6),  $59.9$  (C-2),  $31.2$  (C-15, C-16, C-17),  $28.4$  (C-14),  $27.4$  (C-8),  $19.3$  (C-9/10),  $18.4$  ppm (C-9/10).

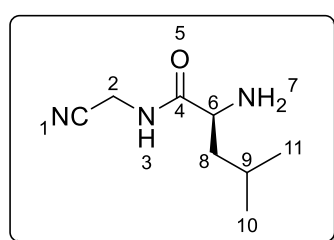
**IR** (neat):  $\tilde{\nu} = 3691, 3438, 3316, 2973, 2926, 1695, 1501, 1370, 1236, 1015\text{ cm}^{-1}$ .

**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_8\text{H}_{12}\text{N}_3\text{O}_2^+$ : 182.0925 Found 182.0934.

**(S)-2-amino-N-(cyanomethyl)-4-methylpentanamide (IV-66a)**

Compound **IV-91a** (0.8 g, 3 mmol, 1.0 equiv.) was taken up in formic acid (0.4 M, 7.4 mL) and stirred at room temperature for 16 h. After concentration in vacuo, the obtained colorless mixture was neutralized by NaOH (1 M) until pH = 8. The mixture was then extracted by EtOAc (3 x 20 mL), concentrated in vacuo and purified by flash column chromatography on silica gel (89:9:2 DCM/MeOH/aqueous NH<sub>3</sub>) to obtain the compound as a colorless oil (0.473 g, 2.8 mmol, 94% yield).

R<sub>f</sub> = 0.27 (90:9:1 DCM/MeOH/aqueous NH<sub>3</sub>)



C<sub>8</sub>H<sub>15</sub>N<sub>3</sub>O  
M = 169.23 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>) δ = 4.17 (s, 2H; H-2), 3.55 (t, J = 8.0 Hz, 1H; H-6), 1.74-1.67 (m, 1H; H-9), 1.4-1.36 (m, 1H; H-8a), 1.28-1.16 (m, 1H; H-8b), 0.86 (d, J = 6.5 Hz, 3H; H-10/11), 0.88 ppm (d, J = 6.5 Hz, 3 H; H-10/11).

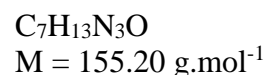
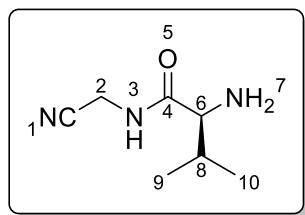
**<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>) δ = 172.8 (C-4), 117.4 (C-1), 51.6 (C-6), 41.7 (C-2), 27.0 (C-8), 23.8 (C-9), 22.6 (C-10/11), 21.9 ppm (C-10/11).

All analytical data matched those found in the literature.<sup>41</sup>

**(R)-2-amino-N-(cyanomethyl)-3-methylbutanamide (IV-66b)**

The solution of *N*-2-(tert-Butoxycarbonyl)-*N*-(cyanomethyl)-*D*-valinamide **VI-91b** (22 g, 86 mmol, 1.0 equiv.) in formic acid (0.4 M, 215 mL) was stirred at room temperature for 16 h. After concentration in vacuo, the obtained colorless mixture was neutralized by NaOH (1 M) until pH = 8. The mixture was then extracted by EtOAc (3 x 150 mL), concentrated in vacuo and purified by flash column chromatography on silica gel (94:4:2 DCM/MeOH/aqueous NH<sub>3</sub>) to obtain the compound as white powder (9.8 g, 64 mmol, 74% yield).

R<sub>f</sub> = 0.23 (94:4:2 DCM/MeOH/aqueous NH<sub>3</sub>)



**$^1\text{H NMR}$**   $\delta = 3.64$  (dd,  $J = 8.0, 6.5$  Hz, 2H; H-2),  $2.99$  (d,  $J = 4.0$  Hz, 1H; H-6),  $1.96$ - $1.84$  (m, 1H; H-8),  $0.87$  (dd,  $J = 8.0, 12.0$  Hz, 3H; H-10/9),  $0.77$  ppm (dd,  $J = 8.0, 12.0$  Hz, 3H; H-10/9)

**$^{13}\text{C NMR}$**   $\delta = 175.5$  (C-4),  $117.7$  (C-1),  $59.8$  (C-6),  $42.1$  (C-2),  $31.6$  (C-8),  $19.8$  (C-9/10),  $17.3$  ppm (C-9/10).

**IR** (neat):  $\tilde{\nu} = 3691, 3427, 3364, 2966, 1672, 1602, 1503, 1368 \text{ cm}^{-1}$ .

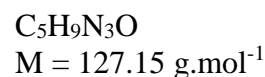
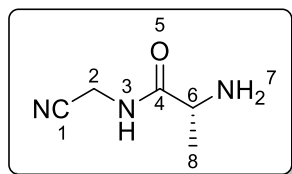
$[\alpha]_D^{25} = -14$  ( $c = 0.965$ , MeOH) (literature:  $[\alpha]_D^{25} = -4$  ( $c = 1.03$ , MeOH))

**Mp** =  $118$ - $119^\circ\text{C}$

### (R)-2-amino-N-(cyanomethyl)propanamide (IV-66c)

*N*-Boc-D-Alanine (15 g, 75.7 mmol, 1.0 equiv.) was dissolved in THF (264 mL, 0.3 M) and the mixture was cooled to  $-25^\circ\text{C}$  ( $\text{N}_2$ /acetone bath). After that, *N*-methyilmorpholine (9.6 mL, 1.1 equiv.) and *iso*-butylchloroformate (12 g, 1.1 equiv.) were added successively to the mixture and a white precipitate formed instantly. After 15 mins stirring, a prepared solution of aminoacetonitrile bisulfate (13.4 g, 1.1 equiv.) in 17 mL water was then added, followed by adding solution of NaOH 1M (4.44 g in 100 mL water, 1.4 equiv.) at  $0^\circ\text{C}$ . The mixture was then warmed to room temperature and kept stirring for further 18 h. The obtained mixture was concentrated in vacuo, extracted with EtOAc (3 x 150 mL). The organic phase was then washed with water, sat.  $\text{NaHCO}_3$  (aq.), brine, dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo. The product obtained was directly treated with formic acid (0.4M, 200 mL) and stirring at room temperature for 16 h. After concentration in vacuo, the obtained colorless mixture was neutralized by NaOH (1 M) until pH = 8. The mixture was then extracted by EtOAc (3 x 150 mL), concentrated in vacuo to obtain title compound IV-70c as yellow oil (8 g, 35.6 mmol, 47% yield for total 2 steps).

**Rf** = 0.15 (94:4:2 DCM/MeOH/aqueous  $\text{NH}_3$ )



**$^1\text{H}$  NMR**  $\delta = 8.48$  (s, 1H; H-3), 4.25 (s, 2H; H-2), 3.74 (q,  $J = 8.0$  Hz, 1H; H-6), 1.34 ppm (d,  $J = 8.0$  Hz, 1H; H-8).

**$^{13}\text{C}$  NMR**  $\delta = 166.6$  (C-4), 117.7 (C-1), 48.7 (C-6), 27.3 (C-2), 18.3 ppm (C-8).

**IR** (neat):  $\tilde{\nu} = 3691, 3607, 3365, 1731, 1678, 1602, 1501, 1249 \text{ cm}^{-1}$ .

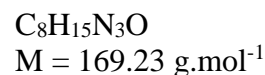
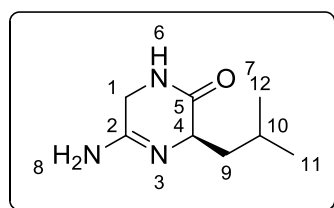
$[\alpha]_D^{25} = +5.7$  ( $c = 1.15$ , MeOH) (literature:  $[\alpha]_D^{25} = +2.8$  ( $c = 0.95$ ,  $\text{CHCl}_3$ ))

Analytical data matched those found in the literature.<sup>42</sup>

### (R)-5-amino-3-isobutyl-3,6-dihydropyrazin-2(1H)-one (IV-68a)

Hydroxylamine (0.216 mL, 50% w/w solution in water, 1.25 equiv.) was added to a solution of **IV-66a** (0.473 g, 2.8 mmol, 1.0 equiv.) in MeOH (0.3 M, 9 mL). The solution was kept stirring at room temperature for 4 h. After then, Raney® 2800 Nickel (slurry in water) (~0.5 g) was added to the resulted mixture to occur the reaction under hydrogen atmosphere. After 16 hours, crude product was filtered through Celite® and washed by MeOH, followed by concentration in vacuo. The crude product was purified by flash column chromatography on silica gel (80:19:1 DCM/MeOH/aqueous  $\text{NH}_3$ ) to furnish title compound **IV-68a** as a pale yellow oil (258 mg, 3.7 mmol, 56% yield).

**Rf** = 0.21 (89:9:2 DCM/MeOH/aqueous  $\text{NH}_3$ ).



<sup>42</sup> H. Moser, A. Fliri, A. Steiger, G. Costello, J. Schreiher, A. Eschenmoser, *Helvetica Chimica Acta* **1986**, *69*, 1224-1262.

**<sup>1</sup>H NMR** (400 MHz, DMSO *d*-6)  $\delta$  = 7.77 (br s, 1H; H-6), 3.78 (dd,  $J$  = 16.5, 1.0, 2H; H-1), 3.61 (dd,  $J$  = 6.0, 4.0, 1H; H-4), 1.80-1.87 (m, 1H; H-10), 1.46 (ddd,  $J$  = 12.0, 8.0, 4.0 Hz, 1H; H-9a), 1.36 (ddd,  $J$  = 12.0, 8.0, 4.0 Hz, 1H; H-9b), 0.88 (d,  $J$  = 8.0 Hz, 3 H; H-11/12), 0.86 ppm (d,  $J$  = 8, 3H, H- 11/12).

**<sup>13</sup>C NMR** (101 MHz, DMSO *d*-6)  $\delta$  = 171.8 (C-5), 156.7 (C-2), 56.0 (C-4), 42.2 (C-9), 41.7 (C-1), 23.9 (C-10), 23.3 (C-11/12), 21.6 ppm (C-11/12).

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>8</sub>H<sub>15</sub>N<sub>3</sub>O<sup>+</sup>: 169.1215 Found 169.1211.

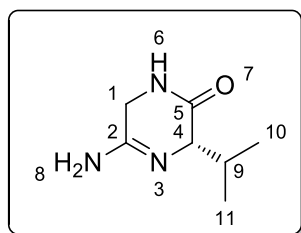
$[\alpha]_D^{25} = -4$  ( $c$  = 0.80, MeOH) (literature:  $[\alpha]_D^{25} = -47$  ( $c$  = 1.00, MeOH)).

Analytical data matched those found in the literature.<sup>41</sup>

### (S)-5-amino-3-isopropyl-3,6-dihydropyrazin-2(1H)-one (IV-68b)

Hydroxylamine (2.1 mL, 50% w/w solution in water, 1.25 equiv.) was added to a solution of **IV-66b** (4.2 g, 25 mmol, 1.0 equiv.) in MeOH (0.3 M, 90 mL). The solution was kept stirring at room temperature for 4 h. After then, Raney® 2800 Nickel (slurry in water) (~5 g) was added to the resulted mixture to occur the reaction under hydrogen atmosphere. After 3 hours, crude product was filtered through Celite® and washed by MeOH, followed by concentration in vacuo. Flash column chromatography on silica gel (80:19:1 DCM/MeOH/aqueous NH<sub>3</sub>) was used to purify the title compound as a pale yellow solid (1.7g, 11 mmol, 44% yield).

**Rf** = 0.16 (DCM/MeOH/aqueous NH<sub>3</sub> 80:19:1)



C<sub>7</sub>H<sub>13</sub>N<sub>3</sub>O  
M = 155.20 g.mol<sup>-1</sup>

**<sup>1</sup>H NMR** (400 MHz, DMSO *d*-6)  $\delta$  = 7.73 (br s, 1H; H-6), 3.71 (s, 2H; H-1), 3.45 (dd,  $J$  = 8.0, 4.0 Hz, 1H; H-4), 2.10-2.15 (m, 1H; H-9), 0.95 (d,  $J$  = 8.0 Hz, 3H; H-10/11), 0.74 ppm (d,  $J$  = 8.0 Hz, 3H; H-10/11)

**<sup>13</sup>C NMR** (101 MHz, DMSO *d*-6)  $\delta$  = 170.9 (C-5), 155.6 (C-2), 62.9 (C-4), 41.6 (C-1) 31.5 (C-9), 19.7 (C-10/11), 17.5 ppm (C-10/11).

**IR** (neat):  $\tilde{\nu}$  = 3192, 3051, 2962, 2874, 1658, 1526, 1454, 1343, 1331, 1100, 805 cm<sup>-1</sup>.

**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>7</sub>H<sub>13</sub>N<sub>3</sub>O<sup>+</sup>: 155.1054 Found 155.1046.

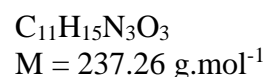
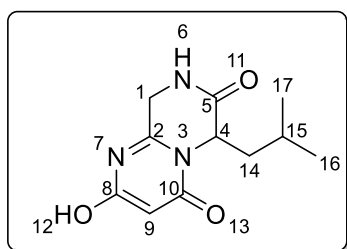
$$[\alpha]_D^{25} = +30 \text{ (} c = 0.975, \text{ MeOH)}$$

$$\text{Mp} = 126\text{-}128^\circ\text{C}$$

**(R)-2-hydroxy-6-isobutyl-8,9-dihydro-4H-pyrazino[1,2-a]pyrimidine-4,7(6H)-dione (IV-70)**

To a freshly prepared solution of NaOMe/MeOH (6 equiv., 1.2M) was added dimethyl malonate (33  $\mu\text{L}$ , 1.5 equiv.) at room temperature, followed by a solution of amidine **IV-68a** (30 mg, 0.2 mmol, 1.0 equiv.) in MeOH (1 mL). The reaction mixture was irradiated by microwave at 130°C for 1h. After cooling to room temperature, the reaction mixture was filtered through Celite® and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (70:28:2 DCM/MeOH/aqueous  $\text{NH}_3$ ) to afford title compound **IV-74** (33 mg, 0.14 mmol, 67% yield).

$$\text{Rf} = 0.18 \text{ (70:28:2 DCM/MeOH/aqueous } \text{NH}_3\text{)}$$



**$^1\text{H}$  NMR** (400 MHz, DMSO *d*-6)  $\delta$  = 8.51 (d,  $J$  = 4.5 Hz, 1H; H-6), 5.25 (s, 1H; H-9), 4.93 (t,  $J$  = 7.3 Hz, 1H; H-4), 4.65 (d,  $J$  = 17.7 Hz, 1H; H-1a), 4.02 (dd,  $J$  = 17.7, 5.0 Hz, 1H; H-1b), 1.79 – 1.57 (m, 2H; H-14a, H-15), 1.47 (dt,  $J$  = 12.6, 7.4 Hz, 1H; H-14b), 0.95 (d,  $J$  = 6.4 Hz, 3H; H-16/17), 0.91 ppm (d,  $J$  = 6.4 Hz, 3H; H-16/17).

**$^{13}\text{C}$  NMR** (101 MHz, DMSO *d*-6)  $\delta$  = 171.3 (C-5), 168.6 (C-10), 161.8 (C-8), 153.5 (C-2), 86.1 (C-9), 52.3 (C-4), 43.9 (C-1), 39.9 (C-14), 24.5 (C-15), 22.9 (C-16/17), 21.9 ppm (C-16/17).

**IR** (neat):  $\tilde{\nu}$  = 3376, 2923, 1650, 1595, 1406, 1317, 1012, 950  $\text{cm}^{-1}$ .

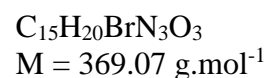
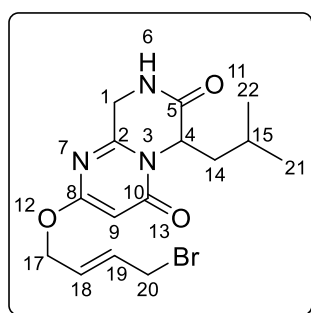
**HRMS** ( $\text{EI}^+$ ): Calcd. for  $\text{C}_7\text{H}_{13}\text{N}_3\text{O}^+$ : 237.1108 Found 237.1110.

**(S,E)-2-((4-bromobut-2-en-1-yl)oxy)-6-isobutyl-8,9-dihydro-4H-pyrazino[1,2-a]pyrimidine-4,7(6H)-dione (IV-71)**

$\text{Cs}_2\text{CO}_3$  (108 mg, 1.1 equiv.) was added to a solution of diketone **IV-70** (50 mg, 0.3 mmol, 1.0 equiv.) in DMSO (3 mL) and the reaction was stirred for 20 min. Then a solution of *trans*-1,4-dibromo-2-butene (77 mg, 1.1 equiv.) was added to the mixture at 20°C, stirring

at 20°C for another 12 h. The reaction was diluted with ethyl acetate and quenched with water at 0°C. The organic layer was washed 3 times with brine and the aqueous phases were extracted 3 times with ethyl acetate. The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was then purified by flash chromatography (5% MeOH in DCM) on silica gel to afford a yellow oil as title compound (10 mg, 0.03 mmol, 9% yield).

R<sub>f</sub> = 0.22 (5% MeOH in DCM)



<sup>1</sup>H NMR  
(400 MHz, CDCl<sub>3</sub>)

δ = 8.56 (d, J = 4.7 Hz, 1H; H-6), 6.03 – 5.88 (m, 1H; H-19), 5.83–5.73 (m, 1H, H-18), 5.60 (s, 1H, H-9), 4.94 (t, J = 7.4 Hz, 1H; H-4), 4.84–4.81 (m, 1H; H-14a), 4.72 (d, J = 17.8 Hz, 1H, H-1a), 4.66 (m, 1H; H-14b), 4.09 (dd, J = 17.9, 5.1 Hz, 1H, H-1b), 3.96 (s, 2H; H-17), 1.78 – 1.68 (m, 1H; H-20a), 1.63 (dt, J = 19.1, 6.4 Hz, 1H; H-15), 1.55–1.42 (m, 1H, H-20b), 0.95 (d, J = 6.4 Hz, 2H; H-21/22), 0.91 ppm (d, J = 6.5 Hz, 3H; H-21/22). 4.82 (s, 1H).

<sup>13</sup>C NMR  
(101 MHz, CDCl<sub>3</sub>)

δ = 167.8 (C-5), 167.5 (C-10), 161.3 (C-8), 155.1 (C-2), 135.6 (C-19, C-18), 122.9 (C-9), 88.4 (C-1), 67.3 (C-17), 60.6 (C-4), 53.0 (C-14), 43.9 (C-20), 24.4 (C-15), 22.7 (C-21/22), 21.7 ppm (C-21/22).

IR (neat):  $\tilde{\nu}$  = 3356, 2924, 2855, 1661, 1544, 1409, 1249, 1096, 1017 cm<sup>-1</sup>.

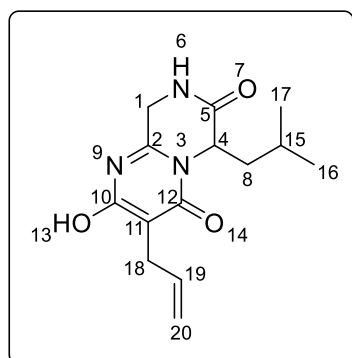
HRMS (EI<sup>+</sup>): Calcd. for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub><sup>+</sup>: 251.1265 Found 251.1265.

### 3-allyl-6-isobutyl-8,9-dihydro-2H-pyrazino[1,2-a]pyrimidine-2,4,7(3H,6H)-trione (IV-75)

To a freshly prepared solution of NaOMe/MeOH (6 equiv., 1.2 M) was added dimethyl 2-allylmalonate (17.7 μL, 1.5 equiv.) at room temperature followed by a solution of amidine **IV-68a** (10 mg, 0.06 mmol, 1.0 equiv.) in MeOH (0.6 mL) were added. The reaction mixture was refluxed for 6 h. After cooling to room temperature, the reaction mixture was filtered through Celite® and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (70:28:2 DCM/MeOH/aqueous NH<sub>3</sub>) to afford a yellow solid as

product (15 mg, 0.054 mmol, 90% yield).

**Rf** = 0.21 (80:19:1 DCM/MeOH/aqueous NH<sub>3</sub>)



C<sub>14</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>  
M = 277.32 g·mol<sup>-1</sup>

**<sup>1</sup>H NMR**  
(400 MHz, MeOD)

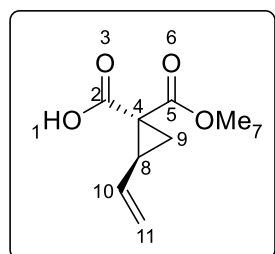
$\delta$  = 5.86 (ddt, J = 16.3, 10.0, 6.2 Hz, 1H; H-19), 5.22 (dd, J = 8.7, 6.2 Hz, 1H; H-4), 5.02 (ddd, J = 17.1, 3.5, 1.6 Hz, 1H; H-20a), 4.92 (ddd, J = 10.1, 3.2, 1.4 Hz, 1H; H-20b), 4.64 (d, J = 17.3 Hz, 1H; H-1a), 4.22 (d, J = 17.2 Hz, 1H; H-1b) 3.16 (dd, J = 6.2, 1.3 Hz, 2H; H-18), 1.85 – 1.71 (m, 2H; H-8a, H-15), 1.65 – 1.54 (m, 1H; H-8b), 1.05 (d, J = 6.4 Hz, 3H; H-16/17), 0.98 (d, J = 6.4 Hz, 3H; H-16/17).

NMR analytical data matched those found in the literature.<sup>41</sup>

### (1S,2S)-1-(methoxycarbonyl)-2-vinylcyclopropane-1-carboxylic acid (IV-78)

To a solution of vinylcyclopropane **III-159** (3 g, 16 mmol, 1 equiv.) in MeOH 1.3 M (12 mL), 1.7 M NaOH (0.776 g, 1.2 equiv. in 11 mL water) was added and stirred for 1.5 h. The resulted mixture was then diluted with EtOAc. The separated aqueous phase was acidified by HCl 1M to get a solution at pH = 2 and then extracted with EtOAc (3 x 100 mL), washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated to obtain colourless solid (2.4 g, 14 mmol, 87% yield).

**Rf** = 0.16 (DCM/MeOH/acetic acid 95:4:1)



C<sub>8</sub>H<sub>10</sub>O<sub>4</sub>  
M = 170.16 g·mol<sup>-1</sup>



**<sup>1</sup>H NMR**  $\delta$  = 11.2 (br s, 1H; H-1), 5.60-5.69 (m, 1H; H-10), 5.42 (d,  $J$  = 8.0 Hz, 1H; H-11a), 5.25 (d,  $J$  = 8.0 Hz, 1H; H-11b), 3.83 (s, 3H; H7), 2.73-2.79 (m, 1H; H-8), 2.14 (dd,  $J$  = 4.0, 8.0 Hz, 1H; H-9a), 2.0 ppm (dd,  $J$  = 4.0, 8.0 Hz, 1H; H-9b).

**<sup>13</sup>C NMR**  $\delta$  = 173.7 (C-2), 170.7 (C-5), 132.0 (C-10), 121.1 (C-11), 53.2 (C-7), 39.6 (C-4), 33.1 (C-8), 23.7 ppm (C-9).

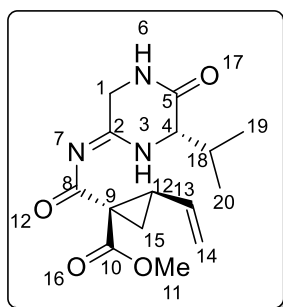
**HRMS** (EI<sup>+</sup>): Calcd. for C<sub>8</sub>H<sub>10</sub>O<sub>4</sub><sup>+</sup>: 170.0579 Found 170.0574.

All analytical data matched those found in the literature.<sup>43</sup>

**methyl (1R,2R)-1-(((S,Z)-6-isopropyl-5-oxopiperazin-2-ylidene)carbamoyl)-2-vinylcyclopropane-1-carboxylate (IV-79)**

To a solution of cyclopropyl monoacid **IV-78** (19 mg, 0.11 mmol, 1.0 equiv.) in THF (0.4 mL 0.3M) was added *N*-methyl-morpholine (13  $\mu$ L, 0.12 mmol, 1.1 equiv.) and *iso*-butylchloroformate (12  $\mu$ L, 0.12 mmol, 1.1 equiv.) successively at  $-25$  °C. A white precipitate formed immediately, then warm up slowly to 0 °C and stirring for 30 min. In the meantime, NaH was added to a solution of amidine **IV-68b** (17 mg, 0.11 mmol, 1.0 equiv.) in DMSO/THF (1:1) (0.4 mL, 0.3 M) at 0 °C, followed by stirring for 30 min. The resulted solution was added to the former mixture, kept stirring for further 1h at 0 °C. The reaction was quenched with sat. NH<sub>4</sub>Cl (aq.) and warmed to room temperature. After concentration in vacuo to remove THF, the resulting aqueous solution was extracted with EtOAc. Then the combined organic phases were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to yield a colourless oil. The crude product was purified by preparative TLC eluted with ethyl acetate to afford two product **IV-79** (5 mg, 0.016 mmol, 14% yield) and **IV-81** (2.5 mg, 0.01 mmol, 7% yield).

**R<sub>f</sub>** = 0.35 (100% EtOAc)



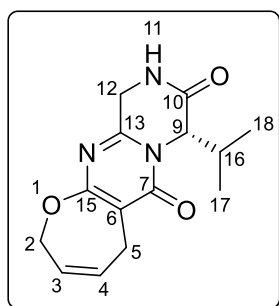
C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>  
M=307.4 g.mol<sup>-1</sup>

<sup>43</sup> M. R. Emmett, M. A. Kerr, *Org. Lett.* **2011**, *13*, 4180-4183.

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta$ = 8.92 (d, $J$ = 7.6 Hz, 1H; H-6), 6.60 (s, 1H; H-3), 5.64 (ddd, $J$ = 17.1, 10.1, 8.8 Hz, 1H; H-13), 5.38 (dd, $J$ = 17.1, 1.1 Hz, 1H; H-14a), 5.18 (dd, $J$ = 10.2, 1.3 Hz, 1H; H-14b), 4.27 (dd, $J$ = 7.7, 6.1 Hz, 1H; H-4), 4.05 (dd, $J$ = 4.9, 3.9 Hz, 2H; H-1), 3.75 (d, $J$ = 2.1 Hz, 3H; CH <sub>3</sub> ), 2.56 (dt, $J$ = 16.5, 8.3 Hz, 1H; H-12), 2.30 (m, 1H; H-18), 2.10 (dd, $J$ = 9.1, 4.4 Hz, 1H; H-15a), 1.90 (dd, $J$ = 8.1, 4.4 Hz, 1H; H-15b), 0.99 ppm (d, $J$ = 6.9 Hz, 4H ; H-19, H-20).	
<b><sup>13</sup>C NMR</b> (101 MHz, CDCl <sub>3</sub> )	$\delta$ = 171.7 (C-5), 171.4 (C-8), 170.3 (C-10), 168.7 (C-2), 133.2 (C-13), 120.2 (C-14), 59.5 (C-4), 52.5 (C-11), 52.4 (C-9), 41.2 (C-1), 37.8 (C-12), 30.1 (C-8), 21.7 (C-15), 19.6 (C19/C-20), 18.0 ppm (C19/C-20).	
<b>IR</b> (neat):	$\tilde{\nu}$ = 3324, 2958, 2924, 2854, 1743, 1712, 1649, 1526, 1440, 1207, 1145, 989 cm <sup>-1</sup> .	
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd. for C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> <sup>+</sup> : 307.1532	Found 224.1037.

**(S)-8-isopropyl-2,5,10,11-tetrahydro-6H-oxepino[2,3-d]pyrazino[1,2-a]pyrimidine-6,9(8H)-dione (IV-81)**

R<sub>f</sub> = 0.28 (100% EtOAc)



C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>  
M = 275.31 g.mol<sup>-1</sup>

<b><sup>1</sup>H NMR</b> (400 MHz, CDCl <sub>3</sub> )	$\delta$ = 6.27 (dt, $J$ = 9.9, 6.0 Hz, 1H, H-4), 6.11 – 6.03 (m, 1H, H-3), 5.09 (d, $J$ = 6.6 Hz, 1H, H-9), 4.87 (dd, $J$ = 13.5, 6.5 Hz, 1H, H-2a), 4.77 (dd, $J$ = 13.4, 6.4 Hz, 1H, H-2b), 4.56 (d, $J$ = 17.6 Hz, 1H, H-12a), 4.29 (dd, $J$ = 17.5, 4.9 Hz, 1H, H-12b), 3.97 (s, 1H, H-11), 3.51 (d, $J$ = 5.7 Hz, 2H, H-5), 2.28 (m, 1H, H-16), 1.13 (d, $J$ = 6.9 Hz, 3H, H-17/H-18), 1.06 ppm (d, $J$ = 6.8 Hz, 3H, H-17/H-18).	
<b>IR</b> (neat):	$\tilde{\nu}$ = 3220, 2923, 2853, 1665, 1548, 1462, 1394, 1215, 1101 cm <sup>-1</sup> .	
<b>HRMS</b> (EI <sup>+</sup> ):	Calcd. for C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> <sup>+</sup> : 275.1270	Found 275.1272.

## 2. Microbial oxidations

All materials and culture media were autoclaved at 121°C during 20 min before their use in experiments. The preparation of the inoculum and strain culture were carried out under sterile conditions.

### 2.1. Microorganism and culture conditions

#### 2.1.1. Sources of microorganism

ATCC: American Type Culture Collection.

NRRL: Agricultural Research Service Culture Collection.

CBS (CBS-KNAW): Culture collection from the Westerdijk Institute, or Westerdijk Fungal Biodiversity Institute, a part of the Royal Netherlands Academy of Arts and Sciences.

BCCM/MUCL: filamentous fungi and yeasts from Belgian Coordinated Collections of Microorganisms/ Mycothèque de l'Université Catholique de Louvain.

DSM: German Collection of Microorganisms and Cell Cultures GmbH from the Leibniz Institute DSMZ.

LD, SL, AN, PC: strains isolated in MCAM, National Natural History Museum.

#### 2.1.2. Preparation of culture media

Microorganisms are preserved on agar slant of PDA or medium A, which consist of glucose 20 (g/L), peptone 5 (g/L), yeast extract 5 (g/L), malt extract (5 g/L) and agar 20 (g/L).

The liquid culture media involved are PDB, YMS, MEA-SW and liquid wheat medium, prepared as follows:

- YMS consist of yeast extract 4 (g/L), malt extract 10 (g/L), soy peptone 5 (g/L) and glucose 16 (g/L).
- MEA-SW consist of malt extract 20 (g/L), soy peptone 1 (g/L), sea salt 40 (g/L) and glucose 20 (g/L).
- Liquid wheat medium: 150 mL solution A and 850 mL solution B
  - solution A consist of wheat extract 67 (g/L)
  - solution B consist of yeast extract 2.4 (g/L), soya peptone 2.4 (g/L), sucrose 24 (g/L)

### **2.1.3. Preparation of incubation buffer**

The medium used for incubation are phosphate buffer (pH=6-8), prepared from the mixture of  $\text{Na}_2\text{HPO}_4$  (0.067 M) and  $\text{KH}_2\text{PO}_4$  (0.067 M), and phosphate-citrate buffer, prepared from a mixture of  $\text{Na}_2\text{HPO}_4$  (0,5 M) and citric acid (0,5 M).

## **2.2. Biotransformations**

### **2.2.1. Preparation of the inoculum**

For each experiment, a preculture of microorganism was grown on slants of medium A at 28°C for 7 days. A mixture of hyphal fragments and spores in sterile glycerol (20%) was prepared from preculture to serve as the inoculum.

### **2.2.2. Strain culture**

Inoculum was added into the YMS or MEA-SW medium (50 mL of liquid medium in a 250 mL erlenmeyer). The culture was kept at 28 °C during 2 days in an orbital shaker (135 rpm). The fungal culture was centrifugated at 4000 rpm during 40min or filtered directly to separate the mycelium and the medium.

### **2.2.3. Incubation in the phosphate buffer**

4 g mycelium pellets of each tested microorganism were suspended in 8 mL phosphate or phosphate-citrate buffer (25 mL erlenmeyer) at different pHs, containing 4 mg of corresponding substrate, previously added in DMF (24  $\mu\text{L}$ ) DMF. The biotransformation assays were kept at 28°C during one or two weeks in an orbital shaker (135 rpm) and monitored by HPLC. Every day or every two days, 900  $\mu\text{L}$  of incubated suspension (including mycelium and medium) were taken, mixed vigorously with methanol (100  $\mu\text{L}$ ), sonicated (20min) and centrifugated at 15000 rpm during 15 min. Then the resulting supernatants were filtered and analyzed by HPLC.

## **2.3. Analytical studies**

### **2.3.1. HPLC analysis conditions**

Supernatants were analyzed on a Gilson HPLC interfaced to a computer running the Gilson Unipoint software. The system involved pumps 305 and 306, gradient dynamic mixer 811B and autoinjector 234, the column (Macherey-Nagel, Nucleosil 100-5 CN RP (250 x 4.6)) and the detector was a Shimadzu-SDP6A. All the product detection was carried out at

235 nm.

- DKP substrate (cyclo-(L-Ala-L-Tyr)):

Eluted with a isocratic solvent system (B) 100% H<sub>2</sub>O/ACN (90/10) for 20min with a flow rate of 0.5 mL/min.

- Geranylated- DKP substrate:

Eluted with a gradient solvent system: (A) 100% H<sub>2</sub>O (with 0.1% TFA) for 5min, followed by a gradient to 100% (B) 100% H<sub>2</sub>O/ACN (90/10) over 15 min, and held at 100% (B) for 4 min with a flow rate of 0.5 mL/min.

- Quinazolino-DKP substrate:

Eluted with a gradient solvent system: (A) 100% H<sub>2</sub>O (with 0.1% TFA) for 10min, followed by a gradient to 100% (B) 100% H<sub>2</sub>O/ACN (95/5) over 15 min, and held at 100% (B) for 5 min with a flow rate of 0.5 mL/min.

### **2.3.2. LC-MS analysis conditions**

LC-MS data of mycelium extracts were obtained by liquid chromatography (Shimazu, UHPLC Nexera), using a Kinetex column (1,7 $\mu$ , C18 100 Å, 100x2,1mm, from Phenomenex), coupled with mass spectrometry (Shimazu, MS2020) using atmospheric pressure chemical ionization (APCI). A 35 min program was developed and used for the quinazolino-DKP substrate analysis: Flow rate 0.5 mL/min, 5 to 10 % A over 6 min, 10 to 30% A over 9 min, 30 to 40% A over 5 minutes, 40 to 45% A over 5 minutes, 45 to 70% A over 5 minutes and 70% A over 5 min. (A: MeCN with 0.05% formic acid; B: H<sub>2</sub>O with 0.05% formic acid).

### 3. Computational methods and results

#### 3.1. Technical details

Calculations were carried out with the Gaussian09 package<sup>44</sup> and all structures, were fully optimized at the DFT level by means of the M06 functional<sup>45</sup>. All geometry optimization of TS have been performed both at the restricted and unrestricted-M06 level. The 6-31G(d,p) basis set was applied for all atoms. Each stationary point has been characterized with frequency analysis and shows the correct number of negative eigenvalues (zero for a local minimum and one for a transition state). All transition states (**III-187**, **III-188**, **III-189**, **III-190**, **III-192a** and **III-192b**) were verified by stepping along the reaction coordinate (intrinsic reaction coordinate calculations) and confirming that they transformed into the corresponding reactants/products. Final energy calculations at the M06 level associated with the 6-311++G(2d,2p) basis set, including solvation effect, have been achieved on the M06/6-31G(d,p) geometries. Solvent effects are accounted for by means of single point calculations with the integral equation formalism version of the polarizable continuum model (IEFPCM) for dimethyl sulfoxide (DMSO). To get accurate geometries and energies, the SCF convergence criterion was systematically tightened to  $10^{-8}$  au, and the force minimizations were carried out until the rms force became smaller than (at least)  $1 \times 10^{-5}$  au (“tight” optimization keyword in Gaussian 09). The “UltraFine” grid (99 radial shells and 590 angular points per shell) was used throughout the calculations, as recommended when using Gaussian 09. The Gibbs free energies presented in this manuscript are IEFPCM(DMSO)-M06 /6-311++G(2d,2p)//M06/6-31G(d,p), IEFPCM(DMSO)-B3LYP/6-311++G(2d,2p)//B3LYP/ 6-31G(d,p) and CCSD(T)/6-311++G(2d,2p)//M06/6-31G(d,p) electronic energies (which include solvation-energy corrections from the IEFPCM method) modified with thermal and entropy corrections from gas phase M06/6-31G(d,p) calculations. Due to the well-known errors associated with entropy calculations, we apply a scaling factor of 0.5 to the entropic contributions as recommended in the literature.<sup>46</sup> Therefore, the calculated  $\Delta G$  values reported

---

<sup>44</sup> M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li et al. Gaussian, Inc., Wallingford CT, Gaussian 09, Revision D.01, **2013**.

<sup>45</sup> Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215-241.

<sup>46</sup> a) J. Cooper, T. A. Ziegler, *Inorg. Chem.* **2002**, *41*, 6614-6622; b) (4) J. K. C. Lau, D. V. J. Deudel, *Chem. Theory Comput.* **2006**, *2*, 103-106; c) (5) H. Li, G. Lu, J. Jiang, F. Huang, Z. X. Wang, *Organometallics* **2011**, *30*, 2349-2363.

in this study include the ZPE, enthalpic temperature correction, solvation energy, and half the gas phase entropy.

### 3.2. Computational details on optimized geometries and energies

Table 1: Absolute electronic energies, gas phase and solvation free energies for all molecules at the IEFPCM(DMSO)-M06/6-311++G(2d,2p) level.

	<b>E (M06/6- 31G(d,p))</b>	<b>Thermal correction to Enthalpy</b>	<b>Thermal correction to Gibbs Free Energy</b>	<b>E (IEFPCM(DMSO)- M06/ 6-311++G(2d,2p))<sup>a</sup></b>
<b>III-133c</b>	-538.465951	0.209420	0.159930	-538.489476
<b>III-187</b>	-538.427348	0.208449	0.162387	-538.462213
<b>III-134c</b>	-538.465601	0.211961	0.165214	-538.499065
<b>III-188</b>	-538.410989	0.206995	0.158844	-538.452664
<b>III-136c</b>	-538.468772	0.210916	0.162415	-538.505691
<b>III-158</b>	-500.367933	0.200798	0.149475	-500.399836
<b>III-191</b>	-500.360826	0.203375	0.155098	-500.392340
<b>III-189</b>	-500.324816	0.200064	0.151910	-500.357870
<b>III-190</b>	-500.310371	0.198631	0.148655	-500.349885
<b>III-173</b>	-500.374056	0.202431	0.151080	-500.409294
<b>III-158a</b>	-500.367933	0.200798	0.149475	-500.399836
<b>III-158b</b>	-500.369058	0.200982	0.149677	-500.400939
<b>III-192a</b>	-500.324368	0.199795	0.151975	-500.358086
<b>III-192b</b>	-500.324816	0.200064	0.151910	-500.357870
<b>III-193</b>	-461.071629	0.184118	0.174625	-461.1024403
<b>III-194</b>	-461.068479	1.939247	0.174337	-461.0995215

<sup>a</sup> Energies computed at the M06/6-31G(d,p) geometries

Table 2: Absolute electronic energies, gas phase and solvation free energies for all molecules at the IEFPCM(DMSO)-CCSD(T)/6-311++G(2d,2p) level.

	<b>E (M06/6- 31G(d,p))</b>	<b>Thermal correction to Enthalpy</b>	<b>Thermal correction to Gibbs Free Energy</b>	<b>E (IEFPCM(DMSO)- CCSD(T)/ 6-311++G(2d,2p))<sup>a</sup></b>
<b>III-133c</b>	-538.465951	0.209420	0.159930	-537.582576
<b>III-187</b>	-538.427348	0.208449	0.162387	-537.548683
<b>III-134c</b>	-538.465601	0.211961	0.165214	-537.587554
<b>III-188</b>	-538.410989	0.206995	0.158844	-537.531507
<b>III-136c</b>	-538.468772	0.210916	0.162415	-537.594644
<b>III-158</b>	-500.367933	0.200798	0.149475	-499.550082
<b>III-191</b>	-500.360826	0.203375	0.155098	-499.546695
<b>III-189</b>	-500.324816	0.200064	0.151910	-499.511339
<b>III-190</b>	-500.310371	0.198631	0.148655	-499.495471
<b>III-173</b>	-500.374056	0.202431	0.151080	-499.563963
<b>III-158a</b>	-500.367933	0.200798	0.149475	-499.550082
<b>III-158b</b>	-500.369058	0.200982	0.149677	-499.550889
<b>III-192a</b>	-500.324368	0.199795	0.151975	-499.511339
<b>III-192b</b>	-500.324816	0.200064	0.151910	-499.511487
<b>III-193</b>	-461.071629	0.184118	0.174625	-460.3264909
<b>III-194</b>	-461.068479	1.939247	0.174337	-460.3228821

<sup>a</sup> Energies computed at the M06/6-31G(d,p) geometries.



Table 3: Absolute electronic energies, gas phase and solvation free energies for all molecules at the IEFPCM(DMSO)- B3LYP /6-311++G(2d,2p) level.

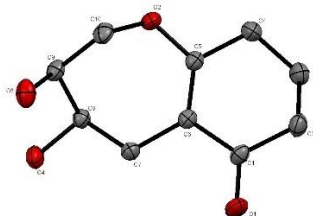
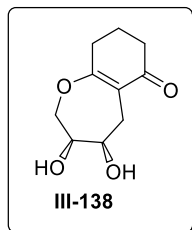
	<b>E (M06/6- 31G(d,p))</b>	<b>Thermal correction to Enthalpy</b>	<b>Thermal correction to Gibbs Free Energy</b>	<b>E (IEFPCM(DMSO)- B3LYP/ 6-311++G(2d,2p))<sup>a</sup></b>
<b>III-133c</b>	-538.465951	0.209420	0.159930	-538.872341
<b>III-187</b>	-538.427348	0.208449	0.162387	-538.843496
<b>III-134c</b>	-538.465601	0.211961	0.165214	-538.877865
<b>III-188</b>	-538.410989	0.206995	0.158844	-538.836172
<b>III-136c</b>	-538.468772	0.210916	0.162415	-538.887141
<b>III-158</b>	-500.367933	0.200798	0.149475	-500.746071
<b>III-191</b>	-500.360826	0.203375	0.155098	-500.745596
<b>III-189</b>	-500.324816	0.200064	0.151910	-500.713961
<b>III-190</b>	-500.310371	0.198631	0.148655	-500.707652
<b>III-173</b>	-500.374056	0.202431	0.151080	-500.765922
<b>III-158a</b>	-500.367933	0.200798	0.149475	-500.746071
<b>III-158b</b>	-500.369058	0.200982	0.149677	-500.747651
<b>III-192a</b>	-500.324368	0.199795	0.151975	-500.713961
<b>III-192b</b>	-500.324816	0.200064	0.151910	-500.714361
<b>III-193</b>	-461.071629	0.184118	0.174625	-461.4244533
<b>III-194</b>	-461.068479	1.939247	0.174337	-461.4208825

<sup>a</sup> Energies computed at the M06/6-31G(d,p) geometries.

## 4. X-Ray Crystallographic Data

### 4.1. Crystallographic information for compound III-137

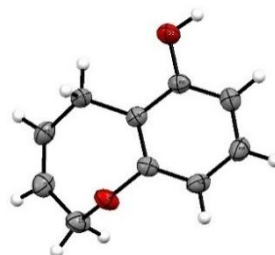
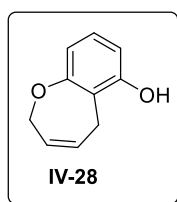
Structure:



Empirical formula	C <sub>10</sub> H <sub>14</sub> O <sub>4</sub>
Formula weight	198.21
Temperature/K	150
Wavelength/ Å	0.71069
Crystal system	orthorhombic
Space group	P b c a
A (Å), b (Å), c (Å)	10.3990(8), 8.8196(7), 20.8153(17)
$\alpha/^\circ$ , $\beta/^\circ$ , $\gamma/^\circ$	90, 90, 90
Volume/ Å <sup>3</sup>	1909.1(3)
Z	8
Density (calculated)/ Mg mm <sup>-3</sup>	1.379
Absorption coefficient/ cm <sup>-1</sup>	0.106
F(000)	848
Crystal size/mm <sup>3</sup>	0.360x0.200x0.030
Index ranges	-10 ≤ h ≤ 14 ; -10 ≤ k ≤ 12 ; -28 ≤ l ≤ 10
Reflections collected	7348
Independent reflections	1963 [R(int) = 0.0385]
Data / restraints / parameters	2580/15/127
Goodness-of-fit on F <sup>2</sup>	1.031
Final R indices [I > 2σ(I)]	R1 = 0.0523, wR2 = 0.1502
Weights a, b	0.0717; 1.2262
Largest diff. peak and hole/ e Å <sup>-3</sup>	0.703(0.061) / -0.621(0.061)

## 4.2. Crystallographic information for compound IV-28

### Structure:



Molecular formula	C <sub>10</sub> H <sub>10</sub> O <sub>2</sub>
Molecular weight	162.18
Crystal dimensions(mm <sup>3</sup> )	0.260x0.200x0.100
Crystal system	monoclinic
Space group	P 2 <sub>1</sub> /c
a (Å), b (Å), c (Å)	10.9911(9)/ 6.0885(5)/ 12.6932(10)
α/°, β/°, γ/°	90, 98.066(3), 90
V(Å <sup>3</sup> )	841.02(12)
Z	4
d(g-cm <sup>-3</sup> )	1.281
F(000)	344
μ(cm <sup>-1</sup> )	0.089
λ(Å)	0.71069
T (K)	150.0
Index ranges	-14 ≤ h ≤ 14 ; -8 ≤ k ≤ 8 ; -17 ≤ l ≤ 16
Reflections measured	11141
Reflections used	1599 [R(int) = 0.0466]
Data/ reflections / parameter	2102/14/112
Final R indices [I > 2σ(I)]	R1 = 0.0405, wR2 = 0.1071
Weights a, b	0.0420 ; 0.2866
GoF	1.014
difference peak / hole (e Å <sup>-3</sup> )	0.227(0.039) / -0.192(0.039)

**Titre :** Synthèse totale de produits naturels d'intérêt biologique en séries dikétopipérazine (DKP) et oxépine : étude de fonctionnalisations oxydantes et de réarrangements oxa-Cope

**Mots clés :** dikétopipérazines, oxépines, réarrangement oxa-Cope, biotransformation, DFT

**Résumé :** La synthèse biomimétique, inspirée par des voies de biosynthèse directes et rapides, est un moyen efficace pour produire des produits complexes. Le travail de cette thèse a porté sur le développement de stratégies collectives à partir d'intermédiaires biomimétiques pour accéder rapidement à trois familles de dikétopipérazines : les gliocladrines (DKPs fonctionnalisés), les quinazolino-DKPs et les oxépino-DKPs. Les fonctionnalisations oxydantes tardives par voies chimiques et biologiques des deux premiers intermédiaires ont été envisagées dans le but d'accéder directement au gliocladrine A et aux oxépino-DKPs. Une fonctionnalisation oxydante régiosélective par la DDQ a pu être découverte et offre un accès à la synthèse totale des aurantiomides. Alternativement, pour synthétiser des oxépino-DKPs : une méthodologie de synthèse, via une réaction cascade de cyclopropanation/réarrangement oxa-Cope vers des 2,5-dihydrooxépines, a été développée. Cette méthode a bien été explorée par des études expérimentales et théoriques (DFT) et a été appliquée aux synthèses totales des radulanines. De plus, nous avons démontré que l'utilisation de cette stratégie était possible dans une synthèse totale à finaliser des produits naturels de type cinérein.

**Title :** Total synthesis of biologically relevant natural products in the diketopiperazine and oxepine series: oxidative functionalizations and oxa-Cope rearrangement studies

**Keywords :** diketopiperazine, oxepine, oxa-Cope rearrangement, biotransformation, DFT

**Abstract:** Biomimetic synthesis, inspired by direct and fast biosynthetic processes, is an efficient way to produce complex natural products. This thesis doctoral work focused on the development of collective strategies, from biomimetic intermediates, to get a quick access to three families of diketopiperazines: gliocladrines (functionalized DKPs), quinazolino-DKPs and oxepino-DKPs. The late-stage chemical oxidation reactions and microbial transformations on the two first intermediates were envisaged to synthesize gliocladrin A and oxepino-DKPs. A regioselective late-stage oxidation operated by DDQ was discovered, bringing new synthetic possibilities to make aurantiomides in a collective manner. An alternative methodology to synthesize oxepino-DKPs was investigated in the meantime. A temperature-controlled tandem cyclopropanation/oxa-Cope rearrangement was developed successfully to prepare 2,5-dihydrooxepines. This method was afterwards elucidated by experimental and computational (DFT) studies and further applied as the key step to finish the intractable total synthesis of radulanins. This oxa-Cope rearrangement approach also led to achieve the installation of 2,5-dihydrooxepine DKP, getting close to the accomplishment of the total synthesis of cinereain.