



HAL
open science

Total Synthesis of Microsclerodermin D

Yong-Peng Liu

► **To cite this version:**

Yong-Peng Liu. Total Synthesis of Microsclerodermin D. Organic chemistry. Université Paris-Saclay, 2020. English. NNT: 2020UPASF024 . tel-03917475

HAL Id: tel-03917475

<https://theses.hal.science/tel-03917475v1>

Submitted on 2 Jan 2023

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.

Total Synthesis of Microsclerodermin D

Thèse de doctorat de l'université Paris-Saclay

École doctorale n° 571, Scienceschimiques : molécules, matériaux,
instrumentation et biosystèmes (2MIB)

Spécialité de doctorat: Chimie

Unité de recherche : Université Paris-Saclay, CNRS, Institut de chimie moléculaire et
des matériaux d'Orsay, 91405, Orsay, France

Référent : Faculté des sciences d'Orsay

**Thèse présentée et soutenue à Orsay,
le 13 Novembre 2020, par**

Yong-Peng LIU

Composition du Jury

Mme. Catherine GUILLOU

Directeur de recherche, CNRS - Institut de Chimie des
Substances Naturelles

Présidente

Mme. Sophie FAURE

Chargé de Recherche, HDR, CNRS - Institut de Chimie de
Clermont-Ferrand

Rapporteur & Examinatrice

M. Grégory CHAUME

Maître de Conférences, HDR, Université Cergy-Pontoise

Rapporteur & Examineur

M. Peter GOEKJIAN

Professeur, Université de Lyon

Examineur

Mme. Valérie DECLERCK

Maître de Conférences, HDR, Université Paris-Saclay GS
Chimie

Directrice de thèse

M. David J. AITKEN

Professeur, Université Paris-Saclay GS Chimie

Co-Directeur de thèse

ACKNOWLEDGEMENTS

First, I would like to thank Dr Catherine GUILLOU who accepted to be the president of my jury, Dr Sophie FAURE and Dr Grégory CHAUME for accepting to be the reporters for my PhD thesis. Thanks also to Prof Peter GOEKJIAN for accepting to be the examiner of my thesis.

Gratefully, I would like to express my special and sincere gratitude to my supervisor Dr Valérie DECLERCK. Without your assistance, patience, motivation and enthusiasm over the past four years, this thesis would have never been accomplished. So many thanks for your help and guidance in experiments, scientific research, thesis writing and revision, even application on scholarship from Chinese Scholarship Council and life in France. Innumerable examples: such as daily discussion, working on GABOB–APTO, accommodation, registration, CAF application and so on. You are so nice. I am so happy and honored to have this opportunity to be your student. Endless thanks for your guidance, support and understanding again.

Secondly, I really would like to appreciate Prof David J. AITKEN as co-director of my thesis for your invaluable guidance throughout my PhD research during the last four years. Your great dynamism, vision and motivation have deeply inspired me a lot. I am so glad to work with you and talk about chemistry with you. So many thanks for your guide and advice, as well as your help in experiments, writing and correction.

Last but not the least, I also would like to thank all other permanents from CP3A group: Marie-Christine, Thomas, Sandrine, Sylvie, Florence, Catherine, Fatima and Isabelle. Great thanks for your help and support in the lab, such as HPLC, chemicals and solvents, consumables. I am so happy to work together with all of you, and you are so nice and more like friends!

My sincere thanks also go to Jean Pierre BALTAZE and Amandine DOS SANTOS for your support in NMR service, and also to Tanya INCEOGLU and Hélène MAISONNEUVE for your support in Mass Spectrometry service.

Besides, great thanks to all my colleagues who I have met during my thesis. Thank Julien, Mathieu, Ahmad, Ali, Samad, and Zong for your help and advice. I was so happy to play escape-game with all of you, and I will cherish our friendship forever. And thank Zeynab for giving me a lot of help and advice in daily life, who is such a nice girl. Thank Xufeng and Dayi for your accompanying and being my close friends. In all, because of all of you, it makes my life in France a big difference.

Additionally, thank Thomas Hjelmgaard for information and results about synthesis of APTO. Thank Andrea and Sebastien for working on the GABOB fragment.

I am extremely grateful to my wife ZhaoBao, my parents and the whole family for your love, support, caring and sacrifice. Without your understanding and support, I would never complete my PhD. Even though I am so far away from home, I always stay together with you. I miss all of you!

ABBREVIATIONS AND ACRONYMS

AA	Amino acid
Ala	Alanine
ALM	Alamethicin
Ac	Acetyl
Arg	Arginine
Asp	Aspartic acid
AD	Asymmetric dihydroxylation
AETD	3-Amino-10-(<i>p</i> -ethoxyphenyl)-2,4,5-trihydroxydeca-7,9-dienoic acid
AMMTD	(2 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i> ,6 <i>S</i> ,11 <i>E</i>)-3-Amino-6-methyl-12-(<i>p</i> -methoxyphenyl)-2,4,5-trihydroxydodec-11-enoic acid
AMPTD	3-Amino-6-methyl-12-phenyl-2,4,5-trihydroxydodeca-7,9,11-trienoic acid
APTO	(2 <i>S</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>S</i> ,7 <i>E</i>)-3-Amino-8-phenyl-2,4,5-trihydroxyoct-7-enoic acid
aq.	Aqueous
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
BopCl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
brsm	Based on recovered starting material
BTCA	Benzyl 2,2,2-trichloroacetimidate
Bu	Butyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
Cbz	Carboxybenzyl
CDI	1,1'-Carbonyldiimidazole
<i>c</i> -Hex	Cyclohexyl
CP3A	Chimie Peptidomimétique, Photochimie et Procédés Alternatifs
CSA	Camphorsulfonic acid
CSO	Camphorsulfonyloxaziridine

Cp ₂ ZrClH	Chloridobis(η ⁵ -cyclopentadienyl)hydrido­zirconium (Schawrtz's reagent)
Cys	Cysteine
DBF	Dibenzofulvene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	Diastereoisomeric excess
DEAD	Diethyl azodicarboxylate
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DHQ-IND	[(1 <i>R</i>)-2-[(2 <i>S</i> ,4 <i>S</i> ,5 <i>S</i>)-5-Ethyl-1-azabicyclo[2.2.2]octan-2-yl]-1-(6-methoxyquinolin-4-yl)ethyl]-2,3-dihydroindole-1-carboxylate
DIC	<i>N,N'</i> -Diisopropylcarbodiimide
DIEA	Diisopropylethylamine
DIPA	Diisopropylamine
DIBAL	Diisobutylaluminum hydride
DMB	3,4-Dimethoxybenzyl
1,2-DME	1,2-Dimethoxyethane
2,2-DMP	2,2-Dimethoxypropane
DMAP	4-(<i>N,N</i> -Dimethylamino)pyridine
DMF	<i>N,N</i> -Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPPA	Diphenylphosphoryl azide
EDCI	<i>N</i> -Ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	Enantiomeric excess
eq.	Equivalent
ESI-MS	Electrospray ionization mass spectrometry
Et	Ethyl

EWG	Electron withdrawing group
FDA	United States Food and Drug Administration
Fm	9-Fluorenylmethyl
Fmoc	9-Fluorenylmethoxycarbonyl
FmocOSu	<i>N</i> -(9-Fluorenylmethoxycarbonyloxy)succinimide
FT-IR	Fourier-transform infrared
GABOB	(<i>R</i>)- γ -Amino- β -hydroxybutyric acid
Glu	Glutamic acid
Gly	Glycine
HATU	(1-[Bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxide hexafluorophosphate
HBTU	(2-(1 <i>H</i> -Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	Hydroxybenzotriazole
HPLC	High performance liquid chromatography
HRMS	High-resolution mass spectrometry
HSV	Herpes simplex virus
IBCF	Isobutyl chloroformate
IBX	2-Iodoxybenzoic acid
ICMMO	Institut de Chimie Moléculaire et des Matériaux d'Orsay
IC ₅₀	Half maximal inhibitory concentration
<i>i</i> Bu	Isobutyl
<i>i</i> Pr	Isopropyl
IPCF	Isopropyl chloroformate
IR	Infrared
Leu	Leucine
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
KHMDS	Potassium bis(trimethylsilyl)amide
Lys	Lysine
<i>m</i> -CPBA	<i>meta</i> -Chloroperbenzoic acid

Me	Methyl
Mes	2,4,6-Trimethylphenyl (Mesityl)
MOM	Methoxymethyl
MP	Melting point
2-MP	2-Methoxypropene
MS	Molecular sieve
Ms	Methanesulfonyl
NBS	N-Bromosuccinimide
NF κ B	Nuclear factor kappa B
NMO	4-Methylmorpholine <i>N</i> -oxide
NMR	Nuclear magnetic resonance
NMM	<i>N</i> -Methylmorpholine
Pbf	2,2,4,6,7-Pentamethyldihydrobenzofuran-5-sulfonyl
PFP	Pentafluorophenol
Phe	Phenylalanine
Phth	Phthaloyl
PIFA	Phenyliodine bis(trifluoroacetate)
Piv	Pivaloyl
PMB	<i>para</i> -Methoxybenzyl
PMBz	<i>para</i> -Methoxybenzoyl
PMP	<i>para</i> -Methoxyphenyl
PPTS	Pyridinium <i>para</i> -toluenesulfonate
PTFE	Polytetrafluoroethylene
PTSH	1-Phenyl-1 <i>H</i> -tetrazole-5-thiol
PyBOP	(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
PyBroP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
PyAOP	(7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
QPHOS	1,2,3,4,5-Pentaphenyl-1'-(di- <i>tert</i> -butylphosphanil)ferrocene
PyrAA	3-Amino-4-hydroxypyrrolidone-4-acetic acid
Δ PyrAA	Dehydropyrrolidinoacetic acid derivative
RNA	Ribonucleic acid

R _f	Retention factors
RT	Retention time
r.t.	Room temperature
Sar	Sarcosine
Su	Succinimide
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate.
TBAF	Tetrabutylammonium fluoride
TBCD	2,4,4,6-Tetrabromo-2,5-cyclohexadienone
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
<i>t</i> -Bu	<i>tert</i> -Butyl
Tf	Trifluoromethanesulfonyl
TFAA	Trifluoroacetic anhydride
TFA	Trifluoroacetic acid
Tf ₂ O	Triflic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin-layer chromatography
TMEDA	<i>N,N,N',N'</i> -Tetramethylethylenediamine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
TPPO	Tri(pyrrolidin-1-yl)phosphine oxide
TMSE	Trimethylsilylethyl
Trp	Tryptophan
Trt	Triphenylmethyl (Trityl)
Ts	Toluenesulfonyl (Tosyl)
UNCA	Urethane <i>N</i> -carboxyanhydride (Leuchs' anhydride)
UV	Ultra violet
WHO	World Health Organization

TABLE OF CONTENTS

GENERAL INTRODUCTION	1
CHAPTER 1: INTRODUCTION	5
1. Bioactive natural products	7
2. Peptides and Marine cyclic peptides	19
3. Microsclerodermins	26
3.1. Structure and origin of microsclerodermins	26
3.2. Biological activities	29
4. Previous Syntheses	31
4.1. Shioiri's pionnering studies towards microsclerodermins A and B	31
4.1.1. Preparation of a protected derivative of AMMTD.....	31
4.1.2. Preparation of the modified tryptophan derivative	34
4.1.3. Preparation of a protected GABOB derivative	34
4.1.4. Preparation of the protected PyrAA unit.....	35
4.1.5. Conclusion.....	36
4.2. Other syntheses of microsclerodermin fragments	37
4.2.1. Chandrasekhar's work towards AMMTD.....	37
4.2.2. McLeod's work on the synthesis of protected APTO and AETD	40
4.2.3. Aitken's work on the synthesis of protected APTO and AETD	42
4.2.4. Williams' work towards AMPTD.....	44
4.2.5. Dauban and Dodd's work on the synthesis of protected APTO	46
4.2.6. Davies' work on the synthesis of protected APTO and AETD	48
4.3. Total synthesis of microsclerodermins	50

4.3.1. Ma's work: total synthesis of microsclerodermin E	50
4.3.1.1. Synthesis of a protected derivative of AETD	50
4.3.1.2. Preparation of the dipeptide GABOB–AETD	52
4.3.1.3. Synthesis of the protected dehydropyrrolidinone residue	52
4.3.1.4. Synthesis of a protected derivative of the dipeptide Sar–Trp(2-CO ₂ H).....	54
4.3.1.5. Construction of the tetrapeptide derivative ΔPyrAA–Sar–Trp–Gly.....	55
4.3.1.6. Construction of the hexapeptide and macrocyclization.....	55
4.3.2. Donohoe's work on microsclerodermins B and J	56
4.3.2.1. Synthesis of a protected derivative of AMMTD*	57
4.3.2.2. Preparation of the dipeptide GABOB–AMMTD*	60
4.3.2.3. Preparation of the pyrrolidinoacetic acid residue	61
4.3.2.4. Synthesis of a protected derivative of the dipeptide Sar–Trp(2-CO ₂ H).....	65
4.3.2.5. Construction of a protected tetrapeptide derivative ΔPyrAA–Sar–Trp(2-CO ₂ H)–Gly.....	65
4.3.2.6. Construction of the hexapeptide, macrocyclization and late-stage difficulties	65
4.3.2.7. Synthesis and structural reassignment of dehydromicrosclerodermin B.....	66
4.3.2.8. Synthesis and structural reassignment of microsclerodermin J.....	69
4.4. Synthetic work: conclusion	72
5. Objectives	72

***CHAPTER 2: DIPEPTIDE MASKED PyrAA–SARCOSINE:
SYNTHESIS AND EVALUATION OF THE UNMASKING***

<i>STRATEGY</i>	77
1. Introduction	79
2. Synthetic strategy	80
3. Synthesis of the <i>N</i>-Cbz protected pyrrolidinoacetic acid derivative	81

4. Synthesis of the <i>N</i>-Fmoc protected pyrrolidinoacetic acid derivative	83
4.1. Synthesis of the <i>N</i> -Fmoc- γ -amino- β -ketoester.....	83
4.2. Origin of the racemization in the Masamune's protocol.....	84
4.3. Synthesis of the masked PyrAA–Sar dipeptide	86
4.3.1. Dithioketal protection of the <i>N</i> -Fmoc protected benzyl β -ketoester.....	86
4.3.1.1. Dithioketal protection of ketones	86
4.3.1.2. Protection of <i>N</i> -Fmoc protected benzyl β -ketoester	87
4.3.2. Access to the dipeptide masked PyrAA–Sar	88
4.3.2.1. Hydrolysis of methyl ester.....	88
4.3.2.2. Conversion of the methyl ester into a primary amide	90
4.3.2.3. Deprotection of the benzyl ester	91
4.3.2.4. One-pot dithioketal formation and deprotection of the benzyl ester	92
4.3.2.5. Peptide coupling and conversion of the methyl ester into a primary amide.....	93
4.3.2.6. Conversion of the methyl ester into a primary amide and peptide coupling.....	96
4.4. Deprotection of the dithioketal and spontaneous cyclization	97
4.5. Access to optically pure β -ketoester.....	100
4.5.1. Direct condensation of a Weinreb amide with a lithium enolate.....	102
4.5.2. Coupling with Meldrum's acid followed by treatment with benzyl alcohol.....	103
4.5.3. Use of <i>N</i> -Phth protected substrate in the Masamune's procedure	105
4.5.4. Through Mukaiyama aldol condensation followed by oxidation	105
4.5.5. Homologation of an aldehyde through the Roskamp reaction.....	106
4.5.6. Condensation of <i>N</i> -Fmoc protected UNCA with magnesium hemimalonate and silyl enolether	107

5. Conclusion	114
5.1. Final synthesis of the key dipeptide: (<i>S</i>)-mPyrAA–Sar.....	114
5.2. Final synthesis of the key dipeptide: (<i>R</i>)-mPyrAA–Sar	114
CHAPTER 3: SYNTHESIS OF DIPEPTIDE <i>Trp(6-Cl)–Gly</i>.117	
1. Introduction	119
1.1. Target structure	119
1.2. Synthesis of tryptophan derivatives	119
2. Synthesis of <i>Trp(6-Cl)–Gly</i>	126
2.1. Alkylation of chiral glycine imine derivatives	126
2.2. Strategy	127
2.3. Synthesis of H–[(<i>R</i>)- <i>Trp(6-Cl)</i>]–Gly– <i>Ot</i> -Bu	127
3. Conclusion	130
CHAPTER 4: SYNTHESIS OF DIPEPTIDE	
<i>GABOB–APTO</i>.....	131
1. Introduction	133
2. Synthesis of <i>GABOB–APTO</i>	133
2.1. Strategy	133
2.2. Synthesis of the protected <i>GABOB</i>	134
2.3. Synthesis of protected <i>APTO</i>	135
2.4. Coupling of <i>APTO</i> derivatives with <i>GABOB</i>	139
2.5. Saponification of Boc– <i>GABOB–APTO–OMe</i>	141
4. Conclusion	142

CHAPTER 5: MACROCYCLIC PEPTIDE ASSEMBLY: PEPTIDE COUPLING AND MACROCYCLIZATION.....	145
1. Introduction – strategy	147
2. Hexapeptide assembly	148
3. Macrocyclization and total synthesis of microsclerodermin D....	149
 GENERAL CONCLUSION.....	 151
 BIBLIOGRAPHY	 159
 EXPERIMENTAL PART	 219
 FRENCH SUMMARY.....	 293

GENERAL INTRODUCTION

Aitken research group (currently in CP3A at ICMMO) is interested in various cyclopeptide natural products (for example cyclotheonamide C), and has already developed various synthetic methodologies for the preparation of β - and γ -amino acids and especially of some polyhydroxy- β -amino acids present in microsclerodermins (APTO, AETD). Microsclerodermins this latter, a class of marine cyclic peptides with novel structures and biological activities appeared to us as interesting and challenging targets.

The objective of this project is the total synthesis of microsclerodermin D (Figure 1), which features a 23-membered ring macrocyclic peptide, containing six amino acids, of which three are common: glycine (Gly), sarcosine (Sar) and (*R*)- γ -amino- β -hydroxybutyric acid (GABOB). The other three amino acids possess some structural variations, but they can be classified as a modified tryptophan (TrpAA), a polyhydroxylated β -amino acid (APTO) containing four contiguous stereogenic centers and an original 3-amino-4-hydroxypyrrolidone-4-acetic acid (PyrAA). We plan to develop a modular synthetic route to microsclerodermin D that could be applicable for the preparation of other microsclerodermin family members and analogues thereof. We are also looking forward to make some investigations on their biological activities or potential as anticancer drug.

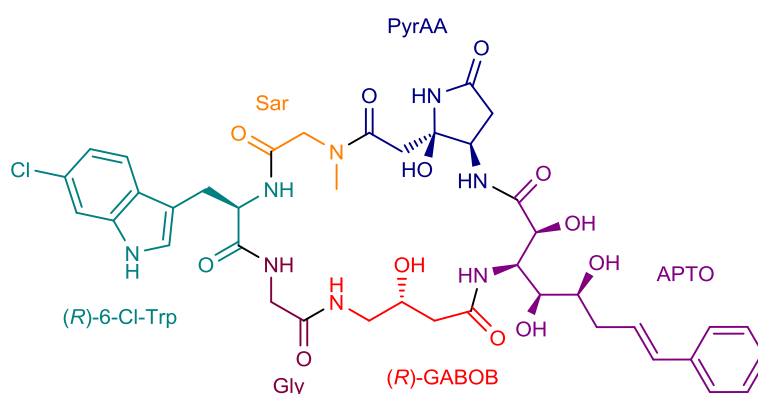


Figure 1: Microsclerodermin D

In Chapter 1, an overview is presented on bioactive natural products, peptides and marine cyclic peptides, as well as a very detailed introduction on microsclerodermins, including their structure and origin, biological activities and their previous syntheses. Subsequently, the objective of this project, the total synthesis of microsclerodermin D, is presented.

In Chapter 2, we focus on the synthesis of a key dipeptide, masked-PyrAA–Sar, required for the preparation of microsclerodermin D, including its synthesis and evaluation of the unmasking strategy. Firstly, an introduction of previous synthesis pyrrolidinoacetic acid derivatives, as well as dipeptide PyrAA–Sar is presented. Subsequently, the synthesis of racemic masked-PyrAA–Sar dipeptide is completed following our proposed synthetic strategy and evaluation of the unmasking strategy, deprotection of the dithioketal and spontaneous cyclization, is described. We then examine access to optically pure β -ketoester. After much effort, the optically pure β -ketoester was obtained *via* condensation of a *N*-Fmoc protected UNCA with a magnesium hemimalonate, facilitating the synthesis of the key dipeptide: masked-(*S*)-PyrAA–Sar and masked-(*R*)-PyrAA–Sar.

In Chapter 3, we describe the synthesis of the dipeptide Trp–Gly fragment required for the preparation of microsclerodermin D. Following a short introduction on the dipeptide Trp–Gly in microsclerodermins and an overview on the synthesis of tryptophan derivatives, the successful synthesis of H–[(*R*)-Trp(6-Cl)]–Gly–O*t*-Bu is presented, as well as the synthesis of racemic dipeptide Trp–Gly.

In Chapter 4, we consider the synthesis of dipeptide GABOB–APTO. After a short introduction on the dipeptide GABOB–APTO fragment required for the preparation of microsclerodermin D, our synthetic strategy is proposed. The successful synthesis of GABOB–APTO is presented, including the synthesis of GABOB and protected APTO.

In Chapter 5, a short introduction is given on the strategy of macrocyclic peptide assembly: peptide coupling and macrocyclization. The installation of tetrapeptide masked-PyrAA–Sar–Trp–Gly and hexapeptide masked-PyrAA–Sar–Trp–Gly–GABOB–APTO is then presented. Subsequently, the important macrocyclization and deprotection of dithioketal into the total synthesis of microsclerodermin D is assessed.

The general conclusion of this thesis is followed by literature references, experimental part and characterization data for all compounds presented in the thesis.

CHAPTER 1

INTRODUCTION

1. Bioactive natural products

Nature has been an inexhaustible source of novel chemotypes and pharmacophores,^{1,2} representing highly promising bioactive agents. Bioactive natural products³⁻¹¹ possess various biological activities and play a significant role in the discovery of novel therapeutics and medicinal agents, including a myriad of organic compounds, roughly classified into such as nucleic acid, carbohydrates, lipids, proteins, peptides, amino acids, alkaloids, terpenoids, polyketides, flavonoids and so forth,^{12,13} which originate as primary and secondary metabolites produced by a variety of organisms, such as animals, plants, microorganisms, sponges, cyanobacteria, vertebrates and invertebrates.¹⁴⁻¹⁶

For thousands of years, natural products have played a significant role in human health care and leads for the development of drugs and valuable bioactive agents to treat various human diseases,^{1,2,17-19} such as artemisinin in the treatment of malaria, or paclitaxel and its analogs in the treatment of various cancers. Historically, several ancient civilizations, such as the ancient Chinese, Egyptians, Indians, Greeks and North Africans have provided written evidence for the use of natural products in traditional medicines as remedies, potions and oils for the treatment of many human illnesses.^{12,20} For instance, the first record on the use of natural products in medicine was written on clay tablets in cuneiform from Mesopotamia dating from approximately 2600 B.C., when people used oils of *Cedrus* species (cedar) and *Cupressus sempervirens* (cypress), *Glycyrrhiza glabra* (licorice), *Commiphora* species (myrrh), and *Papaver somniferum* (poppy juice), all of which are still in use today for the treatment of ailments ranging from coughs and colds to parasitic infections and inflammation.¹ In addition, the Chinese Materia Medica (Chinese herb guides) on the use of herbaceous plants has been extensively documented over the millenia. The Wu Shi Er Bing Fang report 52 prescriptions dating from ab 1000 B.C., the Herbal Classic Shennong Herbal describes 365 substances from plants around 2800 B.C. and the Tang Herbal report 850 drugs around 659 A.D.¹ Even now, the World Health Organization (WHO) estimates that approximately 80% yield of the world's population relies primarily on traditional medicines as sources for their primary health care, especially for millions of people in the vast rural areas of developing countries.²¹

The early days of organic chemistry were closely connected to natural products chemistry. For a long period up to the 1960's, the structural studies of natural products served as the primary

driving force for the discovery of new chemical reactivity.²² As Woodward said, “Organic chemistry has literally placed a new nature beside the old... There is excitement, adventure, and challenge and there can be great art in organic synthesis.”²³

It is noteworthy that an explosive and diversified growth has taken place in the interest of natural products and natural products chemistry,² which have made, and continue to make an essential contribution to the discovery and innovation of novel drugs and bioactive agents, being based on their diversity of structures and biological activities.^{1,18,24,25} A huge number of natural products have been isolated and reported to possess diverse biological activities, such as antibiotic, antiviral, antifungal, anticancer, immunosuppressive and anti-inflammatory etc...²⁶ In the last 40 years, almost 65% yield of new drugs approved were classified as naturally derived (unmodified natural product, modified natural product, or semi-synthetic compound with a natural product as pharmacophore).²⁷

Thus, an overview on some interesting and selective bioactive natural products with diverse structure and biological activities will be presented. It will help us to have a more comprehensive and detailed understanding on bioactive natural products and their discovery and isolation, as well as the importance in the discovery of novel drugs and medicinal agents.

Artemisinin (Figure 2), an endoperoxide sesquiterpene lactone isolated by Tu in 1972 from the Chinese herb *Artemisia annua L.*, is currently recommended as a first-line antimalarial agent by the WHO against multi-drug resistant strains of *Plasmodium falciparum malaria*, *cerebral malaria*, and *infant's malaria*, and also used to treat infections caused by *Schistosoma spp.*, *Pneumocystis carinii*, *Toxoplasma gondii*, *human cytomegaloviruses*, Herpes simplex viruses (HSV) and hepatitis B and C.²⁸⁻³² It has already been described in traditional Chinese medicine as a remedy for chills and fevers,^{29,33-35} and was approved in 1987 by the US Food and Drug Administration (FDA) for use the treatment of malaria as a safe drug with few side effects.²⁷ Artemisinin and its synthetic derivatives have also been shown to be promising prototypes for the development of new antiproliferative agents against certain tumor cells.^{36,37} In 2015, Tu shared the Nobel Prize in Physiology or Medicine to for her discovery and development of artemisinin as a novel therapy against Malaria.^{38,39}

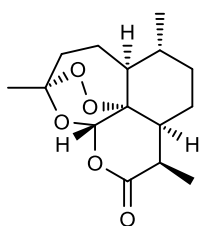


Figure 2: Artemisinin

(+)-Amphidinolide T1 (Figure 3) is a 19-membered ring macrolide, one of amphidinolides series that was first isolated by Kobayashi in 2000 from the Y-56 strain of the marine dinoflagellate *Amphidinium sp.*,⁴⁰ in addition to four other amphidinolides T2, T3, T4 and T5.^{41,42} The amphidinolide family comprises cytotoxic macrolides of different size from 12 to 27 membered ring with diverse structural features and pronounced biological activities which have been isolated by Kobayashi and his research group since 1986.^{43,44} They show potent cytotoxic activity against murine lymphoma L1210 and human epidermoid carcinoma KB cell lines, and potent antileukemic, antineoplastic activity.⁴⁵⁻⁴⁷

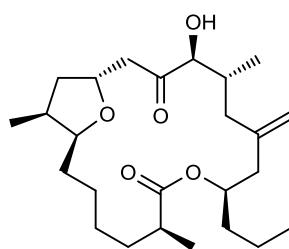


Figure 3: (+)-Amphidinolide T1

Paclitaxel (Figure 4), known as Taxol[®], is perhaps the most exciting plant-derived anticancer drug discovered in the last fifty years. This tricyclic diterpenoid was first isolated by Wall and Wani in 1971 from bark of the Pacific yew, *Taxus Brevifolia*,⁴⁸ and was found to promote the assembly of tubulin into microtubules in 1979 by Schiff and Horwitz.⁴⁹ It also shows excellent and reproducible activity against human solid tumor (such as antileukemic, P388, P1534, L1210 and HCT116 cell lines), and possesses an unusually broad spectrum of potent anticancer activity to treat various types of cancers, including ovarian cancer, breast cancer, lung cancer, Kaposi sarcoma, cervical cancer, pancreatic cancer and others, although some side effects may include hair loss, bone marrow suppression, numbness, allergic reactions, muscle pains, heart problems, increased risk of infection, and lung inflammation.⁵⁰⁻⁵⁵ However, extraction from the bark of Pacific yew gives a very low yield

(< 0.0001% dry weight), and three mature 100 years old trees provide only 1 g of paclitaxel, whereas a given course of treatment need 2 g of the drug, so that entire forests would need to be sacrificed. In 1992, Taxol[®] was approved by FDA and launched on the US market in the following year by Bristol-Myers Squibb for treatment of refractory breast cancer and ovarian cancer.^{50,54-57} In 1995, FDA has approved docetaxel (Taxotere[®]), a semisynthetic analogue developed by Potier in France⁵⁸⁻⁶² which can be prepared from 10-deacetylbaccatin III initially extracted by Potier and his research group in 1981 from the needles of the European yew, *Taxus baccata* L..⁶³ The success of paclitaxel spurred an enormous amount of work on the synthesis of analogues. Although paclitaxel and docetaxel are the only taxanes currently approved for clinical use, there are many analogues developed by various pharmaceutical companies and institutes in clinical trials.^{20,53,56,62,64-70}

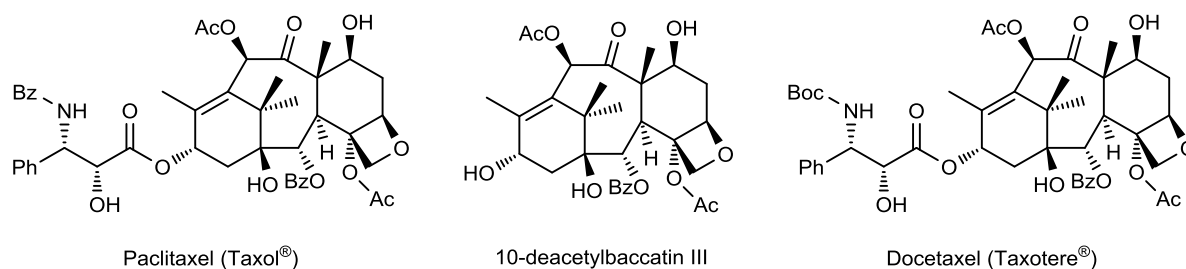


Figure 4: Paclitaxel and derivatives

Caminoside A (Figure 5) is a novel antimicrobial tetrasaccharide glycolipid, first isolated by Andersen in 2002 from the marine Caribbean sponge *Caminus sphaeroconia*. It showed potent activity as the first bacterial type III secretion inhibitor.⁷¹ Three other Caminosides B-D were isolated by the same group in 2006,⁷² and the first total synthesis of Caminoside A has been completed by Yu in 2005.⁷³

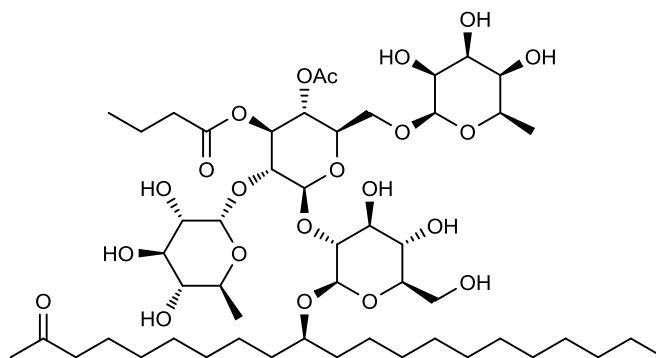


Figure 5: Caminoside A

(+)-Chaetocin (Figure 6) is an epidthiodiketopiperazine alkaloid which is a completely symmetric dimer, first isolated by Sigg in 1970 from the fungus *Chaetomium minutum*.⁷⁴ It possesses various biological activities, such as antibacterial and cytostatic,⁷⁴ thioredoxin reductase-1 inhibitor,⁷⁵ anticancer in several kinds of tumors (gastric cancer, anti-myeloma anti-leukemia, anti-hepatoma).⁷⁶⁻⁸² It is proposed for treatment of diabetes⁸³ and heart disease,⁸⁴ and applications are suggested as an anti-HIV drug⁸⁵ or as a potent histone methyltransferases inhibitor SUV39H1.⁸⁶

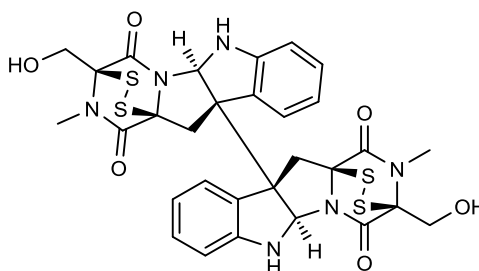


Figure 6: (+)-Chaetocin

Hibarimicinone (Figure 7), containing a quasi-dimeric tetracycline backbone (other family members hibarimicins A, B, C, D, E, G, H and I include a glycoside), was first isolated by Uehara in 2002 from *Microbispora rosea subsp. hibaria* (actinomycetes and culture broth), which are known to possess v-Src tyrosine kinase inhibitory activity and to induce growth and differentiation of Human Myeloid Leukemia HL60 Cells.⁸⁷⁻⁹⁰

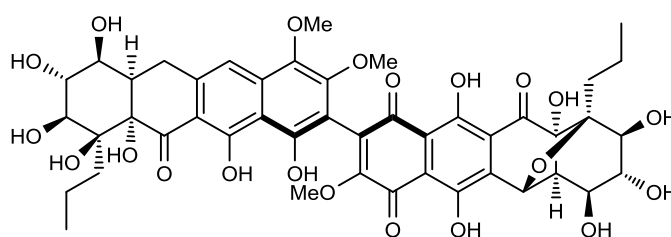


Figure 7: Hibarimicinone

Hyperforin (Figure 8) is a polycyclic polyprenylated acylphloroglucinol, first isolated by Gurevich in 1971 from a flowering plant *Hypericum perforatum L.* (St. John's wort, Hypericaceae family),⁹¹ and whose structure has been determined by Bystrov in 1975.⁹²⁻⁹⁴ It has various therapeutics and biological activities. For example, it has been widely used as phytomedicines for depression treatment by a novel mechanism of action;⁹⁵⁻⁹⁸ it has demonstrated anticancer⁹⁹ and

antitumoral activity *in vivo*, and inhibits the growth of leukemia K562 and U937 cells, brain glioblastoma cells LN229 and normal human astrocytes.⁹⁹⁻¹⁰¹ It presents also antibiotic and antibacterial activity (against Gram-positive bacteria etc...),^{91,100-103} photoprotective and anti-inflammatory effect *in vivo*;¹⁰⁴ AIDS immunodeficiency immunomodulation phagocytosis¹⁰⁵ and acts as an angiogenesis inhibitor *in vitro* and *in vivo*.¹⁰⁶ Hyperforin is an extremely attractive compound for biotechnological and pharmacological research because of its novel activities and structure.

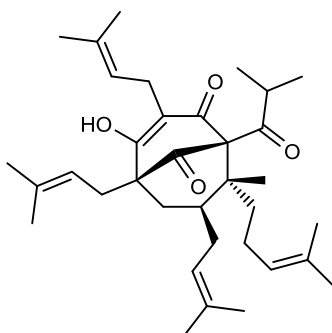


Figure 8: Hyperforin

(-)-Haliclolin A (Figure 9),¹⁰⁷ a novel macrocyclic diamide alkaloid with a novel an unprecedented 3-azabicyclononane skeleton, was isolated by Shin in 2009 from the marine sponge *Haliclona sp.* collected from Korean waters, which exhibited moderate cytotoxicity toward brine shrimp larvae (LC_{50} 260 ppm) and against the K562 leukemia cell line with an IC_{50} of $15.9 \mu\text{g}\cdot\text{mL}^{-1}$; antibacterial activity against diverse microbial strains such as *Bacillus subtilis* with a MIC value of $6.25 \mu\text{g}\cdot\text{mL}^{-1}$, and cytotoxicity.^{107,108} (-)-Haliclolin A is structurally related to sarains A-C, and its first total synthesis has been reported by Huang group in 2016.¹⁰⁹

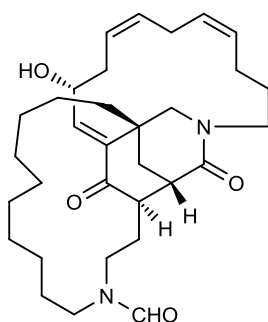


Figure 9: (-)-Haliclolin A

Strychnine (Figure 10), was the first terpene indole alkaloid isolated in crystalline form by Pelletier and Caventou in 1818 from the seeds of *Strychnos nux vomica L.* plant.¹¹⁰ It is a colorless, bitter and white powder, and also found as a notorious poison and typically used intentionally for suicidal or homicidal means. Strychnine poisoning has a very strong stimulating effect (LD_{50} : $0.4\text{-}3\text{ mg}\cdot\text{kg}^{-1}$) on certain functions of the central nervous system.¹¹¹⁻¹¹⁵ It acts as a competitive antagonist of the postsynaptic glycine receptor predominantly in the spinal cord, resulting in a sequence of predictable events: hyperreflexia, severe muscle spasms, convulsions (seizures) and respiratory paralysis.^{111,116-118} Although strychnine is highly toxic to both man and animals, it has been used for hundreds of years as a medicinal remedy for a broad range of ailments. For example, the seeds have long been used as a bitter-tasting gastric medicine, Vomica, for treatment of stomach ailments in Asia, and also as a pesticide against small vertebrates such as rodents in Europe, from the 17th century until the present.^{116,119} Strychnine has been proposed for applications in pharmaceuticals and therapeutics^{115-117,120,121} such as antitumor and anticancer,¹²²⁻¹²⁶ analgesic (gout) and anti-inflammatory,^{120,121,127} and antibacterial.^{120,121,128,129} The structure of strychnine was first determined by Robinson in 1946¹³⁰⁻¹³² and its first total synthesis was reported by Woodward in 1954,¹³³ which is considered one of the classic syntheses in the history of organic chemistry.

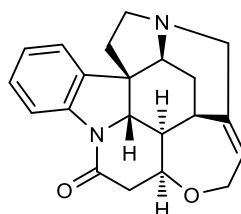


Figure 10: Strychnine

Chlorophyll *a* (Figure 11), the major green pigment of plants, was first isolated in 1817 from *Carapichea ipecacuanha* by Pelletier and Caventou.^{134,135} The chlorophylls are a class of very reactive, sensitive, and complicated substances related to porphyrins (found in hemoglobin) and binding a Mg^{2+} at the center.^{136,137} They are certainly the most widespread organic natural products, and their chemical structure as magnesium complexes was described in 1913, and then confirmed in 1928 by Willstätter.¹³⁸ Numerous chlorophylls are found in plants, algae and cyanobacteria, of which chlorophyll *a* is universal; chlorophyll *b* is present mostly in plants; chlorophyll *c*₁ and *c*₂ occur in various algae, while chlorophylls *d* and *f* are found in cyanobacteria.¹³⁹ The first total

synthesis of chlorophyll *a* was reported by Woodward in 1960,¹⁴⁰ which represents a beautiful example of bold planning and exquisite execution,¹⁴¹ following by an updated synthesis in 1990.¹⁴² Chlorophylls are essential in photosynthesis, as the functional molecule that absorbs sunlight, transduces and uses the energy to synthesize carbohydrates from CO₂ and water, producing oxygen as a waste product excreted into the atmosphere, which is used for respiration by plants and animals. Chlorophyll absorbs most strongly in the blue and red portion, but poorly in the green and near-green portions of the visible spectrum.¹⁴³ Chlorophyll is also widely used in pharmaceutical and clinical applications,^{144,145} for example, it inhibits bacteria and the growth of cancerous cells, stimulates tissue growth, acts as a good antioxidant capable of neutralizing free radicals in the body, and is used in the treatment of ulcers, oral sepsis and proctology.^{146,147} According to some studies in animal model, chlorophyll can reduce the level of triglycerides and cholesterol in the body.¹³⁸

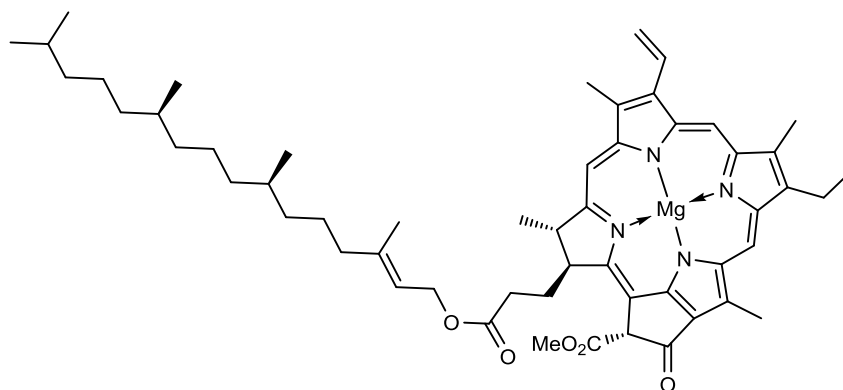


Figure 11: Chlorophyll *a*

(-)-Ptilomycin A (Figure 12), a novel polycyclic guanidine alkaloid, was first isolated in 1989 by Kashman, Kakisawa from the Caribbean sponge *Ptilocaulis spiculijer* and the Red Sea sponge *Hemimycale sp.* It shows antitumor activity, cytotoxicity against P388 (IC₅₀ = 0.1 μg·mL⁻¹), L1210 (IC₅₀ = 0.4 μg·mL⁻¹), and KB (IC₅₀ = 1.3 μg·mL⁻¹); antimicrobial and antifungal activity against *Candida albicans* (MIC = 0.8 μg·mL⁻¹), as well as remarkable activity against HSV at a concentration of 0.2 μg·mL⁻¹.^{148,149} Additionally, Murphy reported that it displayed cytotoxic activity against a series of cancer cell lines, such as K562 (human chronic myelogenous leukaemia: IC₅₀ = 0.35 μg·mL⁻¹); A2780 (human ovarian carcinoma: IC₅₀ = 0.27 μg·mL⁻¹); H460 (human large cell carcinoma: IC₅₀ = 0.35 μg·mL⁻¹); P388 (mouse, lymphoid neoplasm: IC₅₀ = 0.11 μg·mL⁻¹), as well as inhibition of the DNA polymerase activity of the reverse transcriptase of human

immunodeficiency virus type 1 (HIV-1 RT, $IC_{50} = 60 \mu\text{g}\cdot\text{mL}^{-1}$).¹⁵⁰ Molinski reported that it also inhibits melanogenesis of *Cryptococcus neoformans in vitro* by blocking the biosynthesis of laccase in the melanin biosynthetic pathway with an IC_{50} of $7.3 \mu\text{M}$.¹⁵¹

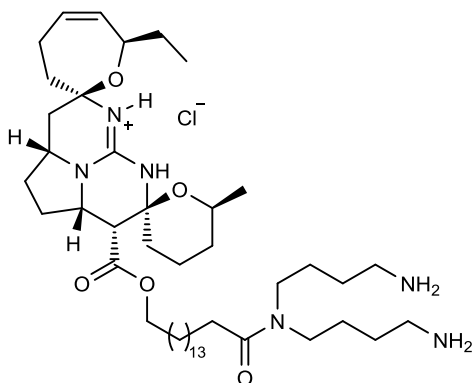


Figure 12: (-)-Ptilomycalin A

(-)-Phomoidride A (CP-225,917) and (-)-Phomoidride B (CP-263,114) (Figure 13), are novel Ras farnesylation inhibitors isolated in 1997 by Dabrah from an unidentified fungus with the characteristics of a sterile *Phoma* species. Phomoidrides A and B showed inhibition of Ras farnesyl transferase from rat brain with IC_{50} of $6 \mu\text{M}$ and $20 \mu\text{M}$ respectively and also inhibition of squalene synthase IC_{50} of $43 \mu\text{M}$ and $160 \mu\text{M}$ respectively.¹⁵² In 2001, Sulikowski reported the isolation and identification of two *C*⁷ epimers of phomoidride A and phomoidride B, and named them as phomoidrides C and D, respectively. It was also suggested that phomoidride B is the first-formed secondary metabolite and the source of the remaining three phomoidrides.¹⁵³

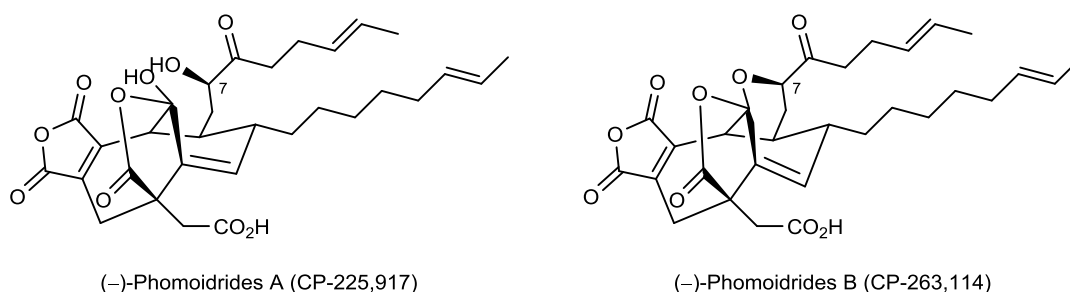


Figure 13: (-)-Phomoidrides A and B

Vinblastine and vincristine (Figure 14), two of the longest lasting bis-indole alkaloids in clinical use, were isolated by two independent groups from the Madagascar periwinkle,

Catharanthus roseus (previously known as *Vinca rosea* L.).^{57,154} Vinblastine (vincaleukoblastine) was first isolated in 1958 by Noble *et al.*,^{155,156} and later vincristine (leukocristine) in 1962 by Svoboda and his colleagues at Eli Lilly.^{157,158} Since their discovery, the Vinca alkaloids have been used by various cultures for the treatment of diabetes, acute lymphocytic leukemia, Hodgkin's disease, cervical, ovarian, breast and testicular cancer, lung cancer, Kaposi sarcoma and lymphomas, and they have been used in clinical oncology for almost 60 years.^{57,159-162} The antitumor activity of Vinca alkaloids results from their capacity to arrest cell division in metaphase by binding to the microtubule protein tubulin, that forms the mitotic spindle.¹⁶³ Vinorelbine (Navelbine[®]), a semisynthetic derivative of vinblastine developed by Potier and launched in 1989 by Pierre Fabre Laboratories in France, also shows inhibition activity of tubulin polymerization and disrupts spindle assembly in the mitotic phase. It has been used in the treatment of lung cancer, breast cancer, and ovarian cancer.¹⁶⁴⁻¹⁶⁶ Additionally, two other derivatives, vindesine¹⁶⁷ and vinflunine,^{168,169} are currently in use for treatment of various cancer. In 2012, a liposomal formulation of vincristine was approved for treatment of relapsed acute lymphocytic leukemia in patients who do not have a Philadelphia chromosome mutation.¹⁵⁴

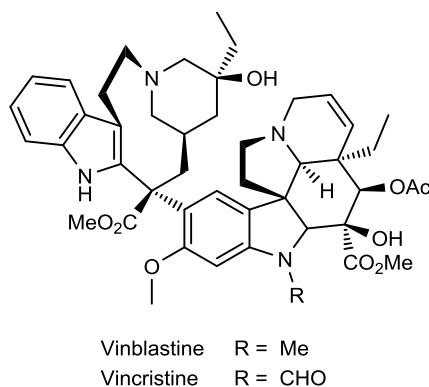


Figure 14: Vinca alkaloids: Vinblastine and Vincristine

Trabectedin (Ecteinascidin 743, Yondelis[®]) (Figure 15), a marine-derived tetrahydroisoquinoline alkaloid, was first isolated in 1992 by Sakai, Rinehart *et al.* from the Caribbean tunicate ascidian *Ecteinascidia turbinata*.^{170,171} It has been used for clinical treatment and application on the basis of its novel chemical structure and its striking activity against various tumor cell lines *in vitro* and *in vivo*.¹⁷² Trabectedin was previously described in 1969, but low extraction yields prevented its isolation, elucidation of its chemical structure and evaluation of its activity for

over a decade. It was early found to protect mice *in vivo* against P388 lymphoma, B16 melanoma, M5076 ovarian sarcoma, Lewis lung carcinoma, and the LX-1 human lung and MX-1 human mammary carcinoma xenografts.^{170,173} A huge amount of research and investigation on trabectedin has been done by many groups, it was found to exhibit excellent safety and efficiency in the treatment of tissue sarcoma cell lines, with preferential activity in ovarian, breast, NSCLC, melanoma, and renal human cell lines explanted from patients.¹⁷⁴⁻¹⁷⁹ Trabectedin was considered as a potent anticancer drug and showed an innovative mechanism of antitumor activity: it interacts with guanine rich sequences of DNA, binds to the minor groove of DNA and inhibits cell proliferation by disrupting the cell cycle.^{172,180-186} Presently, trabectedin is under Phase II trials for the treatment of pediatric sarcomas as well as breast and prostate cancers.^{2,17,24,187} Trabectedin was approved from the European Commission as Yondelis[®] in sales in Europe, Russia and South Korea for the treatment of ovarian cancer and advanced soft tissue sarcoma (STS) by Zeltia and Johnson & Johnson in 2007. Yondelis[®] has been authorized by the European Commission and FDA for the treatment of women's relapsed platinum-sensitive ovarian cancer, soft tissue sarcomas and orphan drug status.^{173,181,188-191}

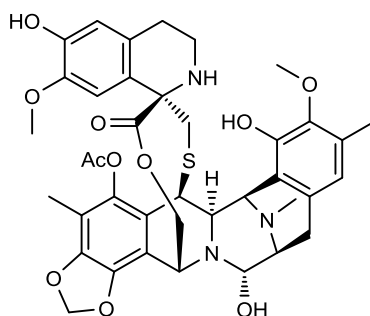


Figure 15: Trabectedin

Calicheamicin γ_1^I (Figure 16) one of the novel family of enediyne class of antitumor antibiotics, was first discovered and isolated in 1986 from the fermentation broth of the bacterium *Micromonospora echinospora ssp. calichensis*. collected from a soil sample in Texas by Lee group. The family members of Calicheamicins count β_1^{Br} , γ_1^{Br} , α_2^I , α_3^I , β_1^I , γ_1^I , δ_1^I , of which Calicheamicin γ_1^I was first isolated and studied on its chemistry and structure in 1986-1989,^{192,193} followed by Calicheamicin β_1^{Br} , γ_1^{Br} was isolated and characterized.¹⁹⁴ Notably, their structure elucidation was reported by the same group in 1992.¹⁹⁵ The chemistry and activity of calicheamicin γ_1^I was first studied by Maiese, and found to exhibit maximal antitumor activity against P388 at $5.0 \mu\text{g}\cdot\text{kg}^{-1}$

(T/C 232) and B16 at $1.25 \mu\text{g}\cdot\text{kg}^{-1}$ (T/C 186) when tested in male BDF₁ mice against P388 leukemia and B16 melanoma *in vivo*, and significant activity against Gram-positive and Gram-negative bacteria *in vitro*.^{196,197} It is possibly one of the most potent antitumor compounds approved for clinical use, which is over 1000 times more potent than adriamycin, a clinically useful antitumor antibiotic, when tested in murine tumor models. Calicheamicin γ_1^I and its analogues possess remarkable biological properties, such as cytotoxicity, anti-bacterial, antitumor.¹⁹⁸ For example, it can bind in the minor groove of DNA and causes DNA double-strand breakage with a high degree of specificity; it is extremely toxic to all cells (such as HL60 leukemia cells, acute myeloid leukemia etc...).^{199,200} Although it possesses very excellent sub-picomolar level activity, it was too toxic to pursue for many years. It has been linked to a specific directed monoclonal antibody against chronic myelogenous leukemia and use in antitumor (potent antitumor effects in breast and ovarian tumor xenografts).²⁰¹⁻²⁰³ Calicheamicin γ_1^I is the first FDA-approved antitumor antibiotic of microbial second metabolites (the first commercially available chemotherapeutic immunoconjugate for clinical use) as Mylotarg[®], which is carried to the site where needed and released *in situ*, thereby reducing the systemic toxicity but not its activity. Some in-depth research and investigation on antibody-calicheamicin conjugates for treatment of acute myeloid leukemia has been done by Hamann's and Zhao's groups and further developed into new drugs.^{1,199,200,204-208}

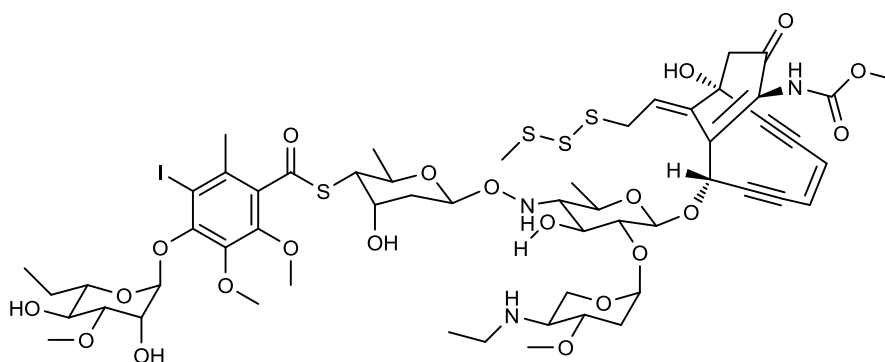


Figure 16: Calicheamicin γ_1^I

Halichondrin B (Figure 17), a marine-derived macrocyclic polyether of the halichondrin family, was first isolated in 1986 by Uemura from sponge *Halichondria okadai* in the Pacific coast of Japan,²⁰⁹ and later also isolated in 1991 by Pettit *et al.* from the western Pacific marine sponge *Axinella sp.*²¹⁰ Four new halichondrins were isolated in 2009 by Munro from the New Zealand deep-water sponge *Lissodendoryx sp.*²¹¹ Halichondrin B and several of its family members are

known to exhibit exceptional antitumor activities towards a variety of cell lines, and showed strong cytotoxicity to bind to tubulin and to inhibit tubulin polymerization, thereby inducing cell cycle arrest and apoptosis.^{212,213} Halichondrin B is the most potent candidate of this family for treatment of breast cancer and other neoplasms,^{214,215} which is a noncompetitive inhibitor of Vinca alkaloids, colchicine and paclitaxel,²¹⁶⁻²¹⁸ and its discovery and development and clinical application has been reviewed.^{47,57,209,219-226} A major obstacle was the issue of supply since only miniscule amounts are available from its marine source.²²⁷ Fortunately, the first total synthesis of halichondrin B was developed by Kishi in 1992.²²⁸ Eribulin (Halaven), an anticancer drug developed by Eisai Research Institute, is a synthetic analogue of halichondrin B, and its mesylate salt (also referred to as E7389) was approved by FDA in 2010 for the treatment of metastatic breast cancer, treatment of prostate, sarcoma, breast, bladder, and ovarian cancers etc..., which are investigated in phase III trials.²²⁹⁻²³¹

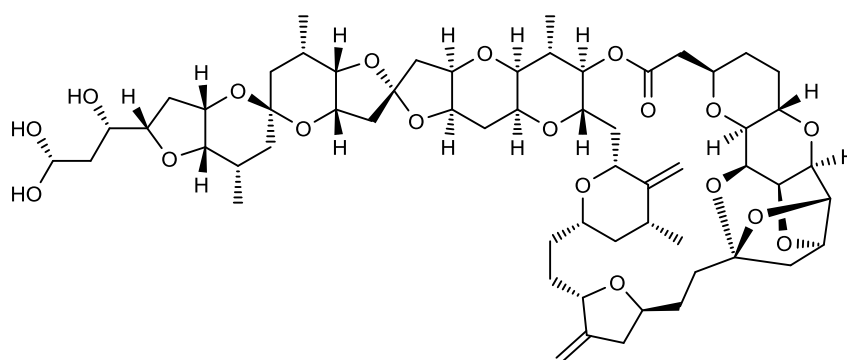


Figure 17: Halichondrin B

2. Peptides and Marine cyclic peptides

Bioactive natural peptides are ubiquitous in all life kingdoms. They are often characterized by short amino acid sequences, usually with less than 20 units of amino acids, and include cyclic and linear peptides, as well as depsipeptides. They are found either free or encrypted in proteins, and thus released during enzymatic proteolysis of proteins or directly isolated from organisms.²³²⁻²³⁵ Nature remains the largest source of bioactive peptides since plants, animals, fungi, microbes and their metabolites contain a vast number of peptides.²³⁶

In recent years, bioactive peptides have received increased attention from the pharmaceutical and biotech industries, and play a pivotal role as a source for discovery and development of drugs

and candidates.^{237,238} Bioactive peptides have a positive impact on body functions or conditions, which play an important role in metabolic regulation and modulation,^{239,240} and may ultimately influence human health by affecting the digestive, endocrine, cardiovascular, immune and nervous systems.²⁴¹ It is thought that they may fill the gap between small molecules and peptides drugs. Insulin, a peptide hormone produced by our pancreas to control the blood glucose levels at any given moment, helps to regulate our body's metabolism of carbohydrates, fats, and proteins, which has been widely used for treatment of type I and II diabetes.²⁴² Some natural peptides and their derivatives have high commercial value and success in pharmaceutical markets, and some of them are already in preclinical and clinical pipelines for treatment of various diseases,²⁴³ for example enfuvirtide (HIV fusion inhibitor) and liraglutide for treatment of type II diabetes.

Currently among more than 1500 different bioactive peptides reported in a database, more than 1250 peptides present different functional significance.²⁴⁴ Numerous bioactive peptides have been isolated from a great variety of marine and terrestrial organisms and species, such as sponges, bacteria, cyanobacteria, animals, plants, fungus and microbes, and are also known to exhibit diverse biological activities such as antithrombotic, anti-cancer, antitumoral, anti-proliferative, antimicrobial, anticoagulating, antiviral, anti-diabetic, anti-coagulant, anti-hypertensive, antioxidant, antiobesity, hypocholesteremic, analgesic and calcium-binding activities.^{220,232-236,238,240,241,245-269}

Thus, a short introduction on some selective peptides with diverse structural features and pronounced biological activities will be presented. Similarly, it will promote us to have a better understanding on peptides and marine cyclic peptides and their discovery and isolation, as well as the significant role in the exploration of novel peptide drugs and therapeutic agents.

Romidepsin (Figure 18) (Istodax[®], NSC 630176, FK288, FR901228), a structurally unusual bicyclic depsipeptide, was first isolated in 1994 by a research team of Fujisawa Pharmaceutical Company (now Astellas Pharma) in Tsukuba from the culture broth of the terrestrial bacterium *Chromobacterium violaceum*. It shows potent *in vivo* antitumor activity against both human tumor xenografts and murine tumors.²⁷⁰⁻²⁷² Recently, romidepsin has proved to act as a strong HDAC inhibitor and thus has been approved for the treatment of cutaneous T-cell lymphoma and other peripheral T-cell lymphomas by the FDA.²⁷³⁻²⁷⁸

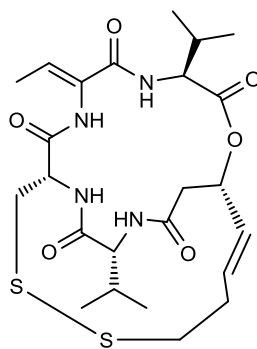


Figure 18: Romidepsin

Vancomycin (Figure 19) is a branched tricyclic glycopeptide antibiotic^{279,280} first isolated in 1953 by Kornfeld at Eli Lilly from the Actinobacteria species *Amycolatopsis orientalis*,²⁸¹ which was used for treatment of a number of bacterial infections by inhibiting proper construction of cell wall in Gram-positive bacteria.²⁸²⁻²⁸⁴ It is recommended intravenously as a treatment for complicated skin infections, bloodstream infections, endocarditis, bone and joint infections, and meningitis.^{285,286} The rapid approval by the FDA in 1958 was prompted by penicillin-resistant *Staphylococcus aureus* and oxacillin-resistant (methicillin-resistant) *staphylococci*.^{287,288}

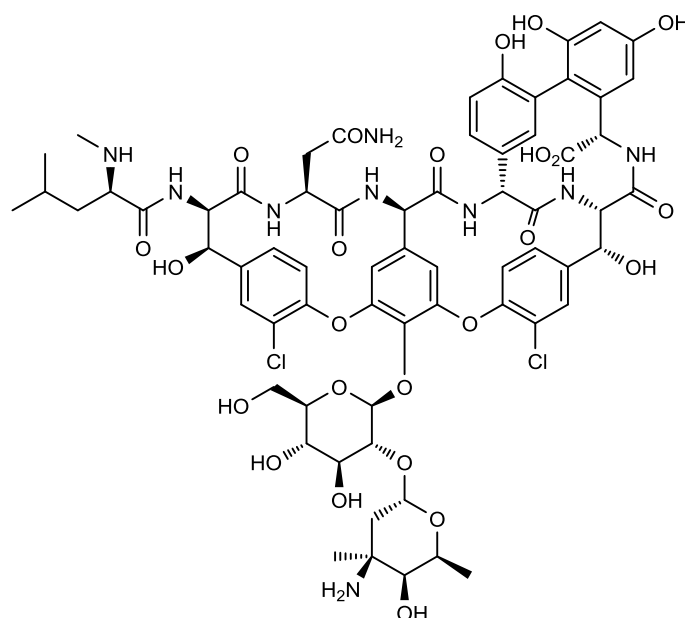


Figure 19: Vancomycin

Alamethicins are a class of well-known linear 19-membered peptides antibiotics, primarily isolated by Meyer and Reusser from *Trichoderma viride* in 1967.²⁸⁹ However, it is revealed that this material was composed of two major groups neutral ALM F30 (about 85%) and acidic ALM F50

(about 12%), as well as a minor group ALM F20 (2%) and trace of ALMs (F40, F60, F70) by Melling and McMullen in 1975.^{290,291} All alamethicin are structurally blocked at the *N*-terminus by an acetyl moiety and at the *C*-terminus by the phenylalaninol. To date, 23 members of natural mixture of alamethicin have been sequenced, of which two examples are shown (Figure 20): Alamethicin I (belonging to F50) and Alamethicin (belonging to F30).^{292,293} They are also shown to possess potent biological activities as antibacterial agent, *in vitro* and *in vivo* against strains *Trypanosoma brucei brucei* strain and *Trypanosoma brucei rhodesiense*.^{294,295} Besides, alamethicins are also known to exhibit voltage dependent ion channel activity in membrane environments and induce excitability phenomena in model membranes and has served as an excellent model for the study of voltage sensitive transmembrane channels.²⁹⁶⁻²⁹⁸

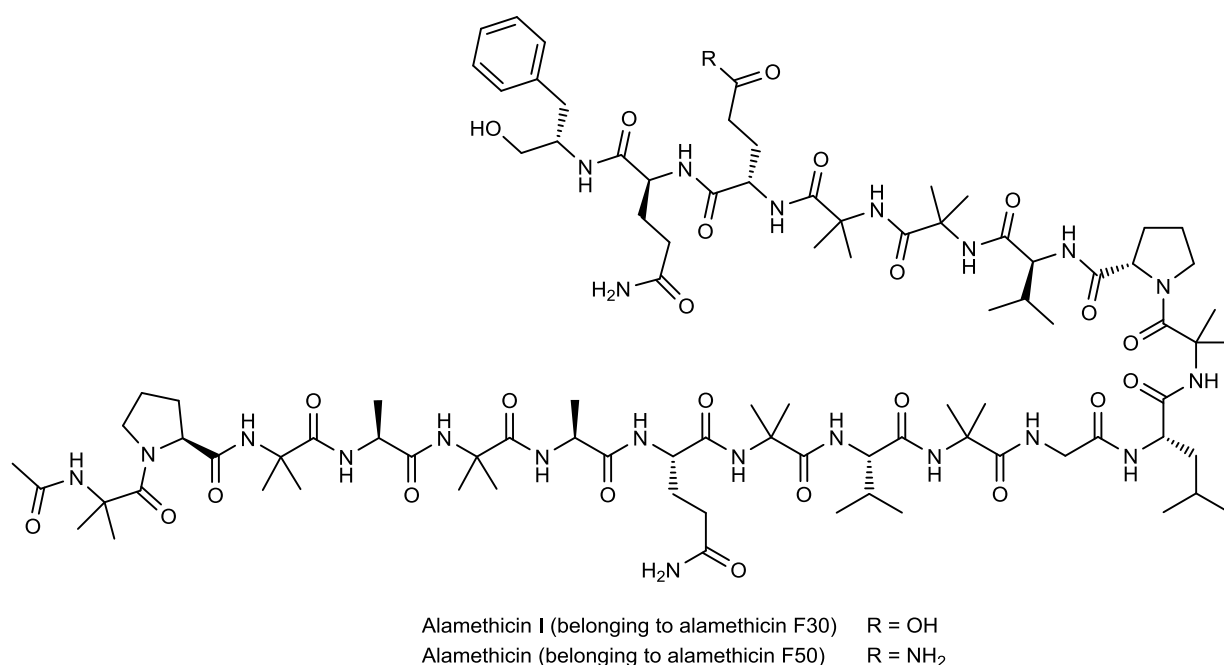


Figure 20: Alamethicin

The oceans stand a uniquely vast source for new bioactive natural products, which is considered as the largest remaining treasure of undiscovered natural products with an unprecedented variety of chemical classes possessing a wide range of biological activities.^{234,299,300} containing a myriad of marine peptides^{2,223,269,301-325} Recently much more attention has been focused on marine cyclic peptides due to their novel chemical structures and diverse biological properties. A considerable number of eminent natural product chemists are interested in marine natural products (peptides), such as Kingston (USA), Faulkner (USA), Fusetani (Japan), Blunt (New Zealand),

Hamann (USA). A huge number of marine peptides have been isolated and reported with various biological activities like antitumor, antibacterial, antifungal, anthelmintic, insecticidal, antineoplastic and anti-inflammatory activities and isolated from a variety of marine organisms, such as sponges, bacteria, actinomycetes, fungi and corals over several decades.^{233-235,247-249,251-255,259,261,262,264,265,267,269,326-329} Marine cyclic peptides are one of the underexplored classes of bioactive peptides that are promising to be a new perspective for new drugs. Various marine cyclic peptides with structural and biological diversity have increased our understanding of properties of novel chemical structures related to the action mechanisms of biological activities.^{233,259,328}

The tetradecapeptide discodermins^{234,268} are a family of novel linear and cyclic peptides first isolated from the sponges of genus *Discodermia*, of which discodermin A-H have been reported and characterized, and show potent inhibition activity of cell growth, and cytotoxic to P388 murine leukemia cells and A549 human lung cell-lines. Especially, discodermin A (Figure 21) is the first isolated marine cyclic peptide with antimicrobial activity extracted from sponge *Discodermia kiiensis* by Fusetani in 1984,^{257,330} highly inhibiting the growth of *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*, and the development of starfish embryos.^{268,330,331}

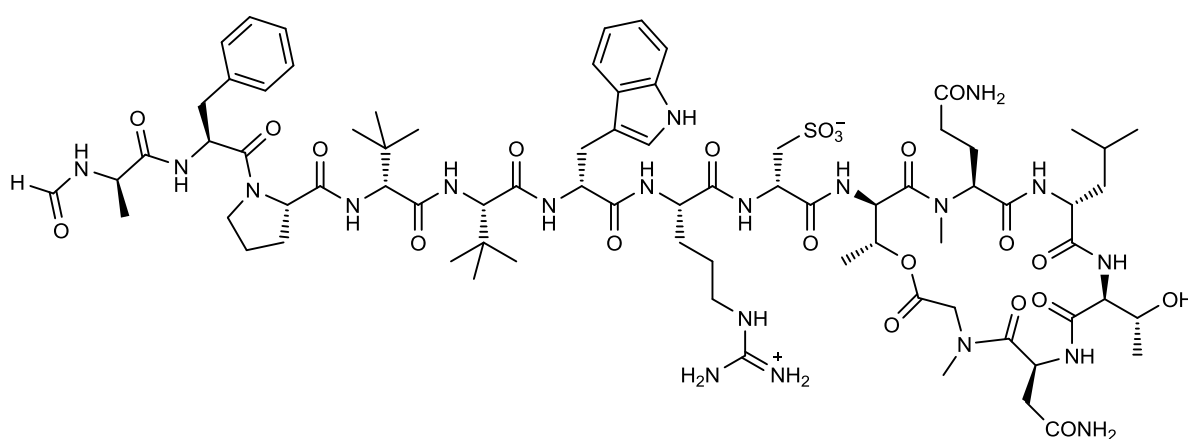


Figure 21: Discodermin A

Theonellamides A-G are a class of bicyclic glycopeptides isolated from *Theonella sp.*, of which theonellamides A-E isolated by Fusetani in 1995 have been found to possess cytotoxic activity towards P388 leukemia cell-line,³³² while a potent antifungal activity was reported for

theonellamide F also isolated by Fusetani in 1989.³³³ Recently, theonellamide G (Figure 22) was isolated by Youssef from Red Sea *Lithistida* sponge *Theonella swinhoei* located in Hurghada (Egypt). Its structure has been elucidated and it was reported to possess potent antifungal activity against two strains of *Candida albicans*, the wild type and amphotericin B-resistant of *Candida albicans* with IC_{50} of 4.49 and 2.0 μM , respectively. Additionally, it showed cytotoxic activity against the human colon adenocarcinoma cell line (HCT16) with IC_{50} of 6.0 μM .³³⁴

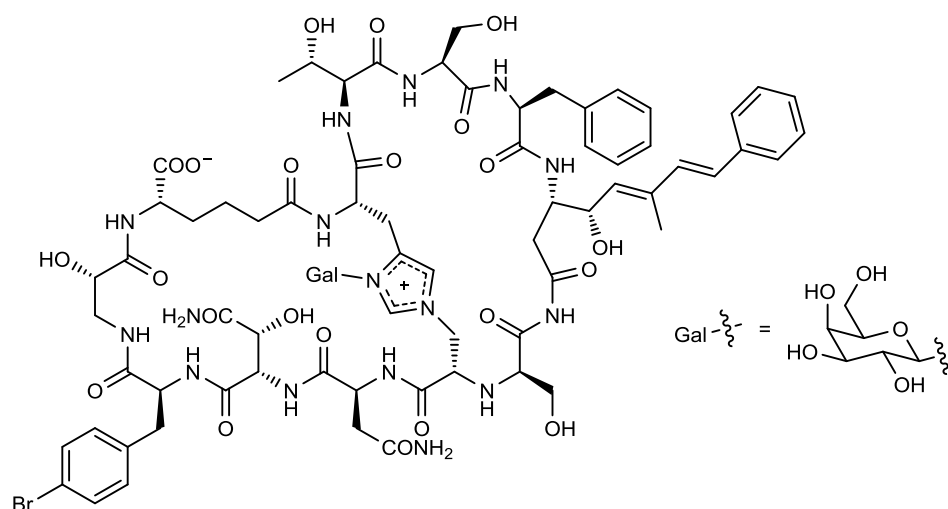


Figure 22: Theonellamide G

Aciculitins (Figure 23) are the first bicyclic glycopeptidolipids obtained from a marine source, the *lithistid* sponge *Aciculites orientalis* at Siquijor Island (Philippines). Isolation and structural elucidation of aciculitins A-C was reported by Faulkner in 1996.^{234,268,335} They show cytotoxic activity against the human-colon tumor cell line HCT116 with an IC_{50} of 0.5 $\mu\text{g}\cdot\text{mL}^{-1}$ and inhibit the growth of *Candida albicans* at a loading of 2.5 $\mu\text{g}\cdot\text{disk}^{-1}$ in the standard disk assay.³³⁵

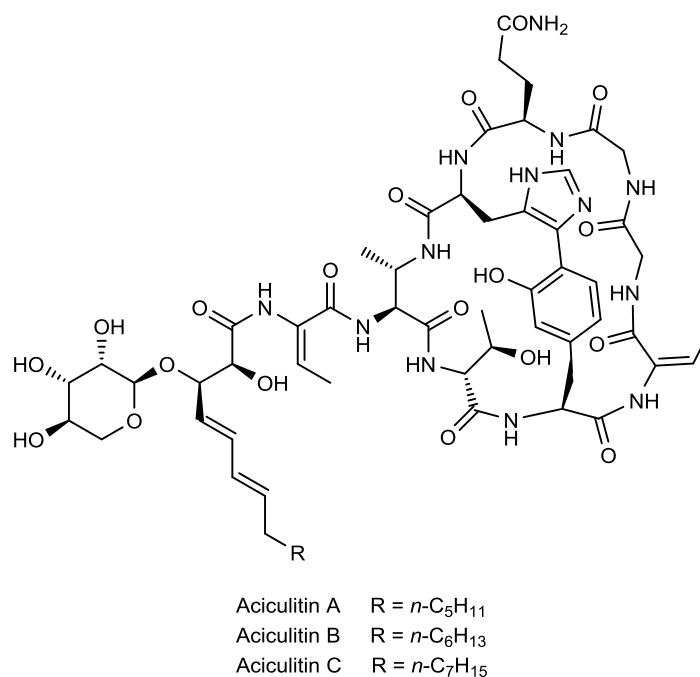


Figure 23: Aciculitin

Thiocoraline (Figure 24) is a well-known 2-fold symmetric or pseudosymmetric bicyclic thiodipeptide isolated by Romero in 1997 from the mycelium cake (fermentation broth) of a marine actinomycete strain, *Micromonospora sp.* L-13-ACM2-092 collected from soft coral collected at the Indian Ocean near the coast of Mozambique, which showed antimicrobial activities against strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus* and *Micrococcus luteu*, and also presented a strong cytotoxic effect against P388, A549 and MEL28 cell-lines with an IC₅₀ of 0.002 μg·mL⁻¹, along with a strong anti-microbial activity against Gram-positive microorganisms, and as well as inhibiting DNA polymerase at an IC₅₀ of 6 μg·mL⁻¹ and binding to supercoiled DNA, and inhibiting DNA synthesis at an IC₅₀ of 0.4 μg·mL⁻¹ and RNA-synthesis at an IC₅₀ of 0.008 μg·mL⁻¹.³³⁶⁻³³⁸ Additionally, it was also found to inhibit the elongation activity of DNA polymerase α in both LoVo and SW620 human colon cancer cells and induce profound perturbations of cell cycle.³³⁸⁻³⁴¹ It has been shown to bind to DNA by high-affinity bisintercalation analogous to echinomycin, but with little or no perceptible sequence selectivity and exhibit exceptionally potent activity in the L1210 mouse leukemia cytotoxic assay (IC₅₀ of 200 pM).³⁴²

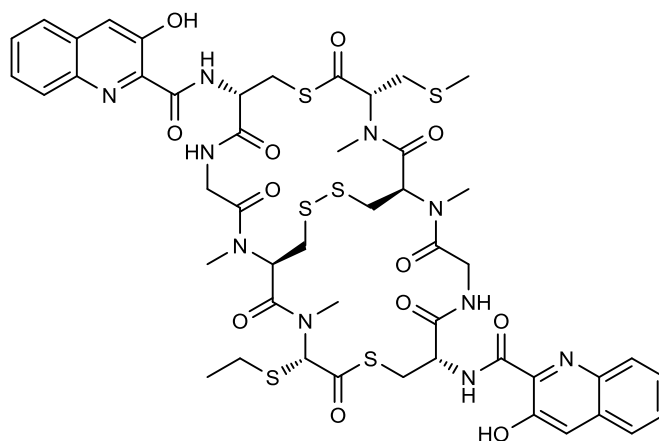


Figure 24: Thiocoraline

3. Microsclerodermins

3.1. Structure and origin of microsclerodermins

Microsclerodermins (Figure 25) are a family of macrocyclic peptides extracted from the *lithistid* sponges *Microscleroderma* sp., *Theonella* sp. and *Pachastrella* sp.³⁴³⁻³⁴⁸ and also produced from three different genera of myxobacteria *Chondromyces* sp., *Jahnella* sp. and *Sorangium* sp.²⁶³ They are characterized by a 23-membered ring peptide macrocycle, which contains six amino acids, of which three are common: glycine, sarcosine and (*R*)- γ -amino- β -hydroxybutyric acid (GABOB). The other three amino acids present some structural variations but can be classified as a modified tryptophan, a polyhydroxylated β -amino acid with four or five contiguous stereogenic centers and an original 3-amino-4-hydroxypyrrolidone-4-acetic acid (PyrAA), which in some cases may be dehydrated to give an unsaturated dehydroxypyrrolidone-4-acetic acid (Δ PyrAA) on the macrocyclic backbone.

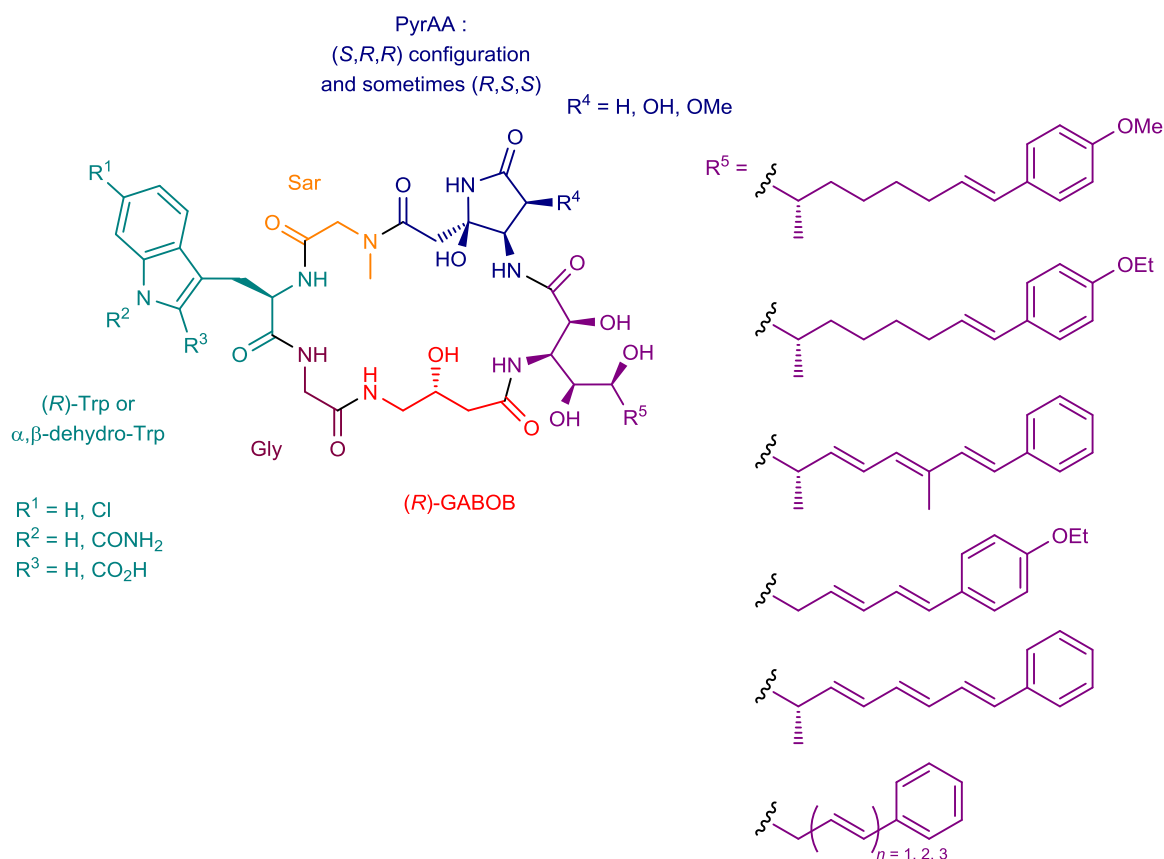
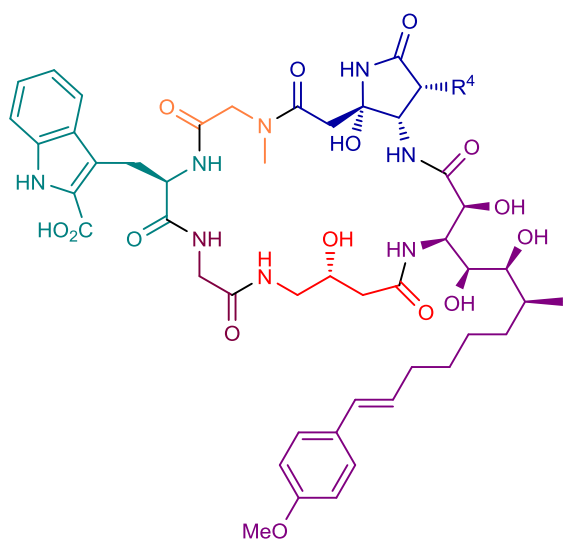
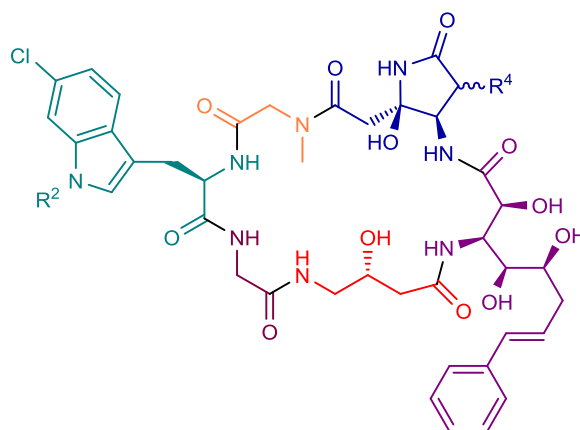


Figure 25: Structure of microsclerodermins

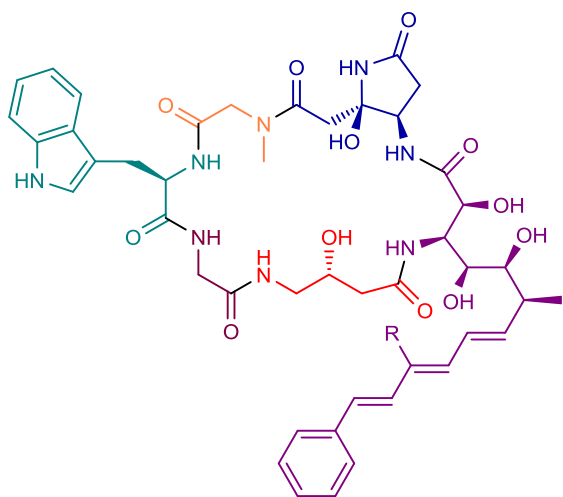
Microsclerodermins were discovered progressively over decades and have attracted more and more attention from the biologists and chemists communities due to their biological activities and the structural complexity (Figure 26). Microsclerodermins A and B were the first two members of this family isolated from a Philippines *Microscleroderma* sp. by Faulkner in 1994.³⁴³ A few years later, Faulkner successively isolated microsclerodermins C-E from *Theonella* sp. and *Microscleroderma* sp. in the Philippines area.³⁴⁴ Then, microsclerodermins F-I were isolated from a deep-water specimen of *Microscleroderma* sp. located in Palau in 2000 and characterized by Faulkner.³⁴⁵ More recently, several new members of the family has been isolated and reported. Microsclerodermins J-K were isolated in 2012 from the deep-water sponge *Microscleroderma herdmani* in Mauritius by Li.^{346,347} In 2013, Müller discovered and isolated microsclerodermins L-M from terrestrial myxobacteria from three different genera *Chondromyces* sp., *Jahnella* sp., and *Sorangium* sp., respectively.²⁶³ More recently, Matsunga isolated microsclerodermins N and O from the deep sea sponge *Pachastrella* sp..³⁴⁸ This family also comprises pederins A and B which were isolated from the cell mass of the myxobacterium *Chondromyces pediculatus* by Kunze in 2008.³⁴⁹



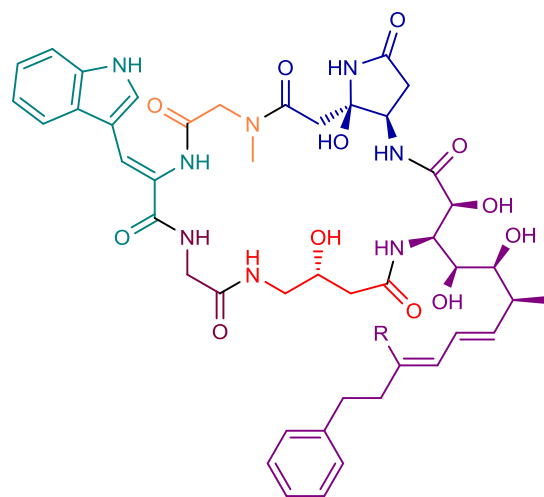
Microsclerdermin A $R^4 = OH$
 Microsclerdermin B $R^4 = H$



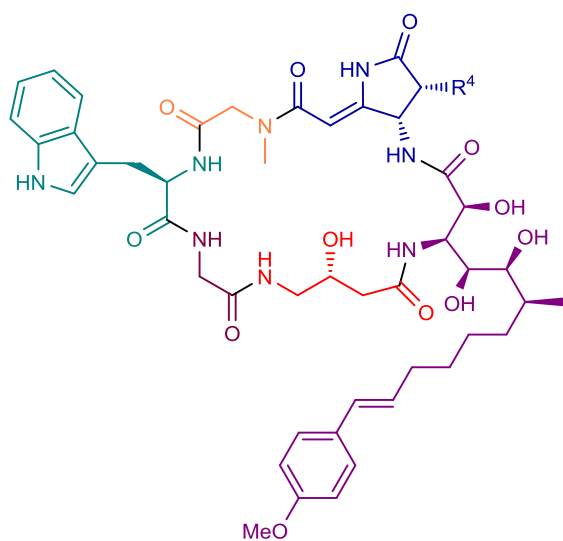
Microsclerdermin C $R^2 = CONH_2, R^4 = H$
 Microsclerdermin D $R^2 = H, R^4 = H$
 Microsclerdermin L $R^2 = H, R^4 = OMe$



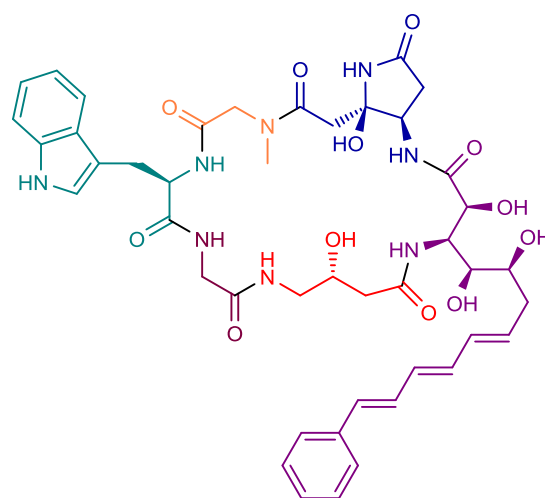
Microsclerdermin F $R = H$
 Microsclerdermin H $R = Me$



Microsclerdermin G $R = H$
 Microsclerdermin I $R = Me$



Microsclerdermin J $R^4 = H$
 Microsclerdermin K $R^4 = OH$



Microsclerdermin M

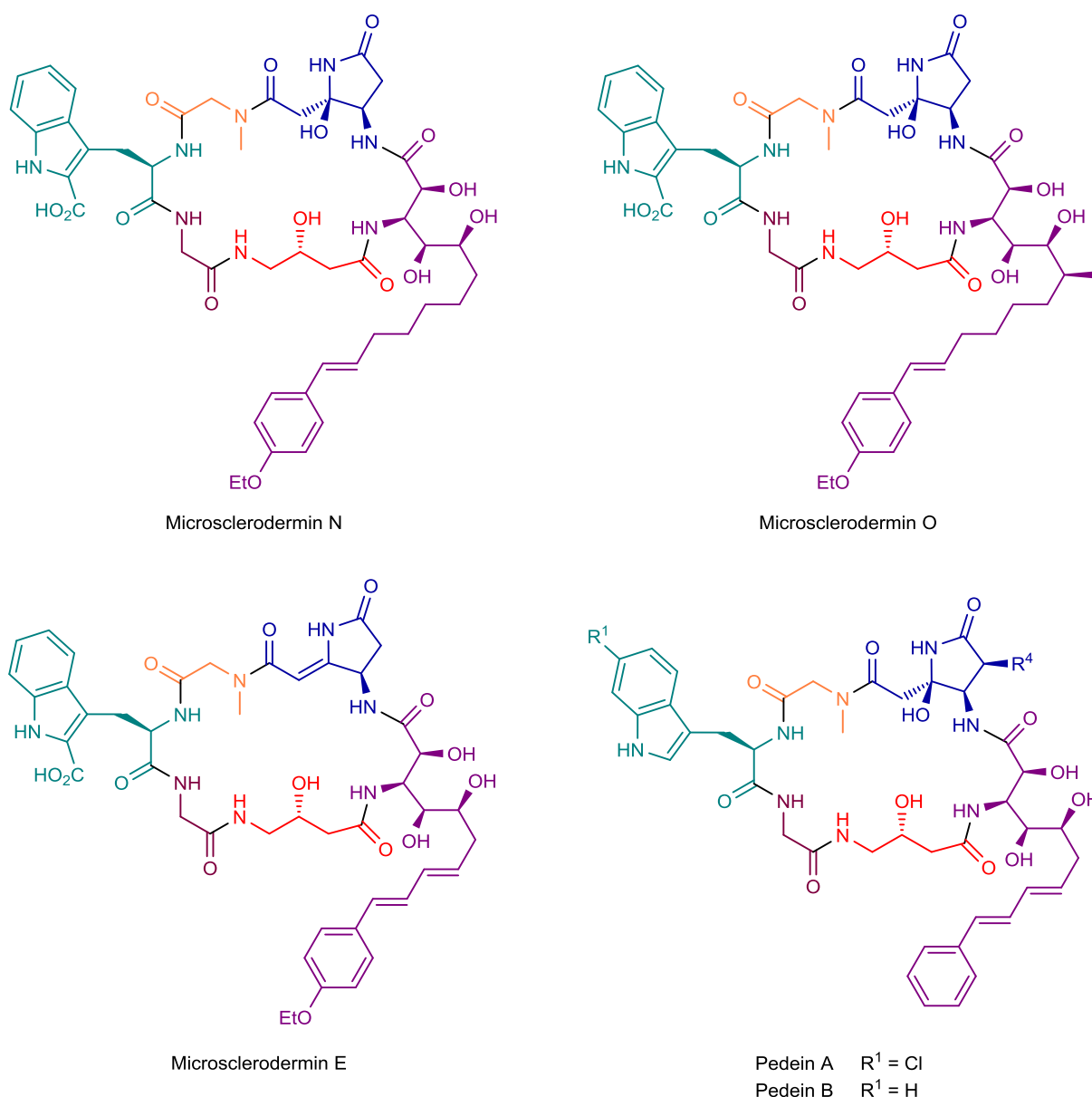


Figure 26: The microsclerodermin family

3.2. Biological activities

Faulkner and his co-workers have been the pioneers in exploring the biological activities of microsclerodermins. Early investigations disclosed that they possess antifungal, antitumor and cytotoxic activities.^{263,343-347} For instance, they have potential *in vitro* antifungal activity against a range of pathogenic fungal species: such as *Candida glabrata*, *Candida krusei*, *Cryptococcus neoformans*, *Botrytic cinerea*, *Fusarium oxysporum*, *Helminthosporium sativum*, *Pyricularia oryzae* and *Aspergillus fumigatus*. All microsclerodermins possess antifungal activity against *Candida albicans* (Table 1), such as microsclerodermin A-B (MIC 2.5 $\mu\text{g}\cdot\text{disk}^{-1}$).^{263,343-347,349} Faulkner supposed that antifungal activity was attributed to the polyhydroxylated β -amino acid moiety,

although direct supporting evidence was lacking. Investigations on microsclerodermin F-I demonstrate that they exhibit good antitumor activities against the HCT116 human colon carcinoma cell line, indicating their potential as anti-cancer agents.³⁴⁵ Recently, Wright disclosed that microsclerodermin A is a novel inhibitor of the nuclear factor kappa B (NFκB) and induces apoptosis in pancreatic cancer cells.³⁵⁰ In addition, pedein A was found to strongly inhibit against the growth of yeasts and fungi, to induce hemolysis of erythrocytes, and cause changes in membrane permeability of *Rhodotorula glutinis*.³⁴⁹ According to Müller's findings, both of microsclerodermins and pedeins were discovered from several myxobacteria, which strongly suggested that some natural products isolated from marine sources such as sponges or invertebrates, probably ultimately originate from associated microbes.²⁶³

Microsclerodermin	Inhibition of <i>Candida albicans</i>		Cytotoxicity against HCT116
	MIC ($\mu\text{g}\cdot\text{disk}^{-1}$)	MIC ($\mu\text{g}\cdot\text{mL}^{-1}$)	IC ₅₀ ($\mu\text{g}\cdot\text{mL}^{-1}$)
A	2.5 ³⁴³	5.0 ³⁴⁶	–
B	2.5 ³⁴³	5.0 ³⁴⁶	–
C	5 ³⁴⁴	–	–
D	100 ³⁴⁴	6.8 ²⁶³	–
E	10 ³⁴⁴	–	–
F	1.5 ³⁴⁵	–	1.8 ³⁴⁵
G	3 ³⁴⁵	–	2.4 ³⁴⁵
H	12 ³⁴⁵	–	1.0 ³⁴⁵
I	25 ³⁴⁵	–	1.1 ³⁴⁵
J	–	20.0 ^{346,347}	–
K	–	10.0 ^{346,347}	–
L	–	18 ²⁶³	–
M	–	0.16 ²⁶³	–
Pedein A	–	1.6 ³⁴⁹	–

Table 1: Examples of inhibition activities and cytotoxicity of microsclerodermins

However, these reported studies on biological activities are limited by the low natural abundance of microsclerodermins, about only 0.001% yield of the dry weight of the sponge, which

means that only few mg of materials could be extracted and isolated by consuming lots of sponges and manpower. Their interesting biological activities and potential as anti-cancer agent have motivated organic chemists to solve the challenge of their total synthesis. In the next part, we will develop in detail the efforts toward their total synthesis.

4. Previous Syntheses

4.1. Shioiri's pionnering studies towards microsclerodermins A and B

Shioiri was the first to show an interest in the synthesis of microsclerodermins. Although he never completed a total synthesis, he prepared all the fragment of microsclerodermins A and B, and has reported some important features about their stability.

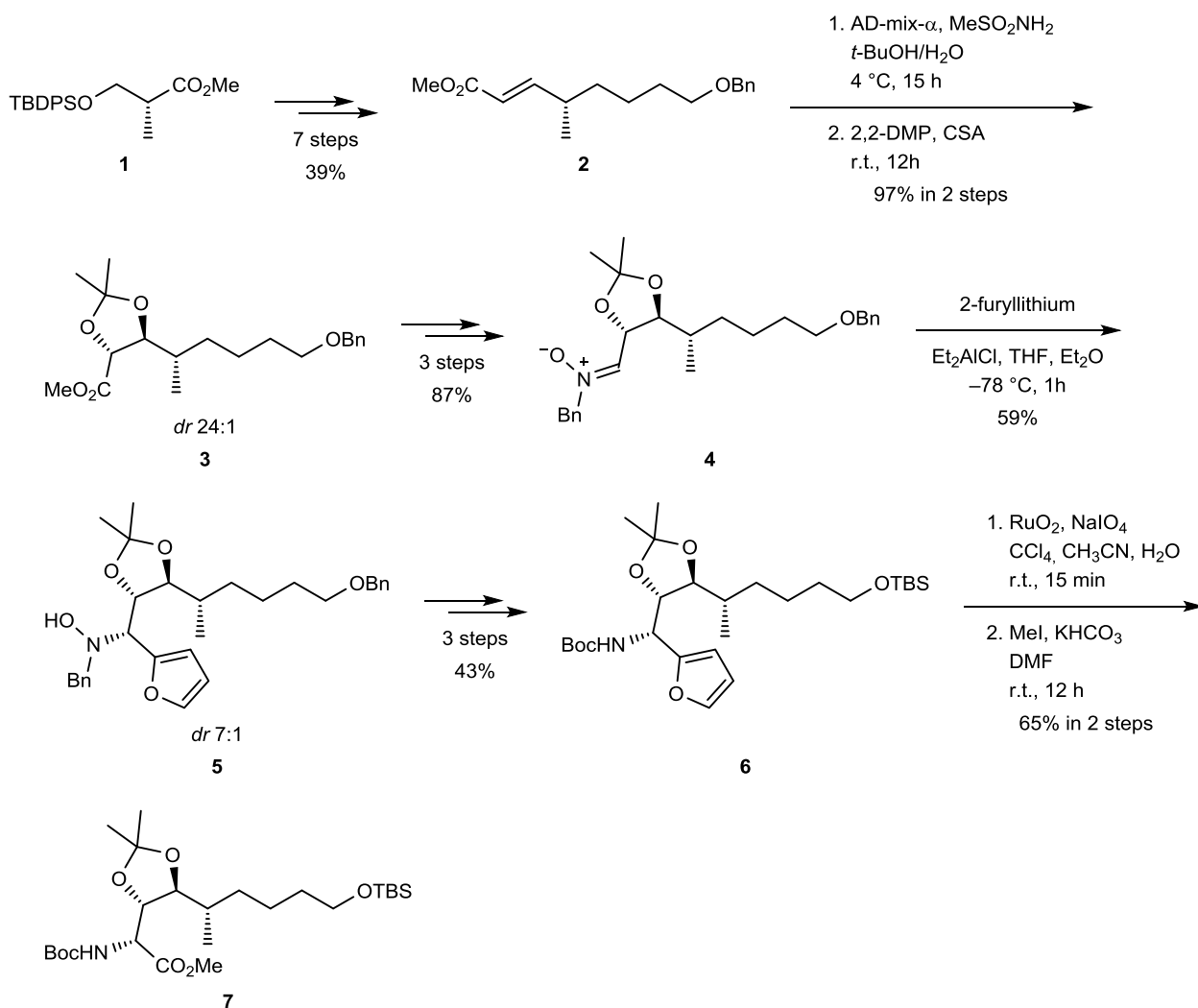
4.1.1. Preparation of a protected derivative of AMMTD

In 1997, Shioiri reported a stereoselective synthesis of a core building block of AMMTD (Figure 27).³⁵¹ This was the first report on efforts towards the total synthesis of microsclerodermins A and B since their isolation by Faulkner in 1994.



Figure 27: AMMTD fragment present in microsclerodermin A and B

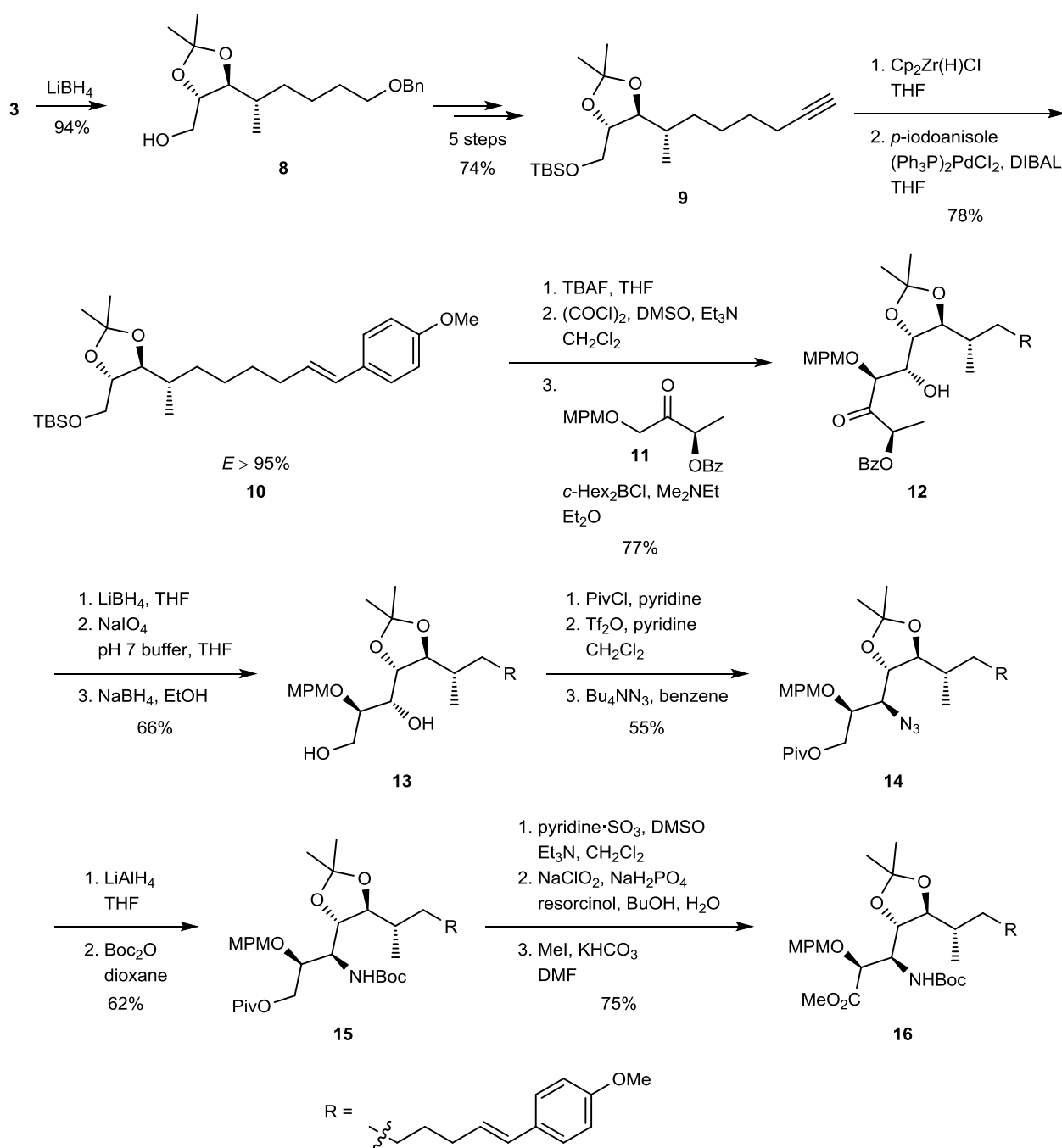
The chiral ester **1** was converted into the unsaturated methyl ester **2** in 39% yield over 7 steps. Sharpless asymmetric dihydroxylation^{352,353} followed by protection of the diol as an acetonide gave the intermediate **3** with an excellent diastereomeric ratio. Functional modification of the methyl ester group provided the nitron derivative **4** in 3 steps in good yield. Addition of furyllithium according to Dondoni's procedure³⁵⁴ gave the furyl intermediate **5** in 59% yield. Protecting group transformation provided **6** in 3 steps, followed by oxidative cleavage of the furyl ring using $\text{RuO}_2/\text{NaIO}_4$ and sequential esterification gave amino ester **7**, featuring the core skeleton of AMMTD with 4 consecutive stereogenic centers, in 5.4% yield over 18 steps (Scheme 1).



Scheme 1: Construction of the core building block of AMMTD

In 1999, Shioiri^{355,356} completed the synthesis of AMMTD in its protected form (Scheme 2). The acetonide alcohol **8** obtained as a synthetic intermediate in his previous work³⁵¹ was first converted into the alkyne **9** in good yield through a 5-step functional group modification sequence. Hydrozirconation of this alkyne using Schwartz's reagent (Cp₂Zr(H)Cl), followed by palladium mediated cross coupling with *p*-iodoanisole for an introduction of the styrene moiety according to Negishi's protocol³⁵⁷ afforded the *p*-anisyl-(*E*)-alkene **10** in good yield. After deprotection of the TBS group to give an alcohol with TBAF, and its Swern oxidation into an aldehyde, followed by Paterson's anti-aldol reaction³⁵⁸ with the ketone **11**, the β -keto alcohol **12** that contained the requisite five contiguous stereogenic centers was obtained efficiently as a single isomer. Reduction of both the keto and benzoyl groups using LiBH₄ gave a triol in which the 1,2-diol moiety was cleaved with sodium periodate. Subsequent reduction of the resulting aldehyde with NaBH₄ produced the alcohol **13** in good yield. Protection of the primary alcohol as a pivaloyl ester,

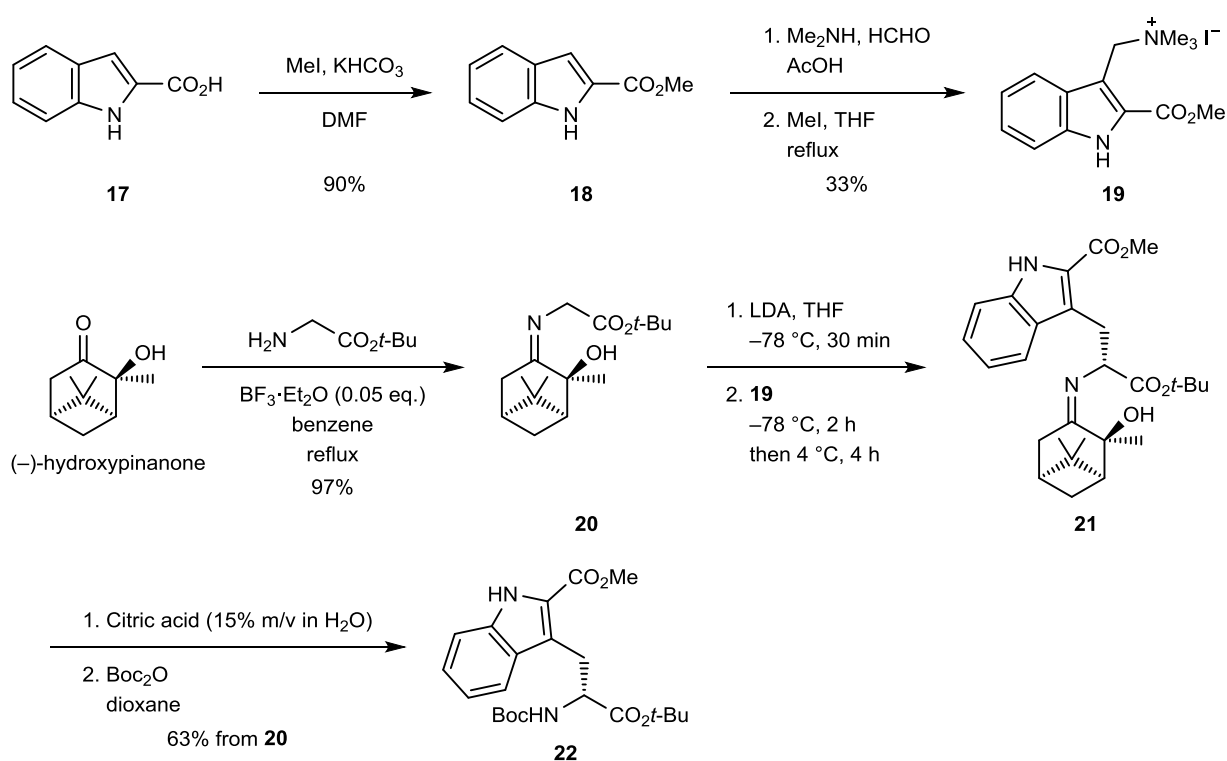
followed by activation of the secondary alcohol with triflic anhydride and azidation using tetrabutylammonium azide, proceeded with inversion of configuration and gave the protected azido alcohol **14** with the required stereochemistry. Reduction of the azide and protection of the resulting amine by a Boc group gave the amino alcohol **15**. Finally, a 2-step oxidation sequence of the alcohol (Parikh-Doering oxidation into an aldehyde followed by Pinnick oxidation into the acid) and protection as a methyl ester gave the protected AMMTD derivative **16** in 2.4% yield over 31 steps from the chiral ester **1**.



Scheme 2: Construction of a protected derivative of AMMTD

4.1.2. Preparation of the modified tryptophan derivative

Microsclerodermins A and B include a (*R*)-2-carboxytryptophan residue. Shioiri report the preparation of this tryptophan derivative in a protected form using hydroxypinanone glycine imine alkylation methodology (Scheme 3).^{359,360} Thus, indole-2-carboxylic acid **17** was first protected as its methyl ester **18**, followed by a Mannich reaction with formaldehyde and dimethylamine and quaternization with methyl iodide to form the gramine derivative **19**. Then α -alkylation of the glycine *t*-butyl ester imine derived from (–)-hydroxypinanone **20** with the trimethylammonium salt **19** proceeded with high diastereoselectivity to create the α -amino acid derivative **21**.^{361,362} Hydrolysis of the chiral auxiliary using citric acid and Boc-protection of the free amine gave the protected tryptophan derivative **22** with good enantiomeric excess (*ee* = 87%; recrystallization from a mixture of hexane/ethyl acetate improved the *ee* to 91%).

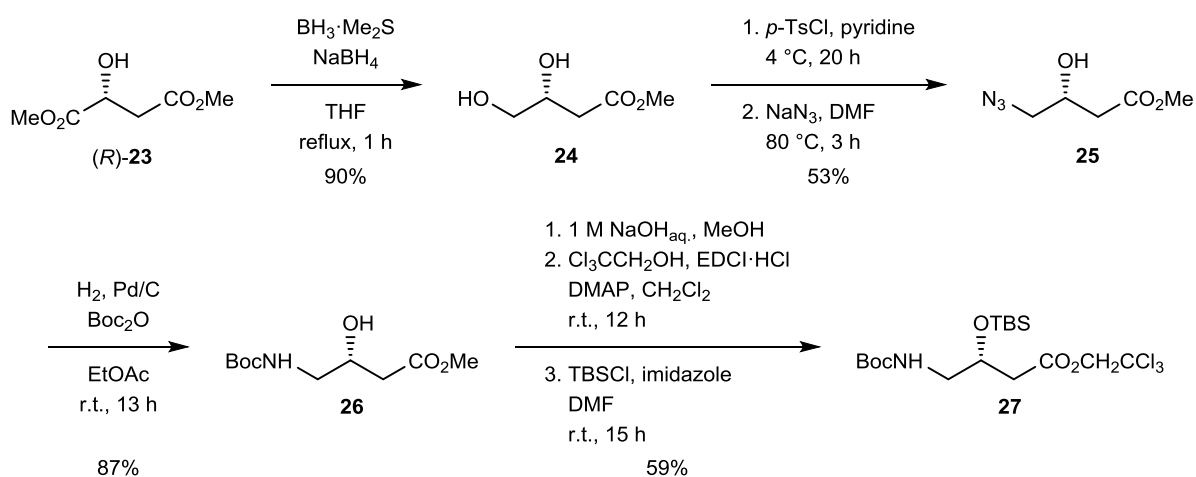


Scheme 3: Construction of a protected 2-carboxytryptophan

4.1.3. Preparation of a protected GABOB derivative

All microsclerodermins incorporate a GABOB residue. Shioiri proposed a synthesis of GABOB from dimethyl (*R*)-malate (Scheme 4). Regioselective reduction of the methyl ester of dimethyl (*R*)-malate **23** with borane-dimethyl sulfide complex yielded the diol **24** in good

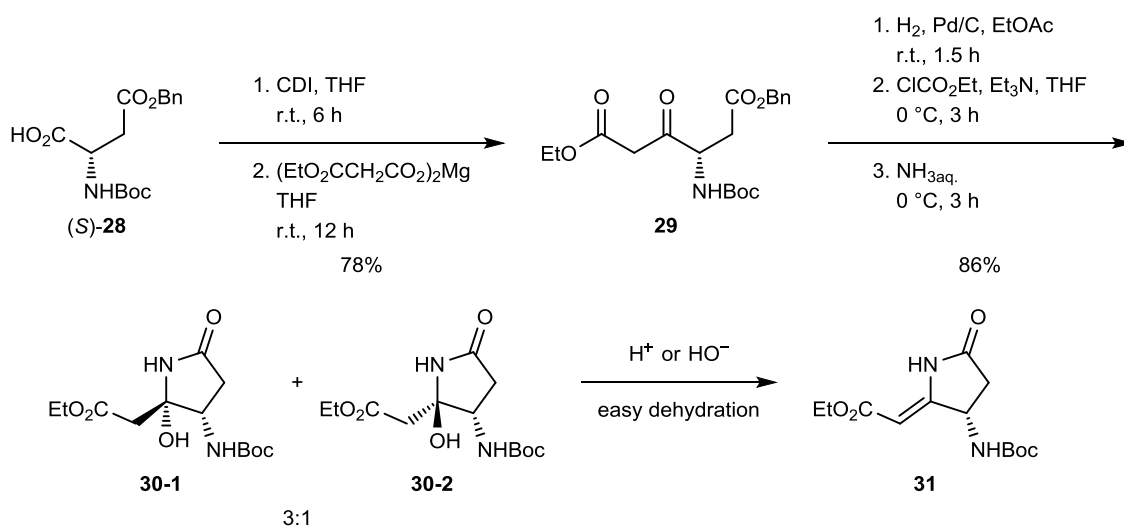
yield.^{363,364} Activation of the primary alcohol³⁶⁵ followed by nucleophilic substitution with NaN_3 gave the azide **25**. One-pot azido group hydrogenolysis and amine protection by a Boc group gave the hydroxy ester **26**. Finally, saponification of the methyl ester followed by protection as a trichloroethyl ester by coupling with 2,2,2-trichloroethanol and protection of the secondary alcohol as a TBS ester gave the fully protected GABOB derivative **27** in 25% yield over 7 steps.



Scheme 4: Construction of a protected GABOB derivative

4.1.4. Preparation of the protected PyrAA unit

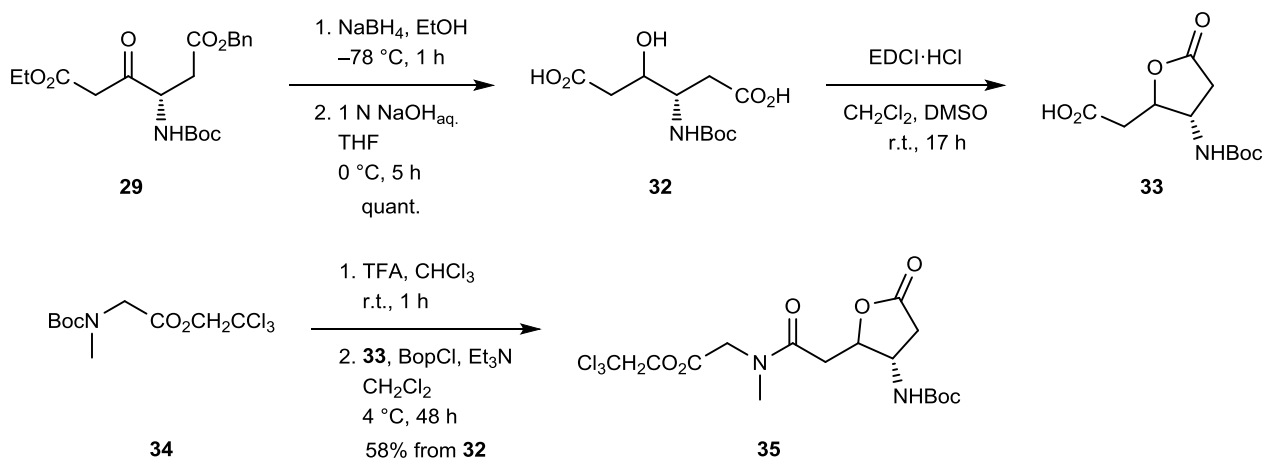
Shioiri also proposed a synthesis of the pyrrolidinoacetic acid residue (PyrAA) from the L-aspartic acid derivative (*S*)-**28** (Scheme 5).^{359,360} Activation of the α -carboxylic acid function with CDI followed by treatment with the magnesium salt of ethyl hemimalonate according to



Scheme 5: Construction of a protected PyrAA derivative

Masamune's protocol³⁶⁶ afforded the β -keto ester **29** in 78% yield. The pyrrolidinone moiety was then installed by hydrogenolysis of the benzyl ester followed by amidation of the resulting acid function through activation as a mixed anhydride and treatment with aqueous ammonia. The resulting γ -ketoamide cyclized spontaneously to give the protected PyrAA residue efficiently as a mixture of diastereoisomers **30-1** and **30-2** in a 3:1 ratio. Significantly, this hemiaminal was easily dehydrated to give the corresponding α,β -unsaturated ester under various acidic or basic conditions.

The easy dehydration of **30-1** and **30-2** meant that it could not be installed in the microsclerodermin macrocycle in this form. To solve this problem, Shioiri proposed the use of a γ -lactone which should be a suitable precursor of PyrAA residue allowing its construction at the end of the total synthesis (Scheme 6).³⁶⁰ Thus, reduction of the β -keto ester **29** into an alcohol followed by saponification of both ester groups and subsequent lactonization of the resulting hydroxy acid **32** using EDCI gave the γ -lactone **33**. Finally, coupling of the lactone **33** with a sarcosine derivative using BopCl yield the dipeptide building block **35** which was expected to be useful for a total synthesis of microsclerodermin.



Scheme 6: Construction of a dipeptide comprised of Sar and a masked-PyrAA residue

4.1.5. Conclusion

Although Shioiri described the synthesis of different building blocks of microsclerodermins A and B between 1997 and 2003, he never reported on the macrocyclic peptide assembly. Nonetheless, his work remains important since he was the first to report on the intrinsic propensity of the PyrAA residue to dehydrate under mild conditions. He logically proposed that a precursor of

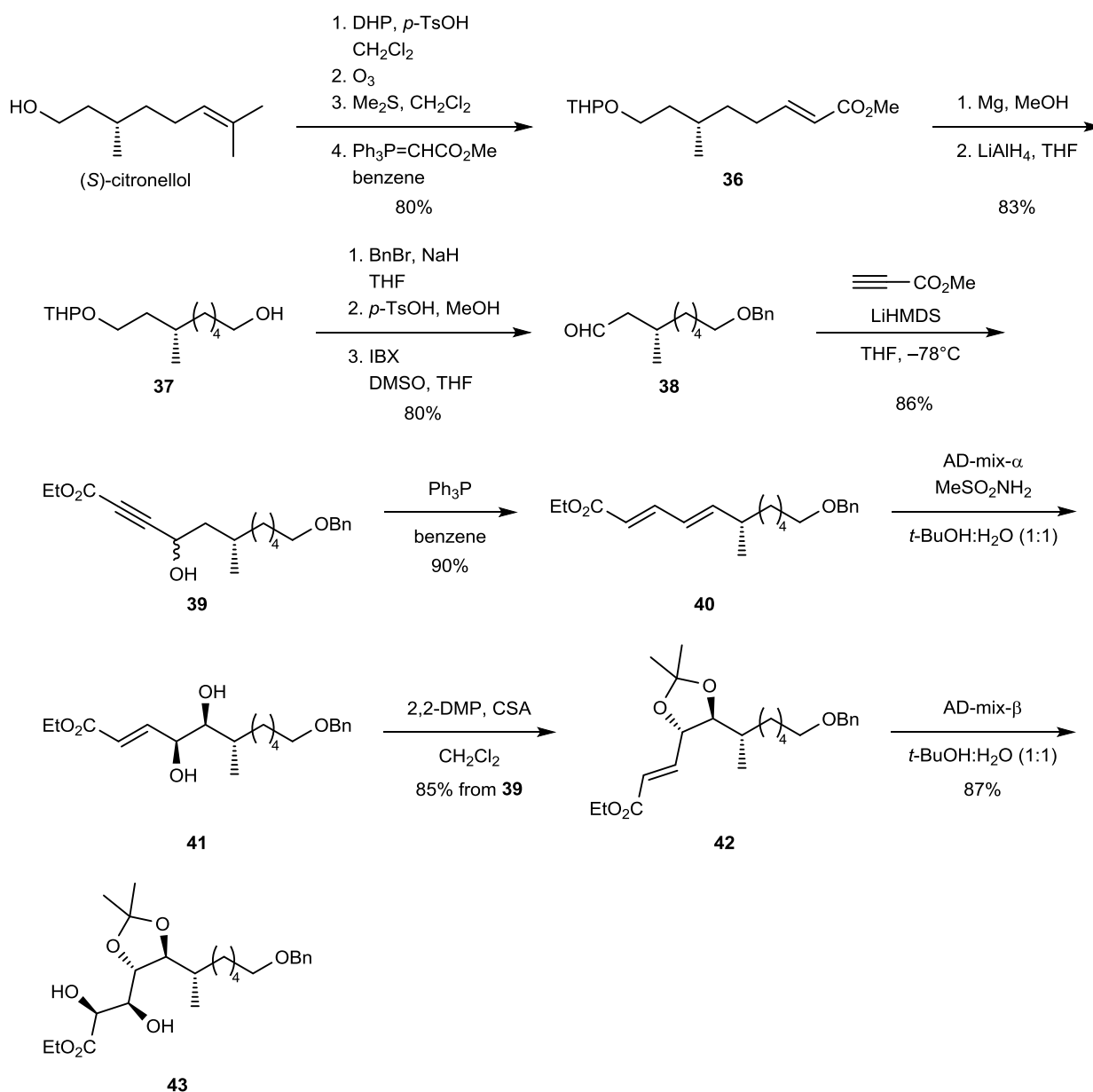
this residue should be employed in the macrocyclic peptide assembly and that the PyrAA residue should be unmasked at the end of the synthesis.

4.2. Other syntheses of microsclerodermin fragments

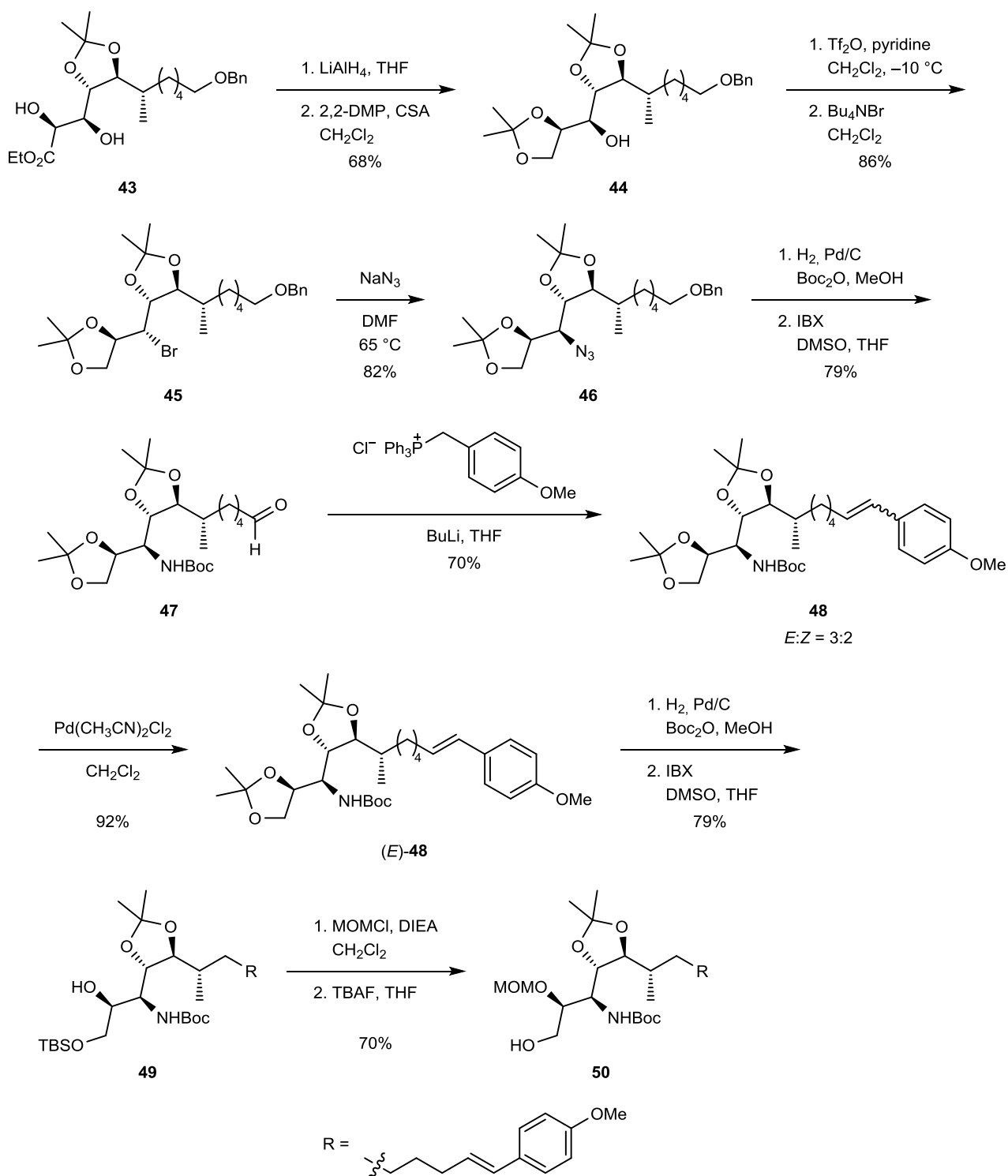
4.2.1. Chandrasekhar's work towards AMMTD

In 2006, Chandrasekhar's group reported the stereoselective synthesis of a protected AMMTD derivative starting from (*S*)-citronellol.³⁶⁷ The synthetic route is based on the deoxygenative rearrangement of a hydroxyalkynoate to generate a polyunsaturated ester followed by a highly enantio- and diastereocontrolled iterative dihydroxylation procedure to install the four contiguous stereocenters of AMMTD.

(*S*)-Citronellol was protected as a tetrahydropyranyl ether, followed by cleavage of the alkene by ozonolysis to provide an aldehyde which was then submitted to a Wittig reaction to give the α,β -unsaturated ester **36** in good yield (Scheme 7). Sequential reduction of the conjugated C=C bond and the ester function³⁶⁸ yielded the alcohol **37**. Protection of the alcohol as its benzyl ether followed by selective deprotection of the THP-ether and then oxidation with IBX³⁶⁹ produced the aldehyde **38** efficiently. This aldehyde was immediately treated with a lithiated ethyl propiolate to furnish the hydroxy alkynoate **39** as an inseparable mixture of two diastereoisomers in 86% yield. The hydroxy alkynoate was then converted into the 1,4-dienoate **40** by Ph_3P -mediated deoxygenative rearrangement which proceeds *via* an allene intermediate.^{370,371} This 1,4-dienoate diene was ready for the intended stereoselective incorporation of hydroxy groups *via* iterative Sharpless asymmetric dihydroxylation. Enantio- and regio-selective Sharpless asymmetric dihydroxylation³⁵³ of **40** with AD-mix- α at C⁴⁻⁵ position provided the diol **41** with a *syn* selectivity which was directly masked as the acetonide **42** using 2,2-dimethoxypropane and catalytic camphorsulfonic acid in 85% yield. However, stepwise Sharpless asymmetric aminohydroxylation^{372,373} was unsuccessful at C²⁻³ position of **42**. Instead, a second Sharpless asymmetric dihydroxylation with the diastereomerically matched chiral reagent AD-mix- β afforded the diol **43** in 87% yield with excellent diastereoselectivity (10:1).

Scheme 7: Synthesis of a protected derivative of AMMTD (1st part)

Reduction of the ester **43** followed by regioselective protection of triol at C¹-C² as with DMP in the presence of CSA gave the 1,2-acetonide **44** (Scheme 8). Thus the free alcohol group was activated as a triflate and then treated sequentially by *tetra*-butylammonium bromide and sodium azide in a double S_N2 reaction that allowed the formation of the azide **46** in 86% yield over 3 steps and with configuration retention compared to alcohol **44**.³⁷⁴⁻³⁷⁷ Subsequently, hydrogenolysis of both the benzyl ester and the azide and then *in situ* protection of the amine by a Boc group, followed by IBX mediated oxidation of the remaining primary alcohol furnished the aldehyde **47** in good yield. The aromatic moiety was then installed in a Wittig reaction between

Scheme 8: Synthesis of a protected derivative of AMMTD (2nd part)

aldehyde **47** and a (4-methoxybenzyl)triphenylphosphonium ylide to produce alkene **48** as a mixture of *E/Z* isomers in 3:2 ratio in 70% yield. Treatment of this *E/Z* mixture with a catalytic amount of $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ allowed a complete isomerization of the *Z*-isomer to give pure (*E*)-**48**.³⁷⁸ Then, selective deprotection of the terminal acetone under mild acidic conditions with PPTS³⁷⁹ followed by protection of the primary alcohol as a TBS ether yielded alcohol **49**. The remaining

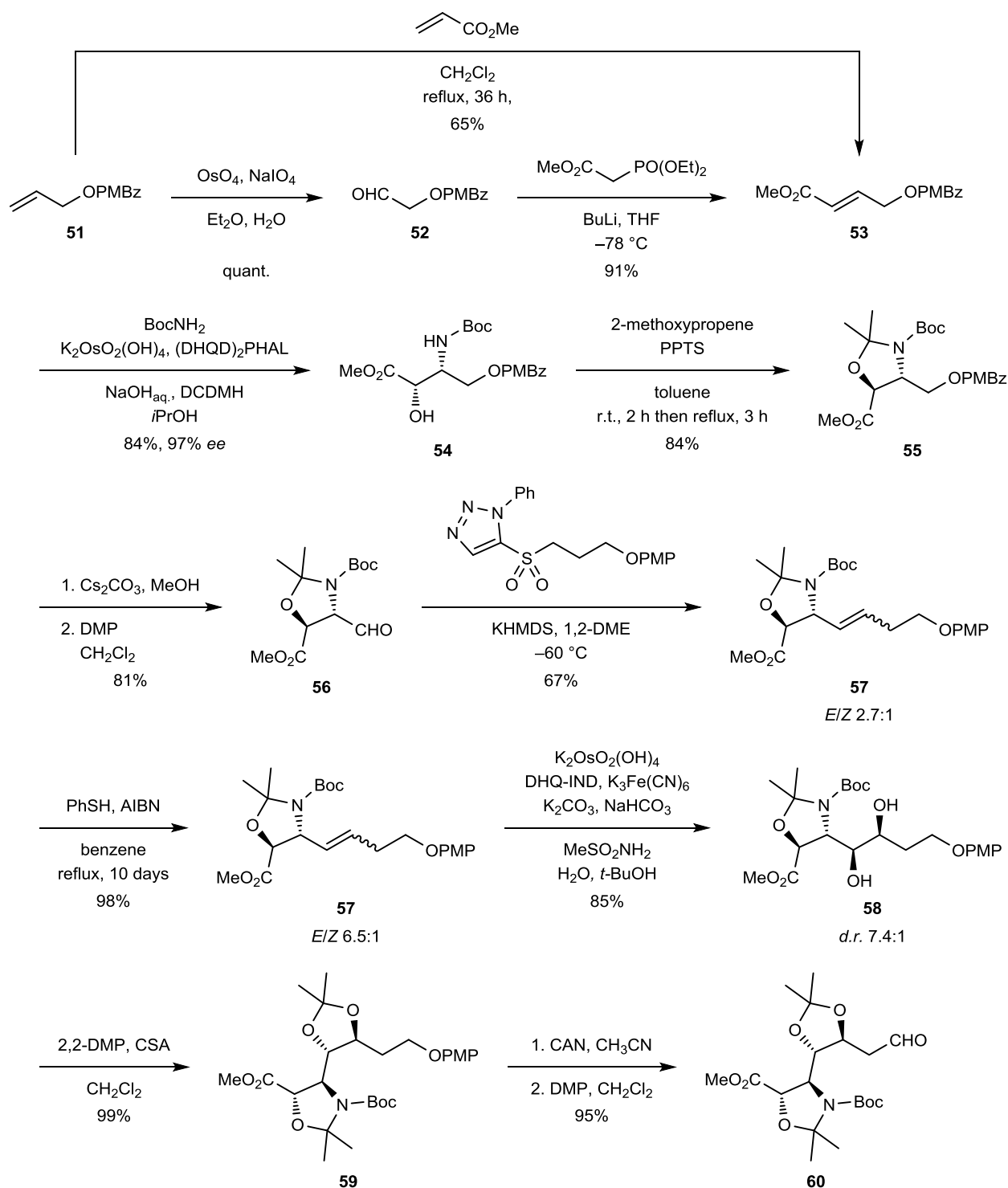
secondary alcohol was protected as its MOM ether and then the primary alcohol was deprotected with TBAF to give the primary alcohol **50** ready for oxidation into an acid.

In this way, Chandrasekhar developed a stereoselective route for the synthesis of a protected AMMTD derivative from (*S*)-citronellol in 3.0% yield over linear 26 steps.

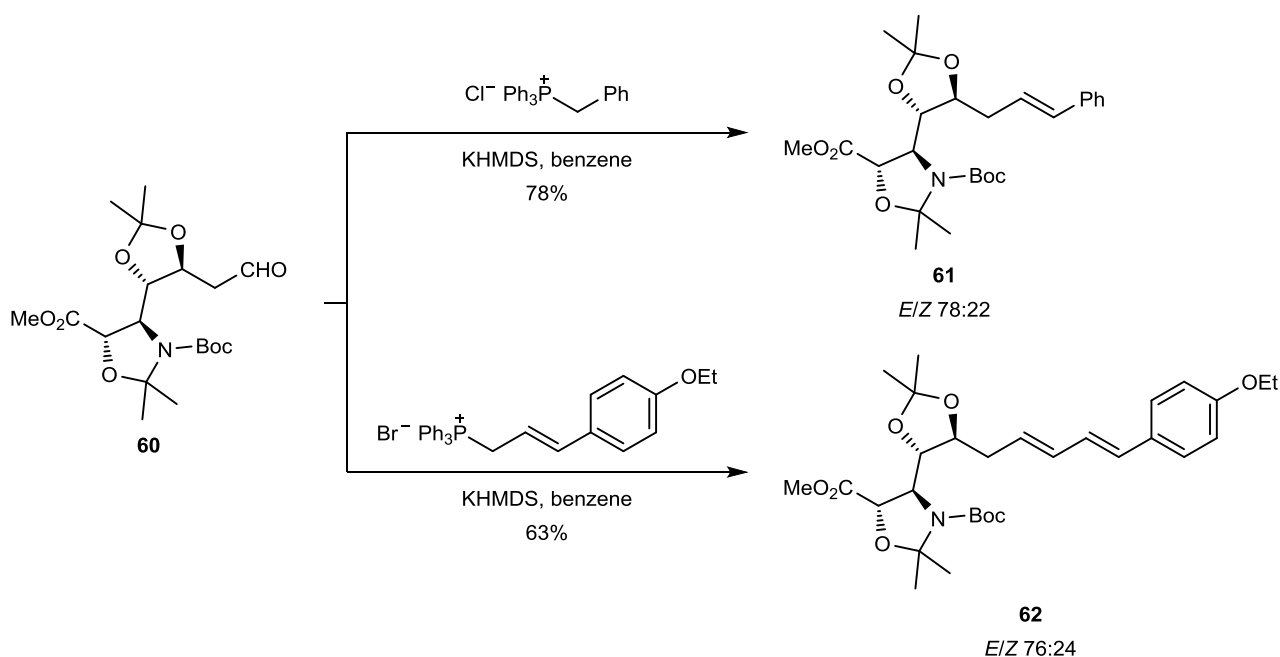
4.2.2. McLeod's work on the synthesis of protected APTO and AETD

In 2007, McLeod *et al.* reported the stereoselective synthesis of two protected polyhydroxy- β -amino acids: APTO, present in microsclerodermin C and D, and AETD, present in microsclerodermin E.³⁸⁰ Starting from simple substrates, four contiguous stereocenters were installed using Sharpless asymmetric aminohydroxylation and dihydroxylation, while Julia olefination allowed the introduction of the styrene moiety.

Oxydative cleavage of allyl 4-methoxybenzoate **51** with OsO₄ gave aldehyde **52** which was used directly in a Horner–Wadsworth–Emmons reaction with methyl diethylphosphonoacetate to provide the pure (*E*)-alkene **53** in excellent yield after flash chromatography (Scheme 9). Alternatively, this alkene **53** was obtained directly by cross metathesis of the allyl ester **51** with methyl acrylate using Grubbs' II catalyst in a more modest yield.³⁸¹ Sharpless asymmetric aminohydroxylation^{373,382} of (*E*)-alkene **53** smoothly produced β -amino alcohol **54** as a single regioisomer with an excellent 97% *ee*. Further protection of this β -amino alcohol as an oxazolidinone using 2-methoxypropene furnished the protected product **55** efficiently. Subsequent removal of the 4-methoxybenzoyl group with Cs₂CO₃ in methanol gave a primary alcohol which was readily oxidized into aldehyde **56** *via* Dess–Martin oxidation.³⁸³ A modified Julia olefination of the oxazolidine-protected aldehyde **56** with 1-phenyl-1*H*-tetrazol-5-ylsulfone³⁸⁴ and KHMDS in 1,2-dimethoxyethane gave the alkene **57** as a mixture of isomers with a moderate stereoselectivity (*E*:*Z* = 2.7:1). Fortunately, radical mediated isomerization using thiophenol in the presence of AIBN improved the *E*:*Z* ratio 6.5:1.³⁸⁵ Sharpless asymmetric dihydroxylation³⁸⁶ of alkene **57** using DHQ-IND ligand gave the corresponding diol **58** as an inseparable mixture of diastereoisomers in a 7.4:1 ratio. Finally, the diol was protected as its acetonide **59** and the PMP ether was removed using CAN to give a primary alcohol which was oxidized into aldehyde **60** using Dess–Martin reagent.

Scheme 9: Access to protected APTO and AETD derivatives (1st part)

With aldehyde **60** in hand, Wittig reaction was employed to give the target compounds (Scheme 10). Treatment of **60** with benzyltriphenylphosphonium chloride and KHMDS as base produced the protected APTO derivative **61** in good yield. When the phosphonium ylide obtained from treatment of 3-(4-ethoxyphenyl)prop-2-enyltriphenylphosphonium bromide with KHMDS was used, the protected AETD derivative **62** was produced in a slight lower yield.

Scheme 10: Acces to protected APTO and AETD derivatives (2nd part)

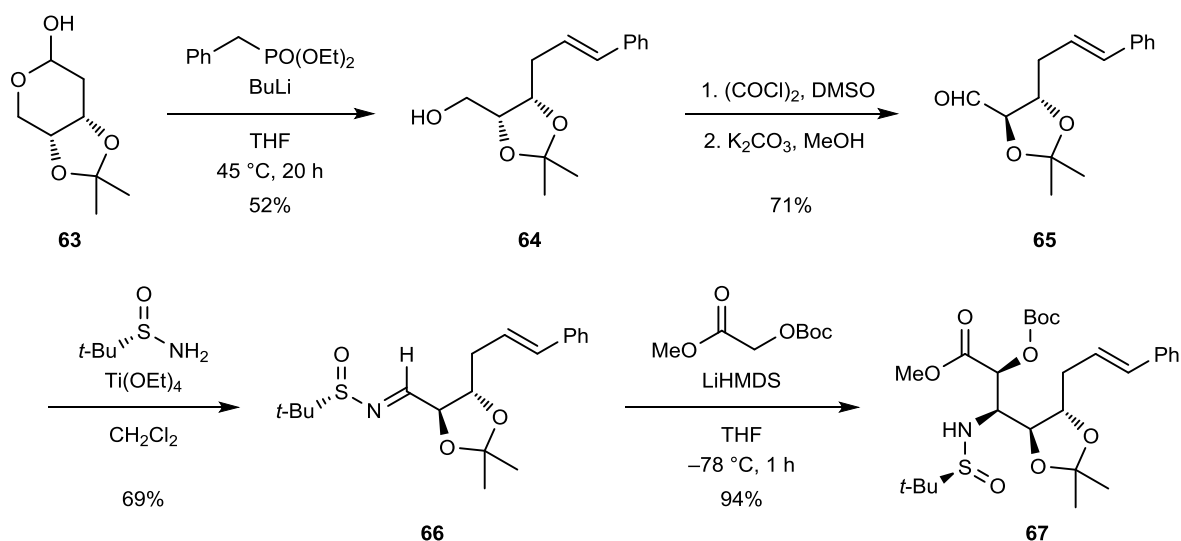
In summary, McLeod developed an efficient synthetic route to APTO and AETD derivatives using Julia olefination and Sharpless asymmetric aminohydroxylation and dihydroxylation. This divergent synthetic strategy allows access to protected derivatives of both APTO and AETD in 21% and 17% yield respectively over 13 steps.

4.2.3. Aitken's work on the synthesis of protected APTO and AETD

The host group for this thesis reported the synthesis of protected APTO and AETD derivatives in 2008,³⁸⁷ starting from 2-deoxy-D-ribose acetonide **63**,³⁸⁸ through an unified methodology based on a completely diastereoselective two-carbon homologation of appropriately selected intermediate chiral sulfinimines.³⁸⁹⁻³⁹¹

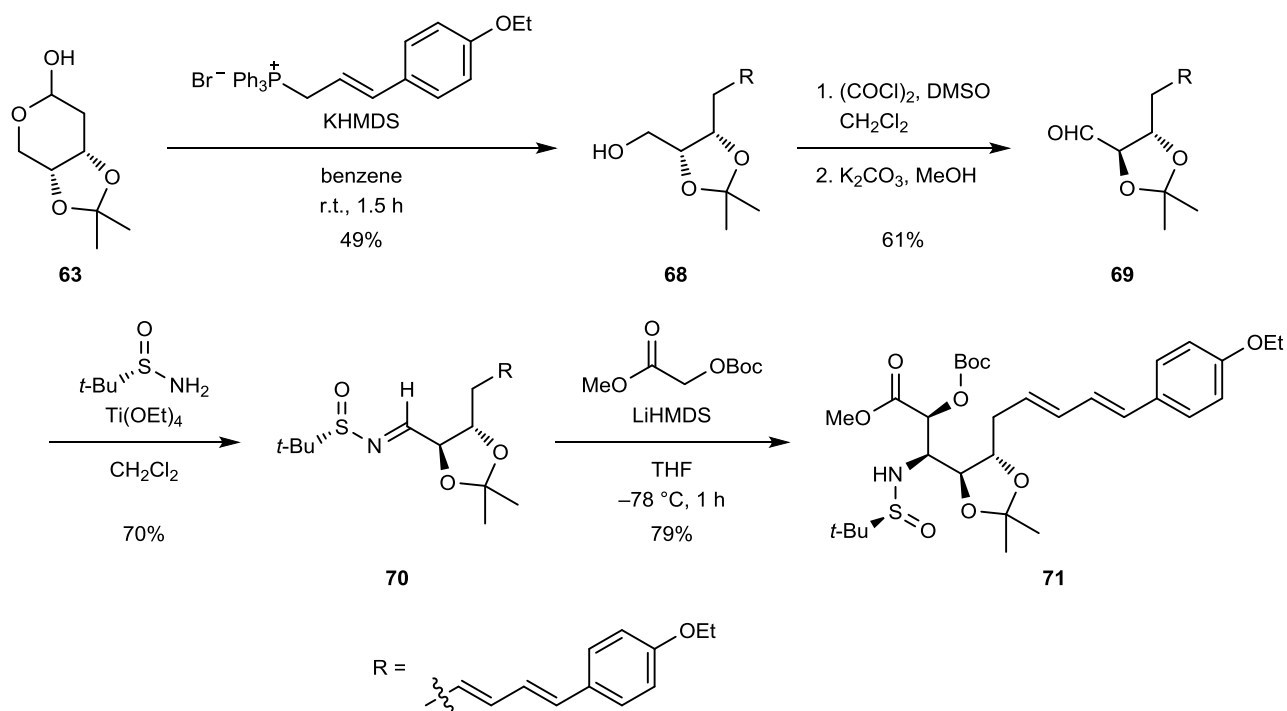
The synthetic route started with a Horner–Wadsworth–Emmons reaction of 2-deoxy-D-ribose acetonide **63** with a phosphonate-stabilized carbanion formed by deprotonation of benzyl diethylphosphonate to furnish the pure (*E*)-alkene **64** in moderate yield (Scheme 11). Subsequently, a modified Swern oxidation³⁹² of the primary alcohol gave an aldehyde which was submitted to epimerization at the α -position according to an adapted literature method³⁹³ by treatment with K_2CO_3 in MeOH to give aldehyde **65** with the requisite stereochemistry. Condensation of this aldehyde with (*S*)-(-)-*tert*-butanesulfinamide in the presence of $\text{Ti}(\text{OEt})_4$ gave

the chiral sulfinimine **66** in 69% yield.³⁹⁴ According to Qin's report, the addition of a bulky *O*-Boc protected glycolate to simple chiral sulfinimines should proceed with a high diastereoselectivity.³⁹⁵ Thus, the two-carbon homologation was performed by addition of the lithium enolate of *O*-Boc methyl glycolate to the sulfinimine **66** to generate the protected APTO derivative **67** as a single diastereomer in excellent yield. It is noteworthy that the stereochemical outcome of this two-carbon homologation is completely controlled by the sulfinyl group and thus proceeds independently of the other neighboring chiral centers in the system. This chiral predominance phenomenon was previously noted for sulfinimine one-carbon homologation with cyanide.³⁹⁴



Scheme 11: Synthesis of a protected APTO derivative

The same strategy was applied for the preparation of a protected AETD derivative (Scheme 12). Initially, attempts to install the styrene moiety *via* Horner–Wadsworth–Emmons reaction using the appropriate phosphonate were unsuccessful. However, when the condensation of acetonide **63** with a phosphonium ylide was conducted under McLeod's conditions,³⁸⁰ the expected diene **68** was obtained as a separable *E/Z*-mixture. Swern oxidation of the primary alcohol followed by epimerization at the α -position provided the aldehyde **69** with the requisite stereochemistry. Finally condensation of this aldehyde with (*S*)-(-)-*tert*-butanesulfinamide gave sulfinimine **70** and subsequent addition of the lithium enolate of *O*-Boc methyl glycolate under optimized conditions gave the protected AETD derivative **71** as a single diastereoisomer in good yield.



Scheme 12: Synthesis of a protected AETD derivative

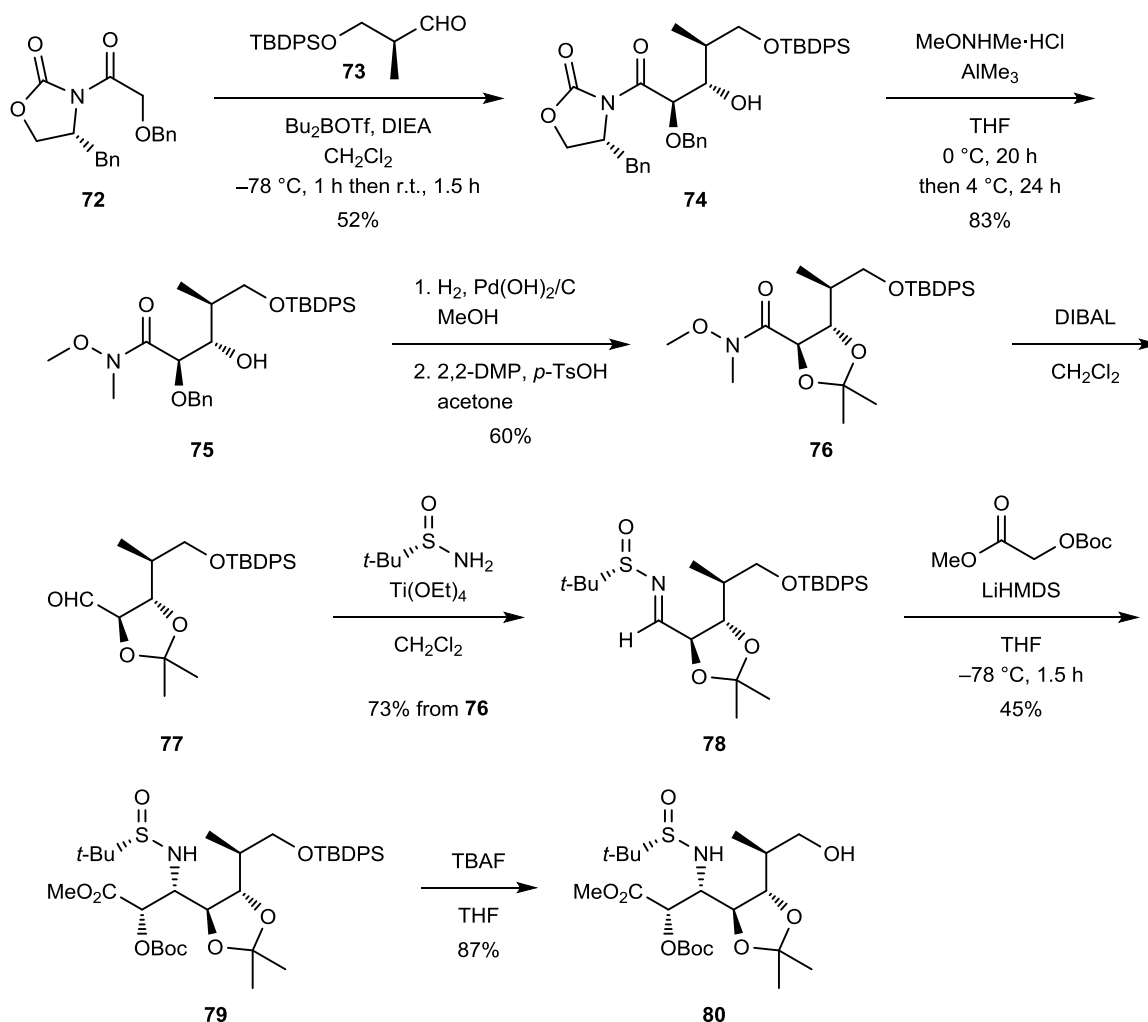
In summary, this work constitutes the shortest synthesis of protected APTO and AETD derivatives in 23% and 16% yield respectively, in only 5 steps. The synthetic route proceeds *via* a highly efficient stereoselective two-carbon homologation of chiral sulfinimines with the lithium enolate of a bulky glycolate.

4.2.4. Williams' work towards AMPTD

An asymmetric synthesis of the core of AMPTD, as the polyhydroxy- β -amino acid in microsclerodermins F-G, was reported by Williams' group in 2009.³⁹⁶ The AMPTD residue has five contiguous stereogenic centers and a conjugated-*trans* triene. The proposed synthetic strategy relied on an Evans glycolate aldol reaction on an aldehyde derived from (*S*)-Roche ester and use the addition of a bulky *O*-Boc protected glycolate on a chiral sulfinimine, similar to the strategy used by Aitken in the preparation of protected APTO and AETD derivatives (See § 4.2.3.).³⁸⁷

Initially, a *syn*-aldol reaction of benzyl glycolate of Evans' chiral oxazolidinone **72** with chiral aldehyde **73** by treatment with Bu_2BOTf gave the monoprotected diol **74** as a single diastereomer (Scheme 13).³⁹⁷ Since the direct hydrogenolysis of the benzyl ether was made difficult by the large steric hindrance of both the oxazolidinone and TBDPS group, the chiral oxazolidinone

moiety was converted into Weinreb amide **75** by treatment with *N,O*-dimethylhydroxylamine in the presence of AlMe_3 . Then hydrogenolysis of the benzyl ether over $\text{Pd}(\text{OH})_2/\text{C}$ and protection of the resulting diol with 2,2-DMP produced acetonide **76**. Stepwise reduction of Weinreb amide into an aldehyde with DIBAL, followed by condensation with (*S*)-(-)-*tert*-butanesulfinamide in the presence of $\text{Ti}(\text{OEt})_4$ gave sulfinimine **78**. This sulfinimine was submitted to the addition of the lithium enolate of *O*-Boc methyl glycolate to produce the protected core of AMPTD **79** bearing the requisite five contiguous stereocenters. Finally TBAF-mediated removal of TBPS group afforded alcohol **80** which was prepared as an advanced intermediate since in principle the primary alcohol could be oxidized into an aldehyde that could be condensed to an appropriate phosphonate in a Horner–Wadsworth–Emmons reaction to install the conjugated *trans*-triene chain of AMPTD.



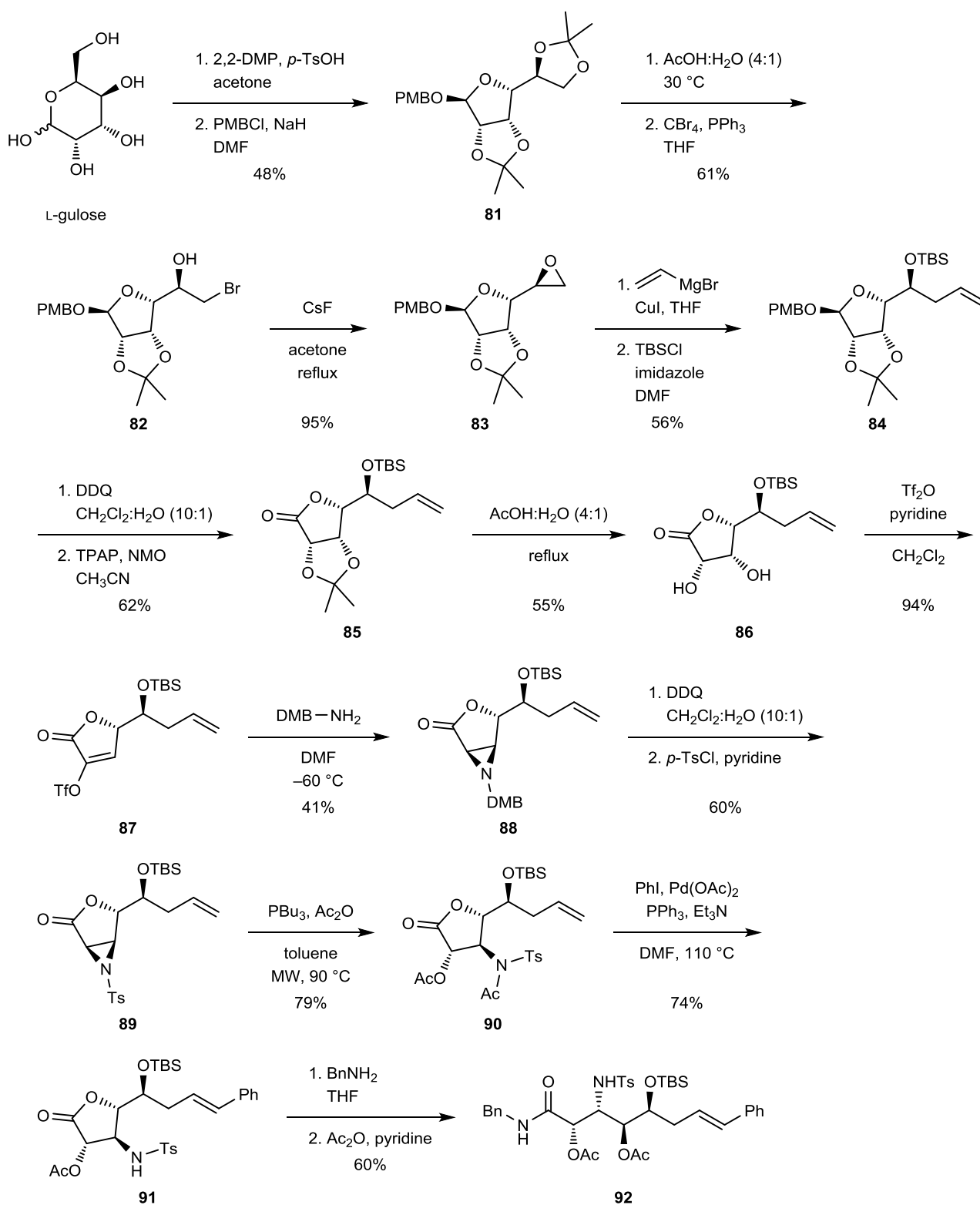
Scheme 13: Construction of the five contiguous stereogenic centers of AMPTD

In conclusion, Williams reported the synthesis of a protected AMPTD core fragment containing five contiguous stereogenic centers in 7.4% yield over 8 steps from the known starting materials using aldol reaction of Evans' chiral oxazolidinone of benzyl glycolate and Aitken's procedure as key steps.

4.2.5. Dauban and Dodd's work on synthesis of protected APTO

In 2009, an alternative pathway to the fully protected form of APTO was reported by Dauban and Dodd³⁹⁸ on the basis of their previous research on 2,3-aziridino- γ -lactones.³⁹⁸⁻⁴⁰⁷ The key step is a regioselective opening of an aziridine derived from L-gulose by a soft nucleophile.⁴⁰⁸

L-Gulose was protected as a diacetonide under standard conditions,⁴⁰⁹ and the remaining free hydroxyl group was protected as its PMB ether to give the fully protected derivative **81** (Scheme 14). The terminal acetonide was selectively hydrolyzed with AcOH/H₂O⁴¹⁰ to give a diol of which the primary alcohol was converted into a bromide using CBr₄/PPh₃⁴¹¹ to give the vicinal bromoalcohol **82**. Upon treatment with CsF in acetone, this bromoalcohol furnished the epoxide **83** in excellent yield.⁴¹² Next, regioselective addition of vinyl cuprate to this epoxide⁴¹³ followed by protection of the free secondary alcohol as a TBS ether gave the orthogonally protected derivative **84**. After removal of the PMB group with DDQ^{414,415} and oxidation with TPAP/NMO,^{401,408,416} the lactone **85** was obtained in good yield. Hydrolysis of the remaining acetonide provided the 2,3-dihydroxylactone **86**. The diol was treated with triflic anhydride in the presence of pyridine to afford the monotriflate **87** which reacted in the presence of a slight excess of 3,4-dimethoxybenzylamine (DMB-NH₂) to give the DMB-protected aziridino- γ -lactone **88** in moderate yield. Thereafter, the DMB aziridine **88** was converted into the Ts-protected substrate **89** by sequential DMB removal using DDQ and tosylation of the free aziridine. Regioselective opening of the Ts-aziridine at C² position⁴⁰⁸ was achieved by treatment with PBu₃/Ac₂O⁴¹⁷ under microwave irradiation to provide the fully protected lactone derivative **90** containing the requisite stereochemistry present in APTO. A Heck coupling with iodobenzene allowed introduction of the styrene moiety and was accompanied by simultaneous removal of the *N*-acetyl group to give lactone **91**. Finally opening of the lactone moiety with benzylamine gave a mixture of mono acetylated protected products at C² and C⁴ and subsequent treatment of the mixture with acetic anhydride in pyridine furnished the fully protected APTO derivative **92**.



Scheme 14: Synthesis of a protected derivative of APTO

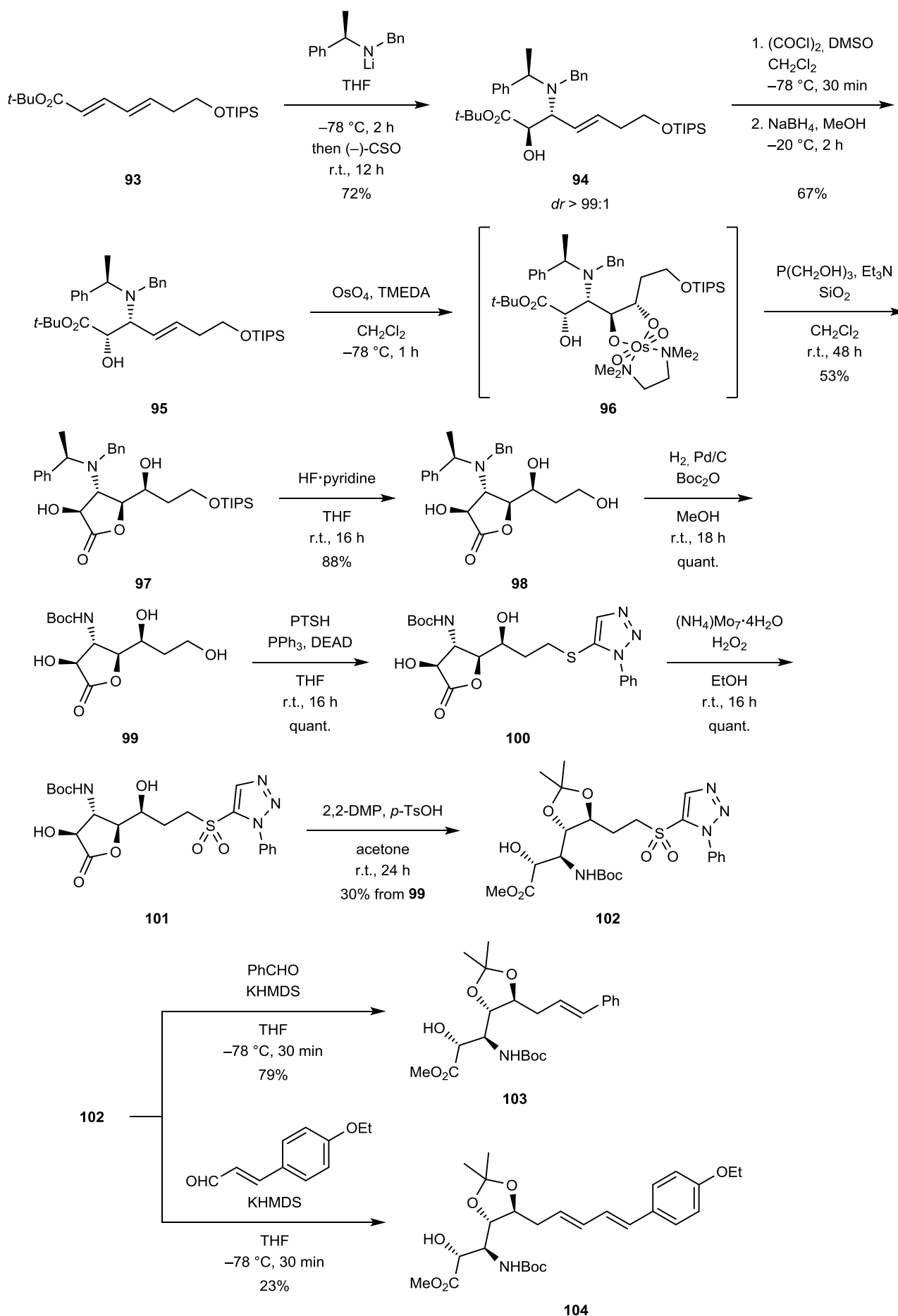
In summary, the synthesis of a fully protected derivative of ATPO was completed in 0.5% yield over 18 steps from L-gulose. This was first example of the use of an aziridino- γ -lactone for the stereoselective synthesis of a β -amino acid derivative.

4.2.6. Davies' work on the synthesis of protected APTO and AETD

More recently Davies *et al.* reported an asymmetric synthetic pathway to protected APTO and AETD derivatives from a simple conjugated diene ester using the conjugated asymmetric addition of a lithium amide, Sharpless asymmetric dihydroxylation and olefination as key steps.⁴¹⁸

(-)-CSO-mediated conjugate asymmetric addition of lithium (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amide⁴¹⁹ to the conjugated diene ester **93** provided the *anti*- α -hydroxy- β -amino ester **94** as a single diastereoisomer (*dr* > 99:1) (Scheme 15). The requisite stereochemistry at C² was obtained in a two-steps epimerization protocol by Swern oxidation of the hydroxyl group followed by diastereoselective reduction using NaBH₄ and yield the *syn*- α -hydroxy- β -amino ester **95**. Then asymmetric dihydroxylation of the *syn*- α -hydroxy- β -amino ester **95** was performed under Donohoe's conditions (See § 4.3.2) through OsO₄/TMEDA complex intermediate **96**,⁴²⁰⁻⁴²³ which was sequentially treated with P(CH₂OH)₃/SiO₂ to produce the lactone **97** presenting all the requisite stereocenters as a single diastereoisomer in moderate yield. Three-steps functional group transformation by deprotection of the TIPS ether using HF·pyridine followed by one-pot hydrogenolysis of the *N*-protecting groups and protection of the resulting free amine by Boc₂O gave the lactonetriol **99** which was unstable and was use fresh for next step. Subsequently, selective Mitsunobu reaction of the primary hydroxyl group of compound **99** with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) by treatment with DEAD/PPh₃ gave the corresponding sulfide **100** quantitatively, although the product is contaminated with Ph₃PO. The mixture was directly oxidized by treatment with (NH₄)₆Mo₇O₂₄·H₂O and H₂O₂ to give the corresponding sulfone **101** which was directly used in the next step without purification. Thus, treatment of the compound **101** with 2,2-dimethoxypropane in the presence of *p*-TsOH produced the acetonide **102** as a single diastereoisomer (*dr* > 99:1 *dr*). Finally, Julia olefination of acetonide **102** with benzaldehyde or (*E*)-3-(4-ethoxyphenyl)acrylaldehyde allowed access to both protected APTO derivative **103** and protected AETD derivative **104**.

To summarize, the protected APTO and AETD derivatives were synthesized in 3.4 and 1.0% yields respectively over 14 steps from commercially available starting materials, using (-)-CSO-mediated conjugate addition for asymmetric aminohydroxylation, Sharpless asymmetric dihydroxylation and Julia olefination to introduce the styrene moiety.



Scheme 15: Synthesis of protected APTO and AETD derivatives

4.3. Total synthesis of microsclerodermins

4.3.1. Ma's work: total synthesis of microsclerodermin E

In 2003, the first total synthesis of a microsclerodermin family member, microsclerodermin E, was reported by Ma *et al.*⁴²⁴ Microsclerodermin E presents a dehydrated pyrrolidinoacetic acid residue (Δ PyrAA) which is therefore not sensitive to the dehydration process reported by Shioiri,^{359,360} making its synthesis somewhat easier. The synthesis consisted of the construction of the tetrapeptide H- Δ PyrAA-Sar-Trp(2-CO₂H)-Gly-OMe and the dipeptide N₃-GABOB-AETD-OH, coupling of these two peptides and macrocyclization between the GABOB and the Gly residue (Figure 28).

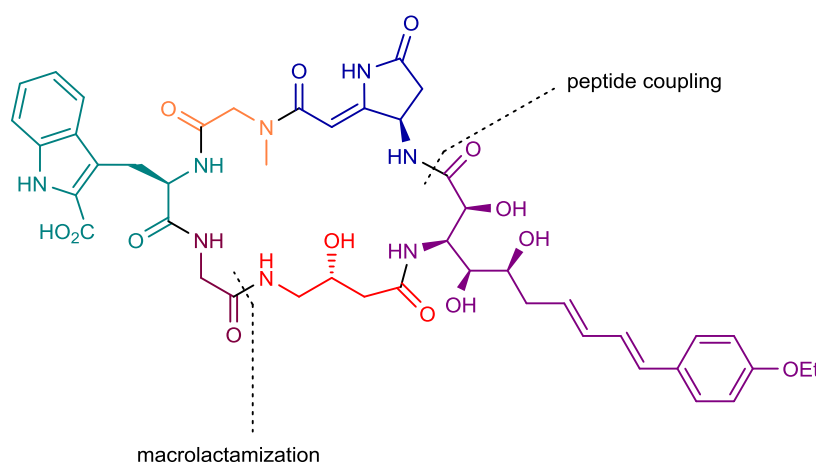
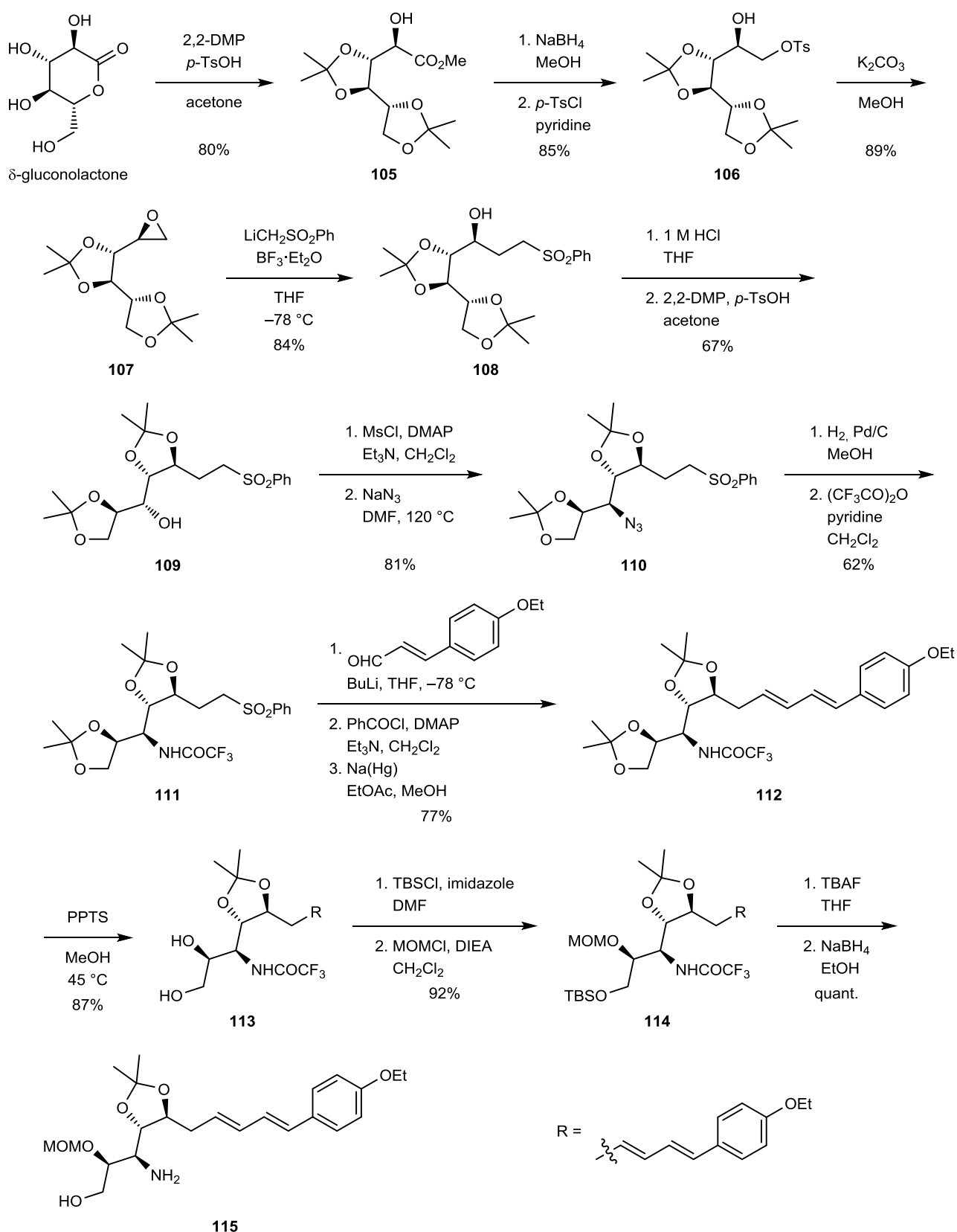


Figure 28: Retrosynthetic analysis of microsclerodermin E

4.3.1.1. Synthesis of a protected derivative of AETD

δ -Gluconolactone was protected as its diacetonide methyl ester **105** by treatment with 2,2-dimethoxypropane in the presence of *p*-TsOH (Scheme 16). Reduction of the methyl ester followed by activation of the resulting primary alcohol with *p*-TsCl³⁶⁵ yielded the tosylate **106** which was treated by K₂CO₃ to produce the epoxide **107**. Addition of the lithiated methyl phenyl sulfone to this epoxide in the presence of BF₃·Et₂O at -78 °C furnished the γ -hydroxy sulfone **108**.⁴²⁵ Hydrolysis of the acetonides using 1 M HCl followed by regioselective reprotection of the free hydroxyl groups gave the new diacetonide **109**. Activation of the free secondary alcohol as a corresponding mesylate followed by treatment with sodium azide furnished the azide **110**.



Scheme 16: Synthesis of a protected derivative of AETD

Reduction of this azide by hydrogenolysis gave the free secondary amine which was directly protected using TFAA to give the trifluoroacetamide **111**. Julia olefination⁴²⁶ of *p*-ethoxycinnamal

with compound **111** afforded the diene **112** as a mixture of diastereoisomers (*E/Z* = 5:1). Selective deprotection of the terminal acetonide using PPTS gave **113**,³⁷⁹ followed by protection of the primary alcohol using TBSCl and of the secondary alcohol as a MOM ether produced the fully protected derivative **114**. Finally, the TBS ether was removed by treatment with TBAF and reductive cleavage⁴²⁷ of the trifluoroacetamide with NaBH₄ provided the AETD derivative **115**, ready for peptide coupling with GABOB.

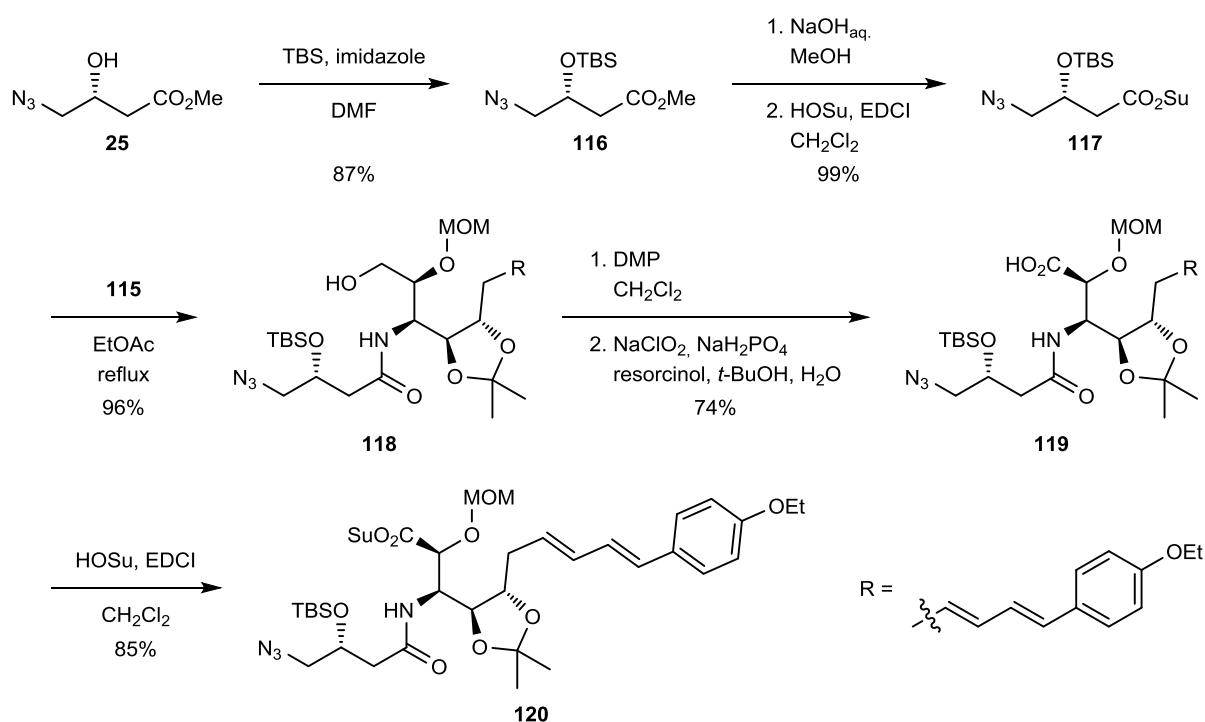
To summarize, Ma's synthesis of a protected AETD derivative ready for peptide coupling was achieved in 14% yield in 19 steps starting from δ -gluconolactone. The four stereogenic centers came from δ -gluconolactone, and the unsaturated tail was installed in a classic Julia olefination.

4.3.1.2. Preparation of the dipeptide GABOB–AETD

Similarly to Shioiri,^{359,360} Ma started the synthesis of a GABOB derivative from the azido derivative **25** obtained from dimethyl (*R*)-malate (Scheme 17). Thus protection of the secondary alcohol by TBSCl gave the protected azide **116**. Saponification of the methyl ester followed by coupling of the resulting carboxylic acid with hydroxysuccinimide produced the activated ester **117**.⁴²⁸ Then, coupling with the free amine of AETD derivative **115** gave the amide **118** efficiently. Oxidation of the primary alcohol into an aldehyde with Dess-Martin reagent and further oxidation of this aldehyde with NaClO₂ gave the carboxylic acid **119** which was then activated as the dipeptide succinimidyl ester **120**.

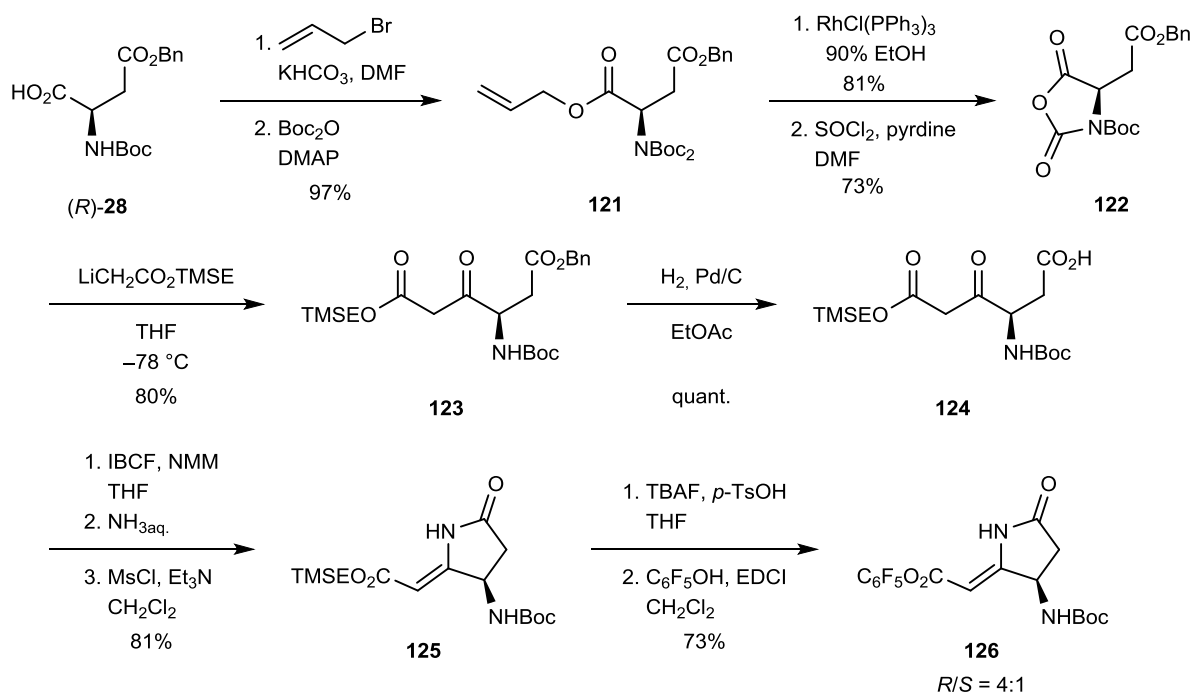
4.3.1.3. Synthesis of the protected dehydropyrrolidinone residue

In a similar way to Shioiri, the Δ PyrAA was prepared from aspartic acid. However, the stereochemistry of this residue is different in microscleordermin E and required the use of the D-enantiomer. Thus protection of the carboxylic acid group of (*R*)-**28** as an allyl ester followed by introduction of a second Boc group on the amino group gave the fully protected D-aspartic acid derivative **121** efficiently (Scheme 18). The allyl group was then removed using Wilkinson's catalyst and treatment of the bis-Boc-aspartic acid derivative thus obtained with thionyl chloride resulted in the formation of the Leuchs' anhydride **122** (urethane *N*-carboxyanhydride, UNCA)⁴²⁹ which is both a protected and activated form of an amino acid. Addition of the lithium enolate of



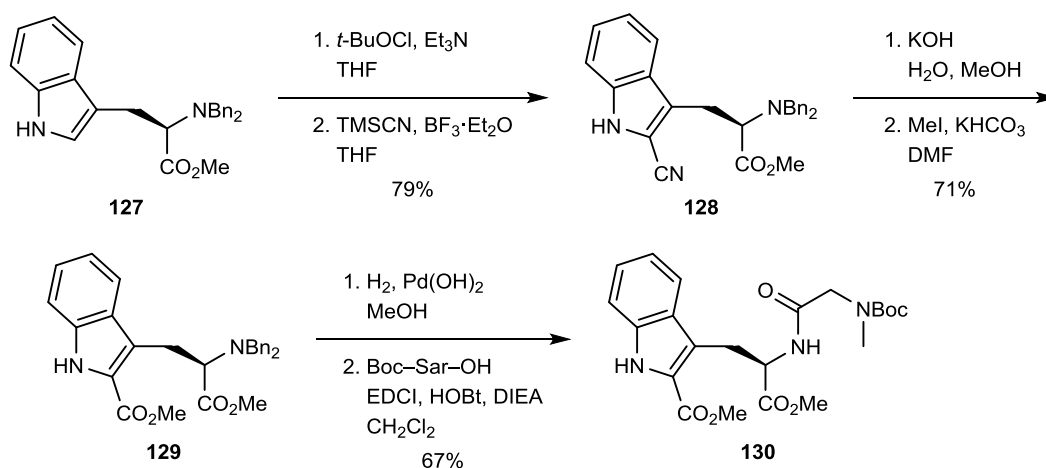
Scheme 17: Preparation of dipeptide GABOB–AETD

trimethylsilylethyl acetate yielded the β -keto ester **123** in excellent yield with no noticeable racemization ($ee > 98\%$). Other activation modes of the amino acid were studied, such as N,N' -carbonyldiimidazole, N -hydroxysuccinimide and pentafluorophenol (using Masamune's or Shioiri's procedure, Nu: Li-enolate or Mg-reagent),³⁵⁹ but resulted in partially or fully racemized β -keto ester. Then, the benzyl group was removed by hydrogenolysis to give the γ -keto acid **124** which was activated as a mixed anhydride using IBCF, and treated with aqueous ammonia to give an intermediate hydroxypyrrolidone which was directly subjected to elimination through mesylation to provide the pyrrolidinone derivative **125** in good yield. Deprotection of the trimethylsilylethyl by TBAF in the presence of p -TsOH to suppress of racemization⁴³⁰ gave the free acid with partial racemization (R/S ratio 4:1 in the best case) and coupling with pentafluorophenyl alcohol using EDCI provided the PFP-activated ester **126** ready for peptide coupling.^{431,432} Herein, the dehydroxypyrrolidinone derivative **126** was obtained in 33% yield over 11 steps.

Scheme 18: Synthesis of a Δ PyrAA derivative

4.3.1.4. Synthesis of a protected derivative of the dipeptide Sar–Trp(2-CO₂H)

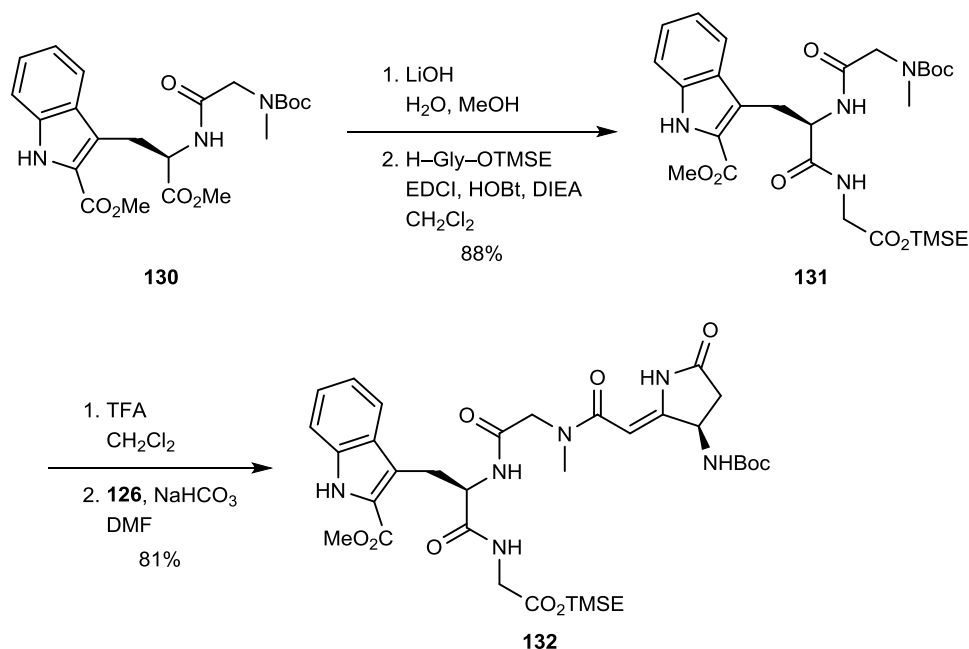
2-Carboxytryptophan was prepared according to Danishefsky's protocol.⁴³³ Thus, cyanation of the protected D-tryptophan derivative **127** was performed by chlorination using *t*-BuOCl followed by treatment with TMS-CN in the presence of BF₃·Et₂O to furnish the cyanotryptophan derivative **128** (Scheme 19). Hydrolysis of the cyano group followed by sequential esterification gave the D-tryptophan derivative **129** in 56% over 4 steps. After removal of both *N*-benzyl groups by hydrogenolysis, the resulting amino ester was engaged in a peptide coupling with *N*-Boc-sarcosine to provide the dipeptide Boc–Sar–Trp(2-CO₂Me)–OMe in 67% yield over 2 steps.



Scheme 19: Synthesis of the dipeptide Sar–Trp

4.3.1.5. Construction of the tetrapeptide derivative Δ PyrAA–Sar–Trp–Gly

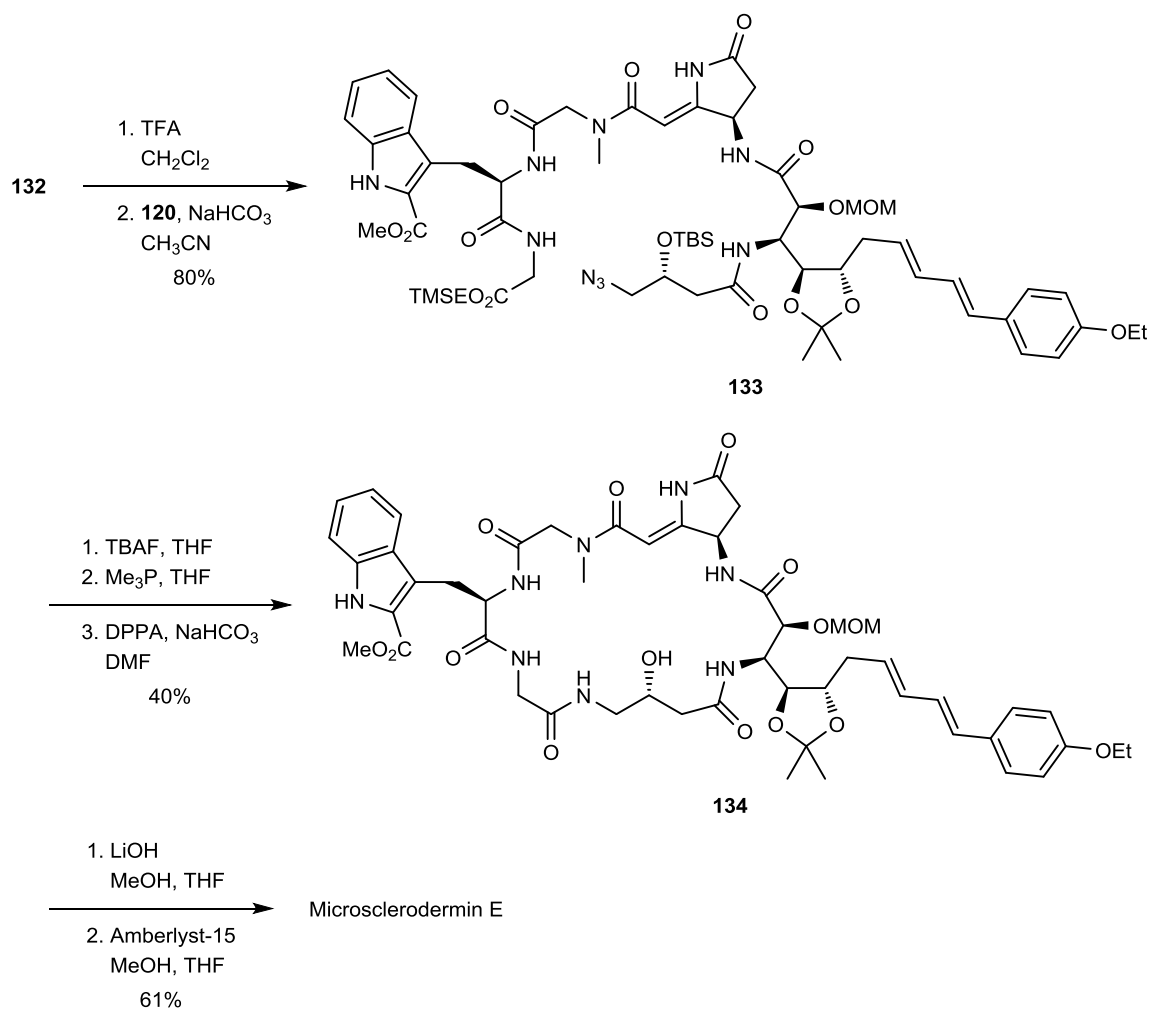
Regioselective saponification of the α -methyl ester of dipeptide **130** and coupling with glycine trimethylsilyylethyl ester gave the tripeptide **131** (Scheme 20). Boc-deprotection of the sarcosine residue by treatment with TFA produced a TFA salt which was directly coupled with the PFP-activated ester **126** to give the tetrapeptide **132** as a mixture of two diastereoisomers (ratio 4:1, from the partially racemized PFP-activated ester **126**).



Scheme 20: Preparation of the tetrapeptide derivative Δ PyrAA–Sar–Trp–Gly

4.3.1.6. Construction of the hexapeptide and macrocyclization

The tetrapeptide **132** was treated with TFA before coupling with the activated dipeptide **120** by simple treatment with aqueous NaHCO_3 to provide the linear hexapeptide **133** in excellent yield (Scheme 21). Both TMSE and TBS protecting groups were removed using TBAF, then Staudinger reduction⁴³⁴ of the intermediate azide using Me_3P ⁴³⁵ gave a free amine. Macrocyclization of this linear hexapeptide mediated by diphenylphosphoryl azide (DPPA)⁴³⁶ afforded the macrolactam **134** in 40% yield after purification by HPLC. Finally, saponification of the methyl ester of the indole ring and cleavage of both the MOM ether and the acetonide with a mildly acidic resin Amberlyst-15⁴³⁷ produced the target microsclerodermin E, whose analytical data were identical with those reported and thus confirming the structure proposed by Faulkner.³⁴⁴



Scheme 21: Construction of the hexapeptide and macrocyclization

In summary, Ma reported the first total synthesis of a microsclerodermin family member: microsclerodermin E, which was obtained in 1% overall yield in 26 linear steps. It should be noted that the pyrrolidinoacetic acid unit is dehydrated making the synthesis relatively easier.

4.3.2. Donohoe's work on microsclerodermins B and J

Starting from 2013, Donohoe's group worked on the total synthesis of microsclerodermins B and J.⁴³⁸⁻⁴⁴⁰ The most challenging part of these two targets was the hydroxypyrrolidinoacetic acid residue which is extremely sensitive and whose hemiaminal moiety was easily dehydrated under basic or acidic conditions, and up to this point had not been targeted in a total synthesis of any microsclerodermin family member. After preliminary studies and observations, they proposed to install the sensitive PyrAA residue at a late stage of the total synthesis (Figure 29). In a similar way to Ma's work on microsclerodermin E,⁴²⁴ the macrocycle was constructed by peptide coupling of

the dipeptide Fmoc-GABOB-AMMTD-OH with the tetrapeptide H- Δ PyrAA-Sar-Trp(2-CO₂TMSE)-Gly-OFm, macrocyclization between the GABOB and the Gly residue, then installation of the hydroxyl group on the pyrrolidinoacetic acid residue and finally assembly of the styrene moiety.

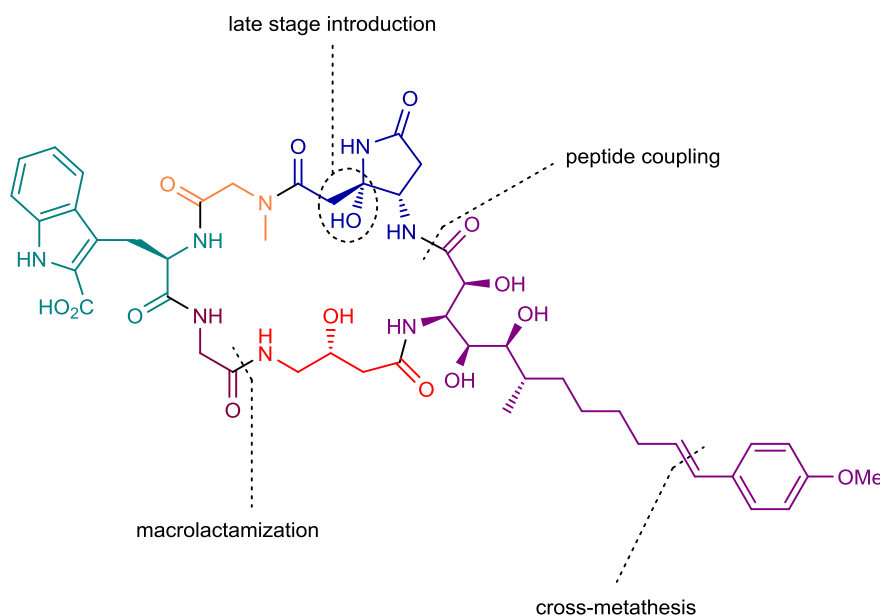


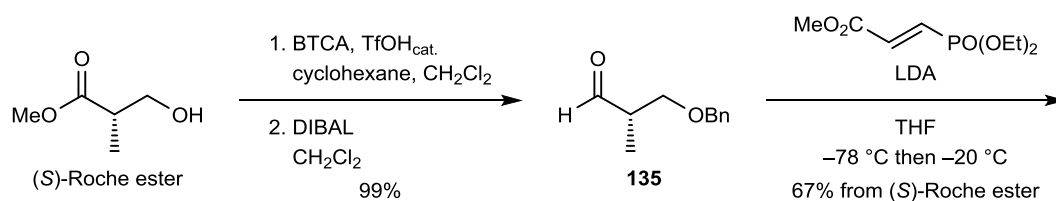
Figure 29: Retrosynthetic analysis of microsclerdermin B

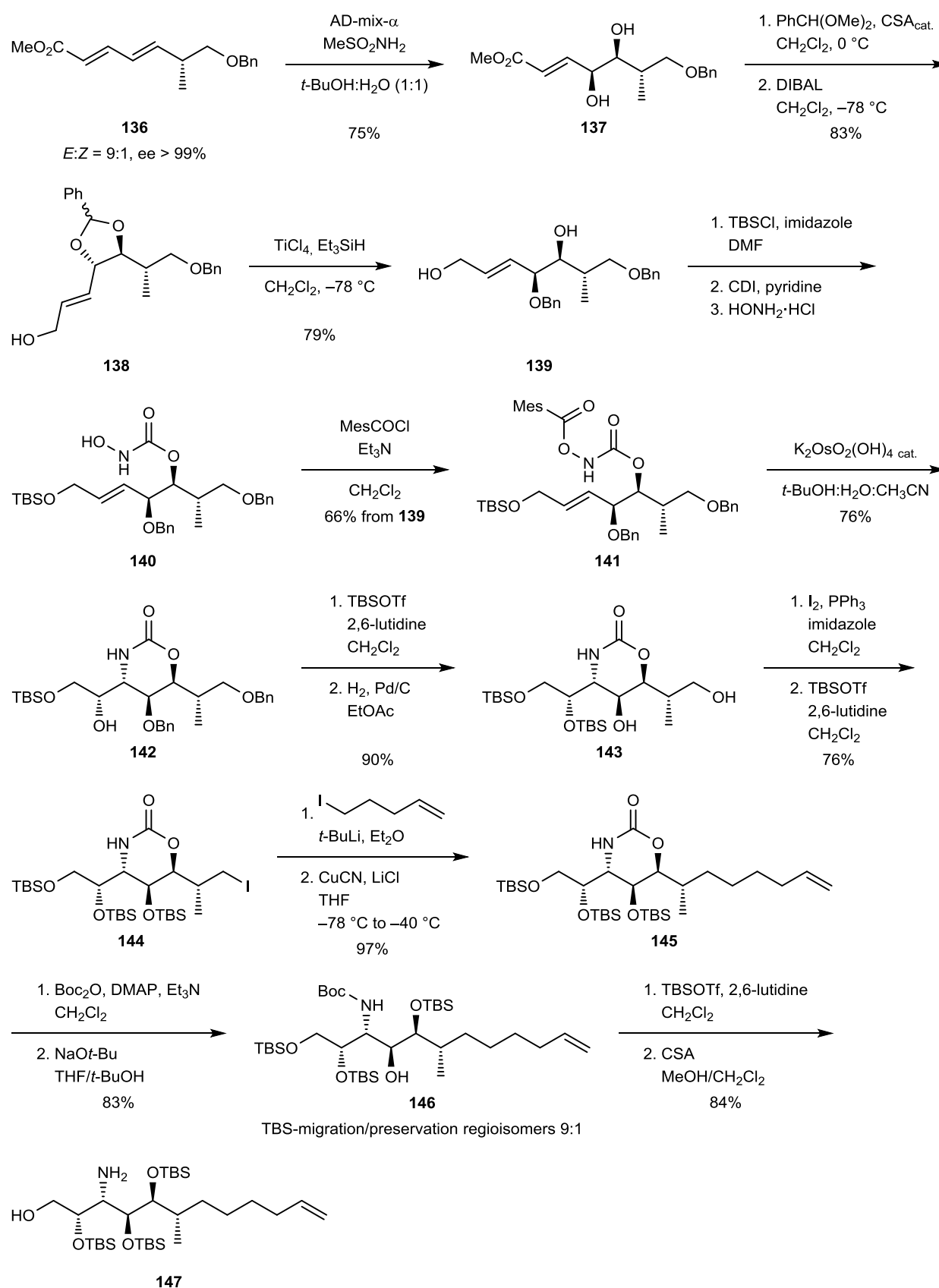
4.3.2.1. Synthesis of a protected derivative of AMMTD*

In 2013, the synthesis of a protected derivative of the polyhydroxy- β -amino acid (AMMTD fragment) present in microsclerdermins A and B was reported by Donohoe's group.⁴³⁸ The synthesis relied on sequential Sharpless dihydroxylation^{352,353} and tethered aminohydroxylation⁴⁴¹ of a diene derived from (*S*)-Roche ester to install the requisite four stereogenic centers. Extension of the aliphatic side chain required a S_N2 reaction of primary iodide with Lipshutz-type lithiocuprate reagent.^{442,443} Since the installation of the hydroxyl group on the pyrrolidinoacetic acid residue by hydroxybromination-debromination was not compatible with the styryl moiety, the plan was to introduce this moiety latter by cross-metathesis at the end of the total synthesis (See § 4.3.2.3.). The precursor of AMMTD has a terminal alkene chain, and is referred to as AMMTD*.

The synthesis commenced with benzylation of the primary alcohol of the (*S*)-Roche ester using benzyl 2,2,2-trichloroacetimidate⁴⁴⁴⁻⁴⁴⁶ (BTCA) followed by reduction of methyl ester with

DIBAL to give the aldehyde **135** which was directly engaged in a Horner–Wadsworth–Emmons reaction with a phosphonate-stabilized carbanion to provide the diene **136** (*E/Z* = 9:1) (Scheme 22). Sharpless dihydroxylation^{352,353} of this diene using AD-mix- α gave the *syn*-diol **137** as a single diastereoisomer. Differentiation of the two hydroxyl groups was then performed by formation of a cyclic ketal with benzaldehyde dimethyl acetal followed by reduction of the methyl ester with DIBAL into the primary alcohol **138**. Upon treatment with $\text{TiCl}_4/\text{Et}_3\text{SiH}$ a regioselective ring-opening⁴⁴⁷ of the acetal probably due to coordination of benzyl ether with TiCl_4 , occurred to afford the monobenzyl ether **139**. Subsequently, the primary alcohol was selectively protected as its TBS ether, and the secondary alcohol was transformed into a one-pot sequential reaction with CDI and hydroxylamine into the hydroxycarbamate **140**. Final aroylation gave the aroylhydroxycarbamate precursor **141** ready for tethered aminohydroxylation reaction. Upon treatment with potassium osmate the aminohydroxylated product **142** was obtained as a single diastereoisomer. Subsequently, the free alcohol was protected with TBS, and both of the two benzyl ethers were removed by hydrogenolysis over Pd/C to generate the diol **143**. Before extension of aliphatic side chain, the primary alcohol was converted into an iodide and the remaining secondary alcohol was reprotected as its TBS ether to give the fully protected iodide **144** efficiently. Elongation of the side chain was accomplished by $\text{S}_{\text{N}}2$ displacement of the iodide with the Lipshutz-type lithiocuprate derived from pentenyl iodide⁴⁴² to give the protected derivative **145**. Before being applicable in peptide coupling, a few modifications were still required. The cyclic carbamate was protected by a Boc group which facilitate the cleavage of the cyclic carbamate with NaOt-Bu to give the alcohol **146** derived from C^4 to C^5 migration of the TBS protecting group as an inseparable mixture of regioisomers (TBS-migration/preservation = 9:1). Finally, the remaining free alcohol was protected as its TBS ether and both the amine and primary alcohol were deprotected with CSA to produce the β -amino alcohol **147** and at this stage the regioisomers were isolated as a single compound, ready for coupling with an appropriate GABOB derivative.





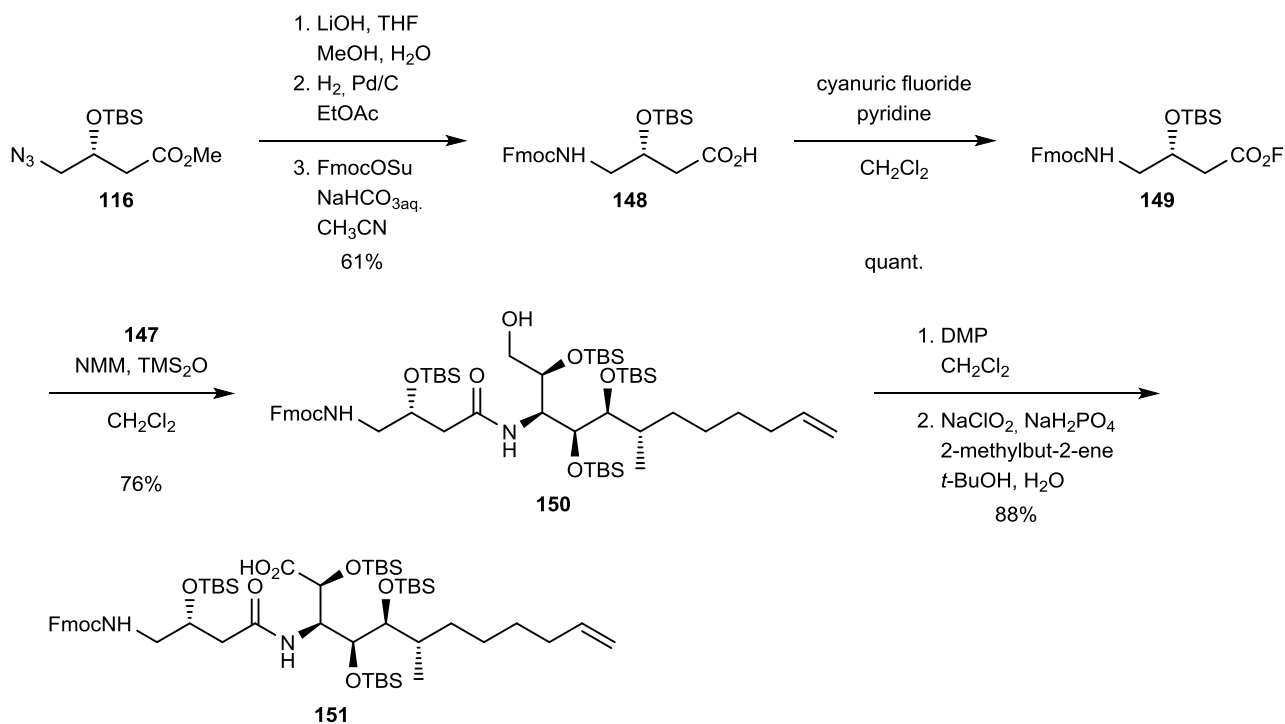
Scheme 22: Preparation of a protected derivative of AMMTD*

In summary, Donohoe *et al.* achieved a synthesis of a protected AMMTD* derivative starting from (*S*)-Roche ester in 7.6% yield over 18 linear steps. The synthetic strategies featured a regio- and

stereoselective tethered aminohydroxylation of a complex homoallylic alcohol, Sharpless dihydroxylation, introduction of side chain by S_N2 displacement and (*E*)-selective Horner–Wadsworth–Emmons reaction as key steps. Moreover, the intended late-stage introduction of the stryl tail of AMMTD should also be applicable for other polyhydroxy β -amino acids present in the microsclerodermin family.

4.3.2.2. Preparation of the dipeptide GABOB–AMMTD*

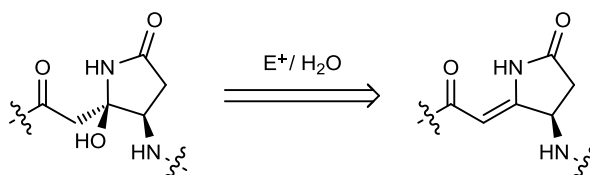
The GABOB derivative was synthesized from the azido derivative **116** by adaptation of the route developed by Shioiri^{359,360} and Ma.⁴²⁴ Saponification of the methyl ester followed by hydrogenolysis of the azide group and subsequent protection of the resulting free amine by a Fmoc group gave the protected γ -amino acid **148** which was then activated as the acyl fluoride **149** using cyanuric fluoride (Scheme 23).^{448,449} Therefore, peptide coupling of this acyl fluoride with the protected AMMTD derivative **147** gave the amide **150** efficiently. Finally oxidation of the primary alcohol into an aldehyde with Dess–Martin reagent and further oxidation of this aldehyde with NaClO_2 gave the dipeptide acid **151** which was ready for further peptide coupling.



Scheme 23: Construction of the dipeptide Fmoc–GABOB–AMMTD*–OH

4.3.2.3. Preparation of the pyrrolidinoacetic acid residue

Based on the fact that the hydroxypyrrolidinoacetic acid residue is sensitive to dehydration, Donohoe proposed an interesting strategy to construct the sensitive hydroxypyrrolidinoacetic acid residue by electrophilic addition on the double bond of Δ PyrAA at a late-stage in the total synthesis (Scheme 24).⁴³⁹

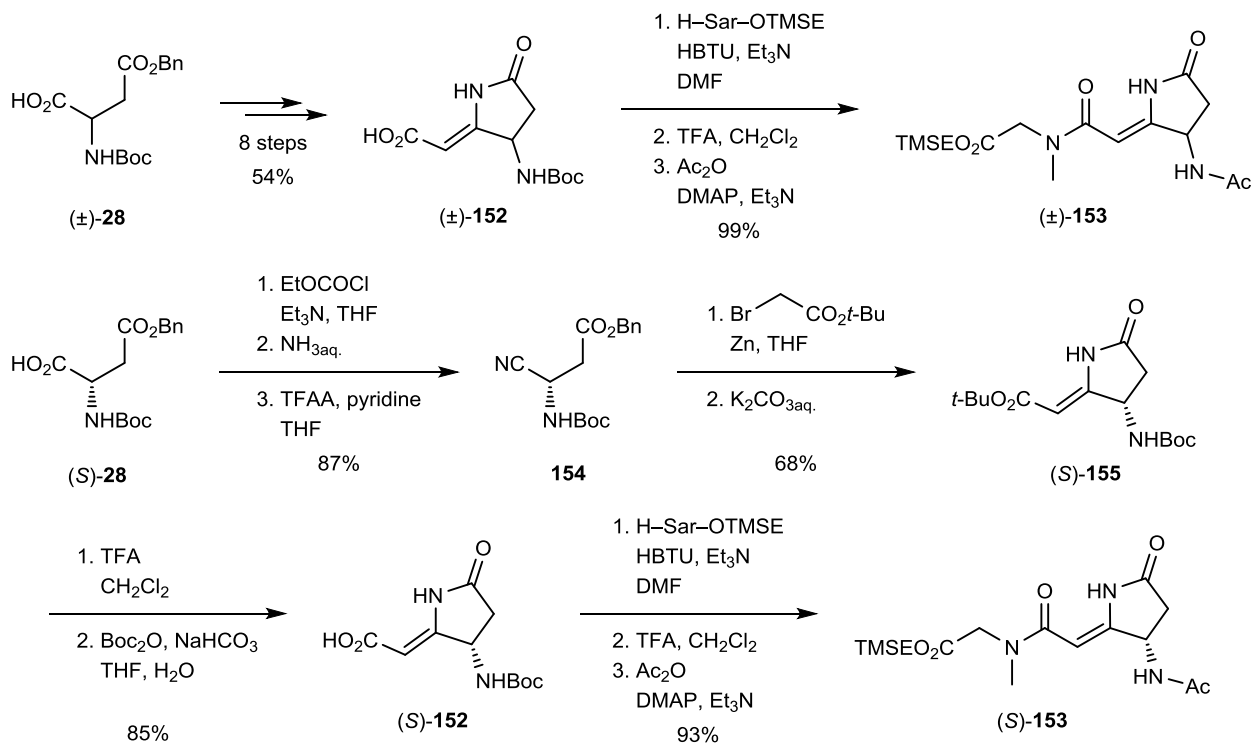


Scheme 24: Late-stage hydration strategy for the preparation of PyrAA residue

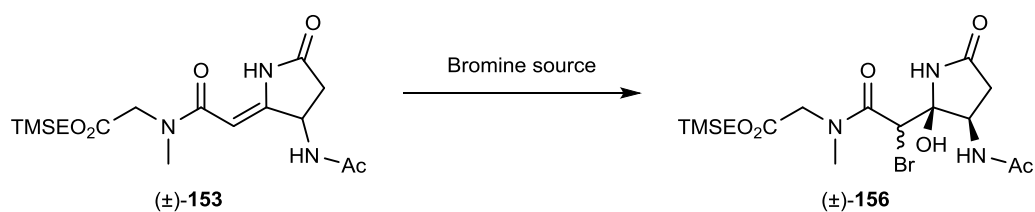
The dipeptide Δ PyrAA–Sar was chosen as a model to study this strategy. Thus, the dehydropyrrolidinoacetic acid residue (\pm)-**152** was prepared in its racemic form by modification of the chemistry reported by Shioiri^{359,360} and Ma.⁴²⁴ Coupling with sarcosine trimethylsilylethyl ester, treatment with TFA to remove the Boc group and acylation with acetic anhydride provided the racemic model dipeptide (\pm)-**153**. Additionally, the enantiopure material was obtained in 8 steps from L-aspartic acid derivative (*S*)-**28** (Scheme 25). Activation of the acid with ethylchloroformate followed by treatment with ammonia produced an amide which was dehydrated into the nitrile **154**. Then, Blaise reaction⁴⁵⁰ of a *t*-butyl bromoacetate derived zinc enolate reagent onto this nitrile and subsequent lactamization gave the dehydropyrrolidinoacetate (*S*)-**155** with excellent stereoselectivity (*ee* 95%). Deprotection of both the *t*-butyl ester and the Boc group followed by re-protection of the free amine with Boc₂O gave the protected derivative (*S*)-**152** which was then coupled with sarcosine trimethylsilylethyl ester, treated with TFA to remove the Boc group and finally acylated with acetic anhydride provided the model dipeptide (*S*)-**155** in 54% overall yield for 8 steps.

While direct hydration of the model dipeptide (\pm)-**153** with either Brønsted or Lewis acids were not effective, the hydroxy group was easily introduced by hydroxybromination using various reagent (NBS, TBCD,⁴⁵¹⁻⁴⁵⁵ Br₂) (Table 2). Thus, the bromohydrin (\pm)-**156** was obtained in good yield as a single diastereoisomer presenting the appropriate 4,5-*cis* configuration of the substituents on the pyrrolidinone ring. The observed selectivity could be the result of the attack of the *N*-acetyl

group on the *N*-acyliminium intermediate **I** to produce a dihydrooxazolium ion **II** which was subsequently hydrolysed⁴⁵⁶ by attack at the acyl carbonyl to yield the 4,5-*cis*-pyrrolidinone (Scheme 26).



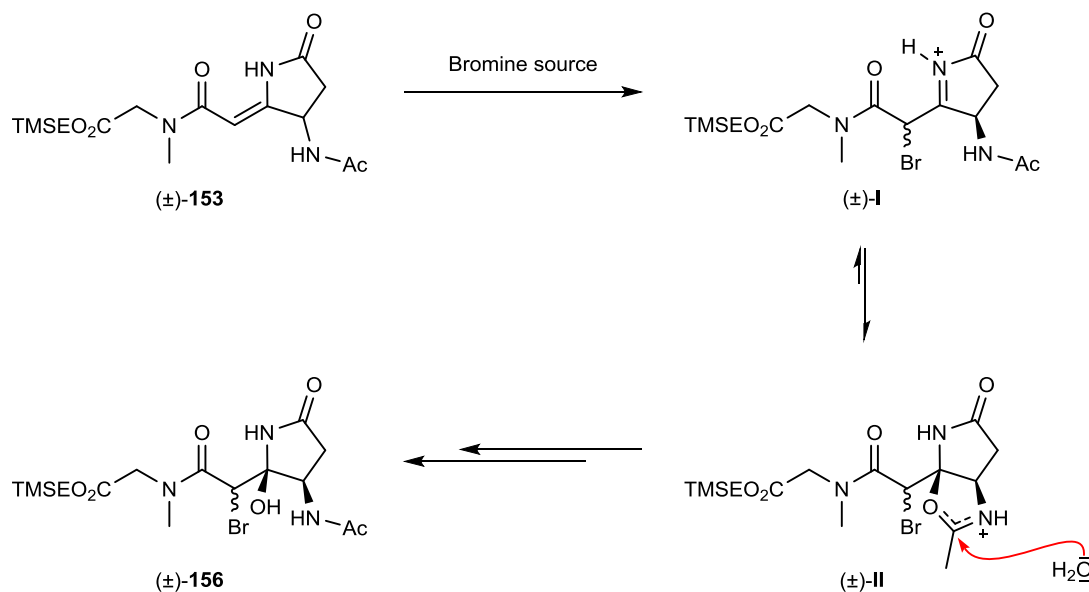
Scheme 25: Synthesis of the model dipeptide Ac- Δ PyrAA-Sar-OTMSE



Entry	Bromine source ^a	Solvent	Yield (%) ^b
1	NBS	THF/H ₂ O	75
2	TBCD	THF/H ₂ O	81
3	Br ₂	CH ₂ Cl ₂ /H ₂ O	76

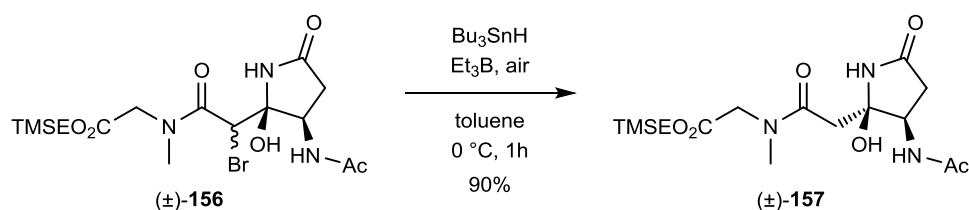
Notes: ^a 2.5 equivalent used; ^b Isolated yields

Table 2: Hydroxybromination of the model dipeptide



Scheme 26: Proposed mechanism for the 4,5-*cis*-diastereoselectivity of hydroxybromination

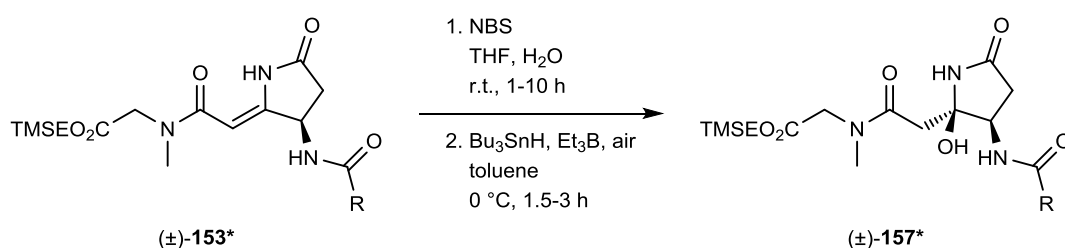
Reductive debromination of the bromohydrin derivative was performed under radical conditions using tributyltin hydride and a catalytic amount of triethylborane as an initiator at low temperature.⁴⁵⁷ In this way, hydroxypyrrolidone derivative (±)-157 was obtained in excellent yield (Equation 1). During this study, Donohoe noted that the use of AIBN as an initiator required a higher temperature and resulted in dehydration, and hydrogenolysis using Pd/C also led to dehydration.



Equation 1: Radical-mediated debromination of bromohydrin (±)-156

Before commencing the total synthesis of microsclerodermin, the compatibility of this strategy with the AMMTD residue, which possesses an electron rich *p*-methoxystyrene moiety susceptible to react with the bromine source, was evaluated.⁴⁵⁷ Thus a series of long-chain dipeptides (similar to the AMMTD fragment) and bearing the styrene moiety, an alkene or an alkyne which could be used as precursors of the styrene moiety, or an alkane (for comparison purpose) were prepared and submitted to the hydroxybromination-debromination sequence (Table

3). Upon treatment with NBS (or TBCD) (entry 1), the undesired bromination of the aromatic ring was observed which therefore excluded to perform in this reaction in the presence of the styryl moiety. Both terminal alkene (entry 2) and terminal olefin (entry 3) led to a regioselective hydroxybromination in good yields (73% and 65% respectively) comparable to the 61% yield obtained on the saturated substrat (entry 4). Radical-mediated debromination gave the corresponding hydroxypyrrolidones efficiently, although reaction on the olefin (entry 2) required the careful control of the amount of Bu_3SnH employed (≤ 1.1 equivalent).



Entry	R	Hydroxybromination Yield (%) ^a	Debromination Yield (%) ^a
1		— ^b	—
2		73	90
3		65	90
4		61	91

Notes: ^a Isolated yields; ^b Undesired bromination on the aromatic ring was observed

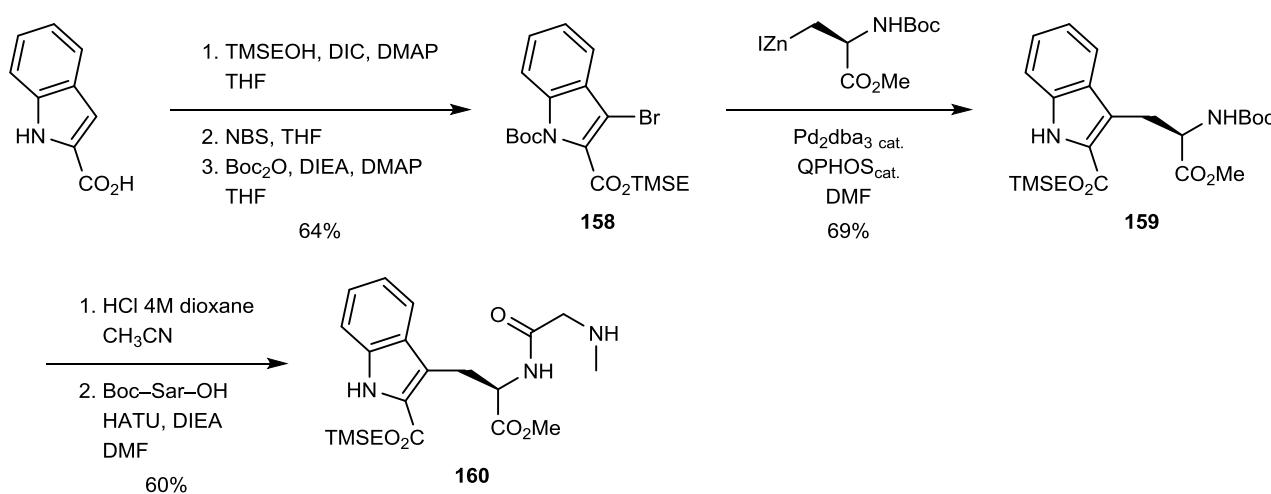
Table 3: Hydroxybromination and debromination of microsclerodermin dipeptide mimics

To explore this strategy further, the olefin substrate was submitted to cross metathesis^{437,458,459} with an excess of *p*-methoxystyrene using Grubbs I catalyst. The expected styrene derivative was obtained efficiently as a single diastereoisomer with the appropriate geometry and with no signs of dehydration of the hydroxypyrrolidone moiety.

In summary, thanks to these model studies, Donohoe provided support for his interesting strategy to create the hydroxypyrrolidinoacetic acid residue directly on the macrocyclic peptide in one of the very last steps of the synthesis of microsclerodermin B.

4.3.2.4. Synthesis of a protected derivative of the dipeptide Sar–Trp(2-CO₂H)

Donohoe developed a new synthetic approach to prepare 2-carboxytryptophan derivative from indole-2-carboxylic acid. Protection of the carboxylic acid as a trimethylsilylethyl ester followed by bromination at C³ position and protection of the indole nitrogen by a Boc group generated the protected 3-bromoindole derivative **158** (Scheme 27). Subsequent Negishi coupling⁴⁶⁰ with an organozinc reagent derived from 3-iodo-D-alanine provided the protected 2-carboxytryptophan derivative **159** in good yield and excellent enantiomeric excess. After removal of the Boc group, coupling with sarcosine produced the dipeptide **160** in 27% yield over 6 steps.



Scheme 27: Construction of the protected derivative of the dipeptide Sar–Trp(2-CO₂H)

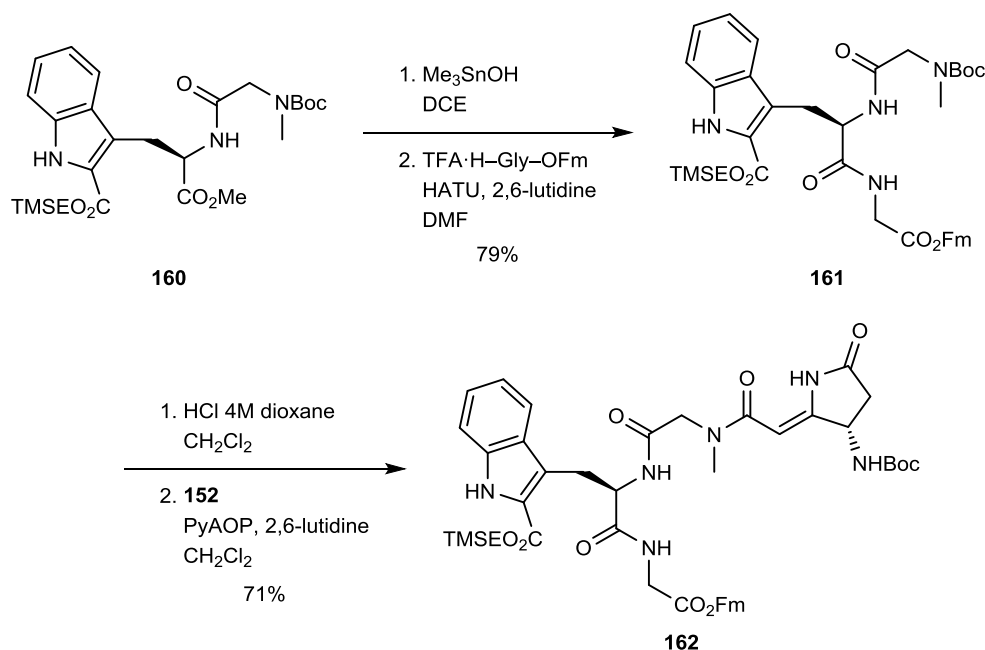
4.3.2.5. Construction of a protected tetrapeptide derivative ΔPyrAA–Sar–Trp(2-CO₂H)–Gly

Selective deprotection of the methyl ester of **160** using Me₃SnOH and coupling with glycine fluorenylmethyl ester produced the tripeptide **161** (Scheme 28). Boc-deprotection of the sarcosine residue by treatment with a HCl solution in dioxane, gave an ammonium salt which was directly coupled with the ΔPyrAA derivative **152** using by PyAOP and 2,6-lutidine to furnish the tetrapeptide Boc–ΔPyrAA–Sar–Trp(2-CO₂TMSE)–Gly–OFm **162**.

4.3.2.6. Construction of the hexapeptide, macrocyclization and late-stage difficulties

The tetrapeptide **162** was treated with TFA in the presence of triethylsilane before coupling with the dipeptide **151** using HATU and 2,6-lutidine to provide a mixture of the linear hexapeptides **163-1** and **163-2** (1:1) resulting from a partial deprotection of a TBS (Scheme 29). After separation, treatment of each hexapeptide with piperidine to deprotect both Fmoc and Fm protecting groups in a

single operation followed by macrolactamization using PyAOP and HOAt produce the two cyclic hexapeptides **164-1** and **164-2** in reasonable yields. Unfortunately, hydroxybromination of the fully protected derivative **164-2** using TBCD failed and only some undefined products were obtained.

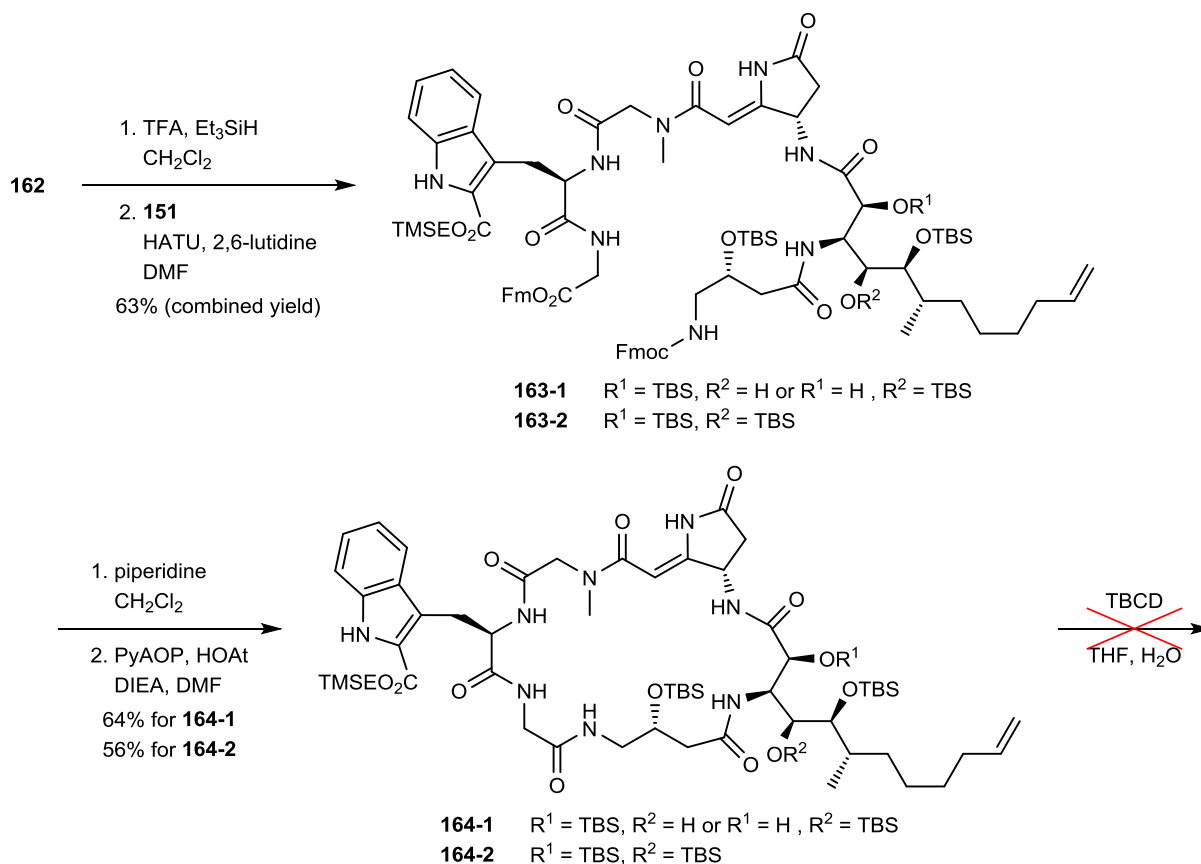


Scheme 28: Preparation of the protected derivative tetrapeptide $\Delta\text{PyrAA-Sar-Trp-Gly}$

4.3.2.7. Synthesis and structural reassignment of dehydromicrosclerodermin B

Although installation of the hydroxypyrrolidinoacetic acid residue failed, Donohoe completed the synthesis of dehydromicrosclerodermin B. Cross-metathesis of cyclic hexapeptides **164-1** and **164-2** with *p*-methoxystyrene required in the presence of a stoichiometric amount of the Grubbs' I catalyst due to the coordination of amide group to the ruthenium catalyst gave the macrocycles **165-1** and **165-2** (Scheme 30). Finally deprotection of TMSE and TBS groups was performed with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)⁴⁶¹⁻⁴⁶³ to give the unprotected macrocycle **166**. Analytical data were compared with that of a sample of dehydromicrosclerodermin B obtained by Li from natural microsclerodermin B.^{346,347} Analysis of ^1H NMR data showed the presence of two rotamers in a ratio of approximately 3:1 for **166**, whereas no rotamer was observed for the naturally derived dehydromicrosclerodermin B. Additionally, examination of the ^{13}C NMR data revealed a large difference for two regions of the molecule: the pyrrolidinone core and the GABOB unit ($\Delta\delta$ up to 2.3 ppm). Furthermore, HPLC studies on a 1:1 mixture of the synthetic

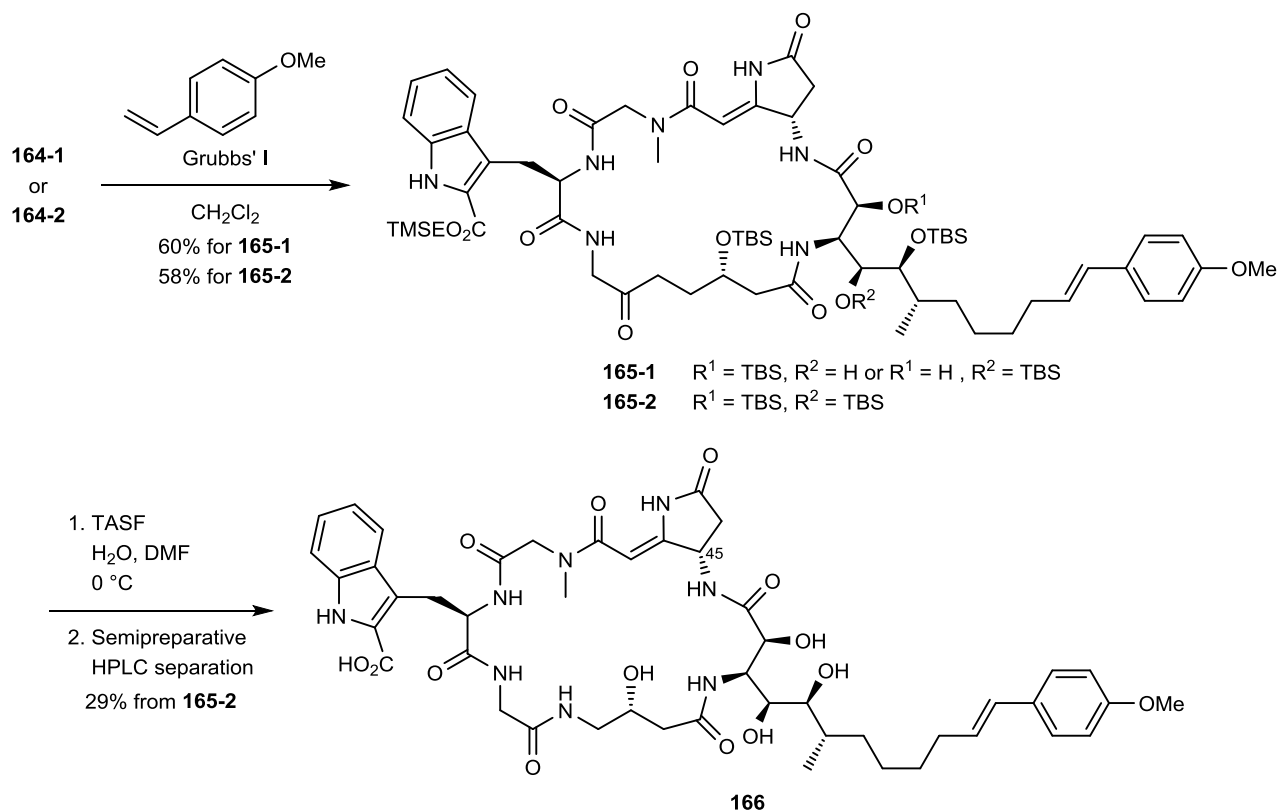
product **166** and naturally derived dehydromicrosclerodermin B³⁴⁶ clearly showed that **166** was not dehydromicrosclerodermin B.



Scheme 29: Construction of the hexapeptide, macrocyclization and attempted hydroxybromination

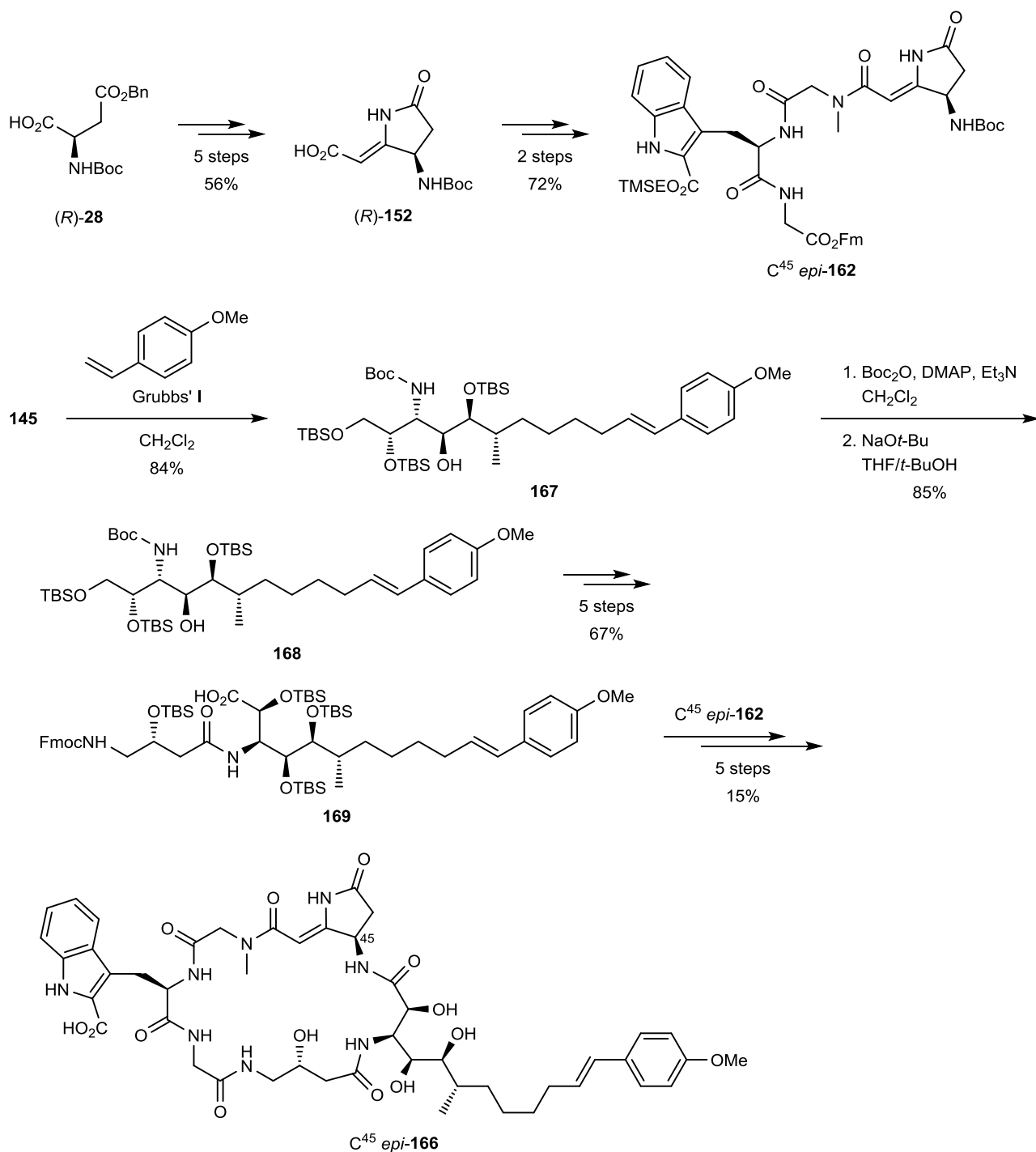
Given the lack of clarity regarding the configuration at C⁴⁴ and C⁴⁵ in the microsclerodermin family, Donohoe proposed that the C⁴⁵ stereogenic center might have been assigned incorrectly. In order to validate this hypothesis, he synthesized the C⁴⁵ *R* epimer, C⁴⁵ *epi-166*. Thus, the tetrapeptide C⁴⁵ *epi-162* was prepared from *D*-aspartic acid derivative (*R*)-**28** following the same procedures described (See § 4.3.2.3, § 4.3.2.4 and § 4.3.2.5) for the synthesis of tetrapeptide **162** (Scheme 31). Since the hydroxybromination of ΔPyrAA is not required for the synthesis of dehydromicrosclerodermin B, installation of the styryl moiety of AMMTD was performed earlier to avoid the problem of late-stage cross-metathesis. Thus, the protected derivative **145** was engaged in the cross-metathesis with *p*-methoxystyrene to give the disubstituted alkene **167** efficiently. The cyclic carbamate moiety was cleaved in the same conditions as described for the terminal alkene derivative **145** (See § 4.3.2.1) to produce the alcohol **168** derived from C⁴ to C⁵ migration of the TBS protecting group. Protecting groups manipulation followed by coupling with the protected

GABOB derivative **149** and oxidation of the primary alcohol group in the same conditions as described for the protected derivative **146** (See § 4.3.2.1) provided the dipeptide **169** in good yield over 5 steps. Finally, peptide coupling followed by Fm and Fmoc group deprotection and subsequent macrolactamization and deprotection of the side chains gave the C^{45} *epi*-**166**.



Scheme 30: Synthesis of (45*S*)-dehydromicrosclerodermin B

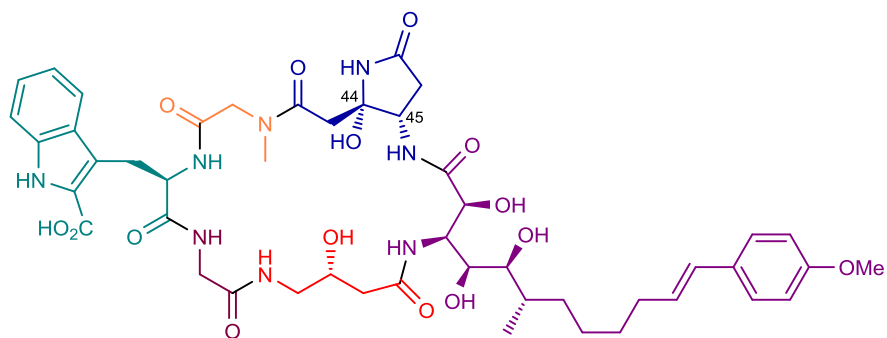
The NMR data for synthetic C^{45} *epi*-**166** showed no rotamers as in the naturally derived dehydromicrosclerodermin B and further evidence that C^{45} *epi*-**166** was actually dehydromicrosclerodermin B was confirmed by ^1H NMR and HPLC analysis with a 1:1 mixture of these two samples in which all the peaks were completely overlapped. Thus, Donohoe concluded that the stereochemistry of microsclerodermin B proposed by Faulkner³⁴³ was incorrect, and that the absolute configuration of the pyrrolidinoacetic acid residue should be reassigned as (44*R*,45*R*) instead of (44*S*,45*S*) (Figure 30).



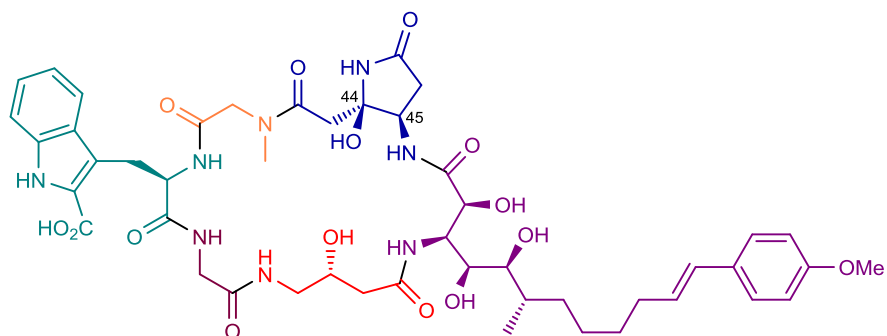
Scheme 31: Synthesis of (45R)-dehydromicrosclerodermin B

4.3.2.8. Synthesis and structural reassignment of microsclerodermin J

This structural reassignment of microsclerodermin B prompted Donohoe to investigate the case of microsclerodermin J^{346,347} which is structurally closely related to microsclerodermin B, and thus suspected that the dehydropyrrolidinoacetic acid residue was (45*S*) instead of (45*R*) (Figure 31).

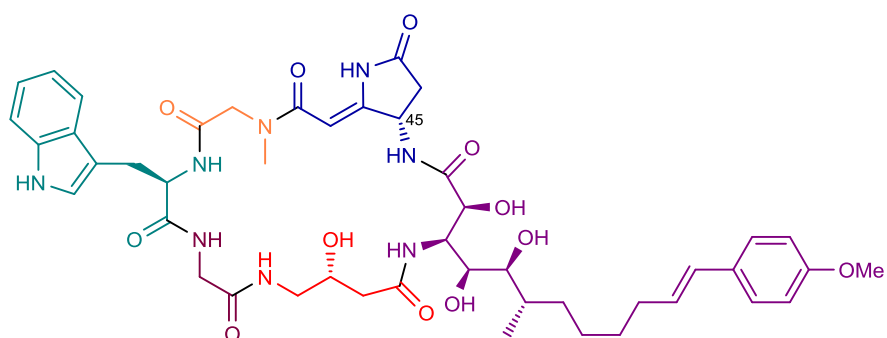


Original structure of microsclerdermin B proposed by Faulkner

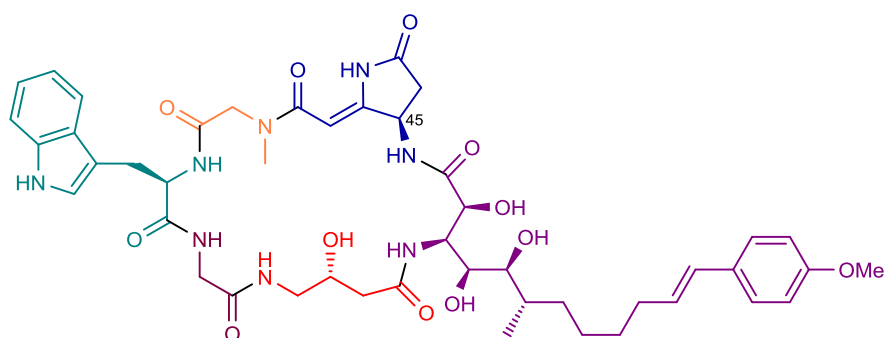


Reassigned structure of microsclerdermin B proposed by Donohoe

Figure 30: Structural reassignment of microsclerdermin B



Original structure of microsclerdermin J proposed by Li

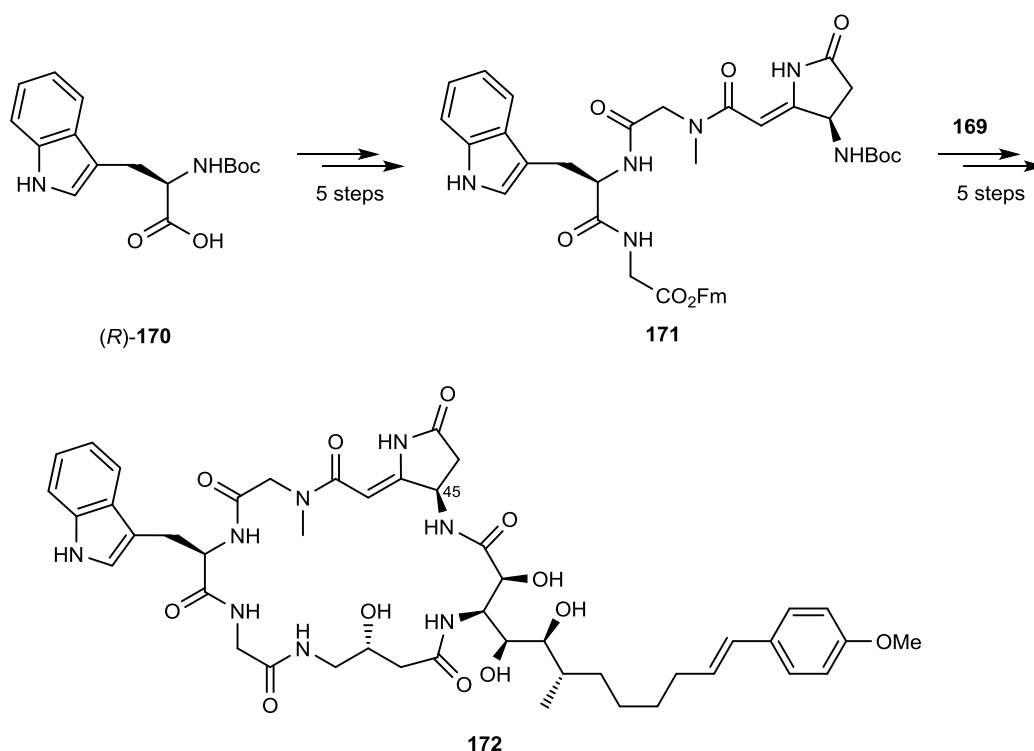


Reassigned structure of microsclerdermin J proposed by Donohoe

Figure 31: Structural reassignment of microsclerdermin J

The only difference between dehydromicrosclerdermin B and microsclerdermin J is that the 2-carboxy-D-tryptophan residue is replaced by D-tryptophan. Thus, the synthesis was adapted to

the D-tryptophan derivative **170**, and the tetrapeptide **171** was obtained in 6 steps following the same procedure (See § 4.3.2.4 and § 4.3.2.5) used to prepare the tetrapeptide **162** (Scheme 32). Finally, peptide coupling followed by Fm and Fmoc group deprotection and subsequent macrolactamization and deprotection of the side chain as described above (See § 4.3.2.7) gave the macrocycle **172**.



Scheme 32: Synthesis of (45R)-microsclerodermin J **172**

No rotamers were observed in the ^1H NMR spectra of (45R)-microsclerodermin J **172**. Comparison of the ^{13}C NMR spectra with that obtained by Li^{346,347} for the natural microsclerodermin J revealed a complete superimposition of the two spectra match ($\Delta\delta$ less than 0.1 ppm). Donohoe concluded that the configuration of the dehydropyrrolidinoacetic acid residue had been mis-assigned, as had been the case microsclerodermin B.

In conclusion, Donohoe prepared dehydromicrosclerodermin B and microsclerodermin J and reassigned the configuration of the ΔPyrAA residue in both cases. He developed highly efficient approaches to the unusual amino acids such as the modified tryptophan fragment *via* Negishi coupling and the pyrrolidinone unit through a Blaise reaction. Although he proposed an interesting

strategy for the late stage introduction of the sensitive hydroxyl group of the pyrrolidinoacetic acid residue, which was validated using model substrates, the approach failed when applied to the hexapeptide macrocycle. Thus, to date, none of the microsclerodermins with the sensitive hydroxypyrrolidinoacetic acid residue have been synthesized.

4.4. Synthetic work: conclusion

Over the decades, many groups worked on the total synthesis of microsclerodermins or of fragments thereof, such as Shioiri, Ma, Donohoe, Aitken, Chandrasekhar, Williams, McLeod, Dauban and Dodd, Davies. As described above, much of the work has focused on the preparation of the unusual amino acids present in microsclerodermins. To date, only two total synthesis have been reported: first Ma described the preparation of microsclerodermin E in 2003,⁴²⁴ and recently Donohoe reported the synthesis of microsclerodermin J in 2016.⁴⁴⁰ The work of Shioiri^{359,360} and later Donohoe⁴⁴⁰ underline that microsclerodermins are extremely sensitive to dehydration of the hydroxypyrrolidinoacetic acid residue. This raises the question if microsclerodermins E, J and K are true natural products or perhaps the results of dehydration during the extraction process. This proposal viewpoint could be evidenced by 3 reasons below:

- only 3 members (microsclerodermins E, J and K) of the microsclerodermin family are reported to have the dehydrated pyrrolidinoacetic acid unit
- as described by Donohoe in the 2016,⁴⁴⁰ Li provide a sample of dehydromicrosclerodermin B which was obtained by dehydration of microsclerodermin B in the HPLC purification process
- combining all results previously reported from Shioiri,^{359,360} Ma⁴²⁴ and Donohoe,⁴⁴⁰ it is clear that the hydroxypyrrolidinoacetic acid unit is extremely sensitive to dehydration and therefore can't be maintained during the synthesis

5. Objectives

The host research group is interested in various cyclopeptide natural products (cyclotheonamide C⁴⁶⁴⁻⁴⁶⁶), and derivatives (rhodopeptin⁴⁶⁷) and has already developed various synthetic methodologies for the preparation of β - and γ -amino acids and notably of some

polyhydroxy- β -amino acids present in microsclerodermins (APTO, AETD).³⁸⁷ The total synthesis of microsclerodermins thereof appeared to us to be a stimulating challenge.

The objective of the research described in this thesis is the total synthesis of microsclerodermin D (Figure 32),³⁴⁴ which features the familiar 23-membered ring macrocyclic peptide of the microsclerodermin family, and contains six amino acids of which three are common: glycine (Gly), sarcosine (Sar) and (*R*)- γ -amino- β -hydroxybutyric acid (GABOB). The other three amino acids possess some structural particularities, but they can be classified as a chlorinated tryptophan (*R*-6-Cl-Trp), a polyhydroxylated β -amino acid (APTO) containing four contiguous stereogenic centers and the sensitive 3-amino-4-hydroxypyrrolidone-4-acetic acid (PyrAA). We planned to develop a modular synthetic route to microsclerodermin D which implicated a non-dehydrated pyrrolidinoacetic acid residue that could be applicable for the preparation of other microsclerodermin family members and analogues thereof.

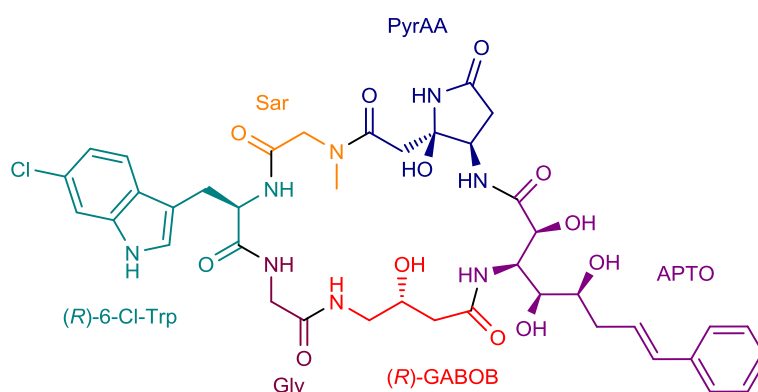
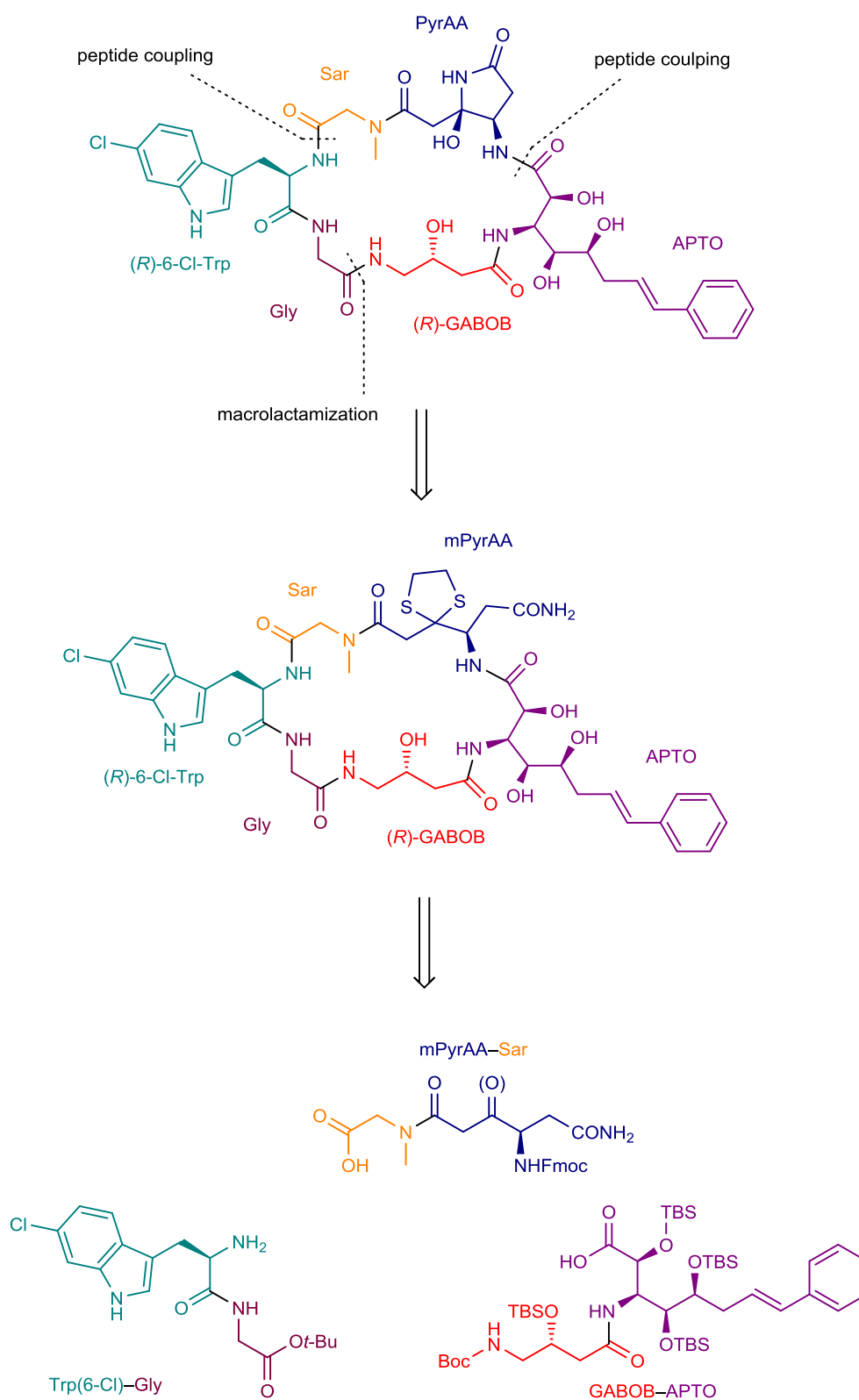


Figure 32: Microsclerodermin D, the target of the total synthesis in this thesis

The choice of microsclerodermin D as a target was based not only on the presence of the intact PyrAA residue, but on the fact that an efficient synthesis of a protected derivative of APTO is already available, thanks to an in-house methodology (See § 4.2.3.).³⁸⁷ The APTO fragment also exists in microsclerodermin C³⁴⁴ which present an additional aminocarbonyl group on the indole nitrogen of the tryptophan residue and in microsclerodermin L²⁶³ which possess an additional substituent on the pyrrolidinoacetic acid residue. Thus, it appeared to us that a synthetic route to microsclerodermin D should also provide a basis for a synthesis of microsclerodermins C and L.

We herein propose a convergent synthetic approach to microsclerodermin D in which the peptide backbone will be constructed from three dipeptide subunits instead of a stepwise manner, and macrolactamization will be performed between the glycine and GABOB residues, where there is little steric hindrance and since glycine can be activated without epimerization (non-chiral center). The major difficulty to be faced is that the hydroxypyrrolidinoacetic acid unit is highly sensitive and dehydrates easily in acidic or basic media. Our proposal is therefore to maintain this residue in a masked form all along the synthetic process and to liberate it in the very last step of synthesis, after formation of the macrocycle and deprotection of the different hydroxyl groups.

Thus, microsclerodermin D would be obtained by final-step deprotection of the masked pyrrolidinoacetic acid residue (mPyrAA) which is expected to undergo spontaneous cyclization (Scheme 33). The protected macrocyclic peptide would be prepared by peptide coupling between three appropriately protected dipeptides: mPyrAA–Sar, Trp(6-Cl)–Gly and GABOB–APTO. Glycine and GABOB residues would be advantageously protected by non-orthogonal groups in order to perform a single step deprotection before macrolactamization with a *t*-butyl ester and a *t*-butyl carbamate being the groups of choice. (*R*)-6-Chlorotryptophan would be prepared by adaptation of literature chemistry and few modifications of Shioiri's procedures for preparation of 2-carboxytryptophan,^{359,360} and a simple peptide coupling with glycine would produce the dipeptide Trp(6-Cl)–Gly. The synthesis of protected APTO residue has been successfully reported by the host group,³⁸⁷ and the synthesis of GABOB is already known in the literature and may require some adaptation of the protecting groups.⁴⁶⁸⁻⁴⁷⁰ The most challenging task would appear to be the construction of the dipeptide mPyrAA–Sar containing a masked equivalent of the pyrrolidinoacetic acid residue that can be carried all through the synthesis and then generate the pyrrolidinoacetic acid unit in the final-step of the synthesis without dehydration.



Scheme 33: Retrosynthetic approach to microsclerodermin D

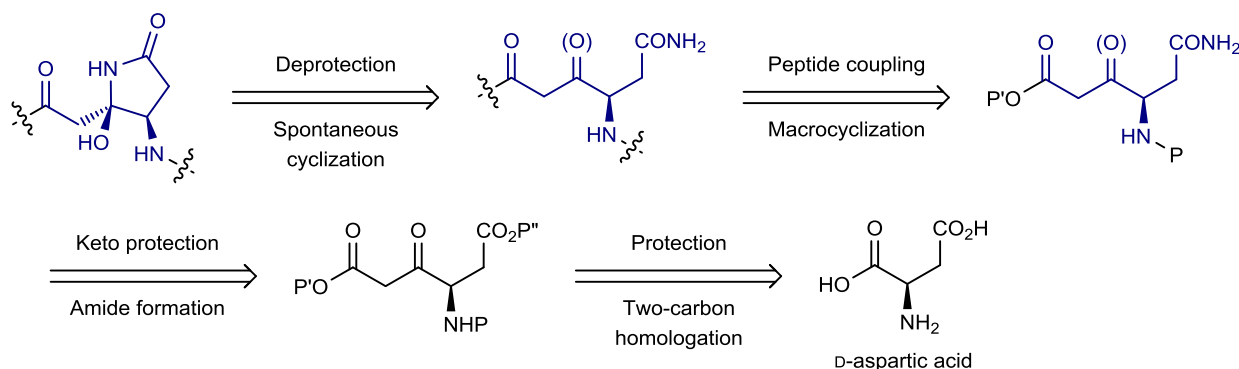
CHAPTER 2

DIPEPTIDE MASKED PyrAA–SARCOSINE: SYNTHESIS AND EVALUATION OF THE UNMASKING STRATEGY

1. Introduction

The success of our proposed total synthesis of microsclerodermin D depends on the ability to introduce the 3-amino-4-hydroxypyrrolidinoacetic acid residue (PyrAA) which is highly sensitive and dehydrates easily in acidic or basic media. To date, efforts toward the synthesis of any microsclerodermin presenting this residue have failed^{359,360} and even if Donohoe was able to establish a masking/unmasking strategy that proved to be valid on a tripeptide model, he was not able to reproduce this transformation on the macrocyclic peptide.^{439,440} Thus, only microsclerodermins E and J presenting a dehydrated PyrAA residue have been prepared.^{424,440} Thus, at the outset of this thesis, establishment of a synthetic access to this unit amenable on the macrocyclic peptide remains an unsolved challenge.

Considering the pioneering work of Shioiri^{359,360} and of Donohoe,^{439,440} we propose to maintain the PyrAA unit in a masked form all along the synthesis process and to liberate it in the very last step after formation of macrocyclic peptide (See Chapter 1, § 5, Scheme 33). This strategy requires the use of a linear precursor of the pyrrolidinoacetic acid residue presenting a primary amide function and a masked keto group (Scheme 34). It was expected that following unmasking of this latter group, spontaneous cyclization of the γ -ketoamide would occur (See Chapter 1, § 4.1.4, Scheme 5) and will be then exploited to install the pyrrolidinone ring by simple deprotection of the keto group. The macrocyclic precursor of microsclerodermin D bearing the masked pyrrolidinoacetic acid residue (mPyrAA) will be obtained by coupling of three dipeptides. Among them, the dipeptide mPyrAA–Sar will be prepared by coupling between appropriately protected mPyrAA and commercially available sarcosine. The mPyrAA residue will be derived from a



Scheme 34: Synthetic strategy to the pyrrolidinoacetic acid residue

γ -amino- β -ketoester which will be obtained from D-aspartic acid through two-carbon homologation of the carboxylic acid function. Although the use of D-asparagin is appealing, it was excluded as starting material since both the keto group and the amide function can't be present at the same time to avoid an unwanted spontaneous cyclization.

The choice of the keto protecting group is crucial to the success of our strategy. Transformations of ketones into ketals and dithioketals are among the most common methods to protect them. Since the keto group must be kept in a masked form all along the synthesis process and liberated in the very last step without the use of Brønsted base or acid (to avoid dehydration of the PrAA residue), dithioketals appeared as a good choice since they are stable in the presence of Brønsted base or acid (and therefore orthogonal to many protecting groups), and are usually deprotected by Lewis acids (such as HgCl_2/HgO), NBS or PIFA (Figure 33).

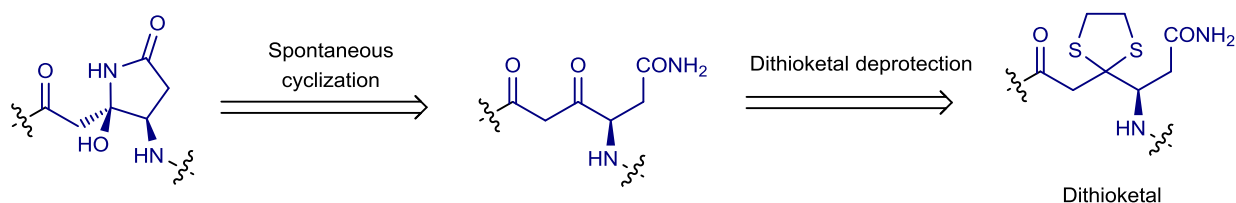
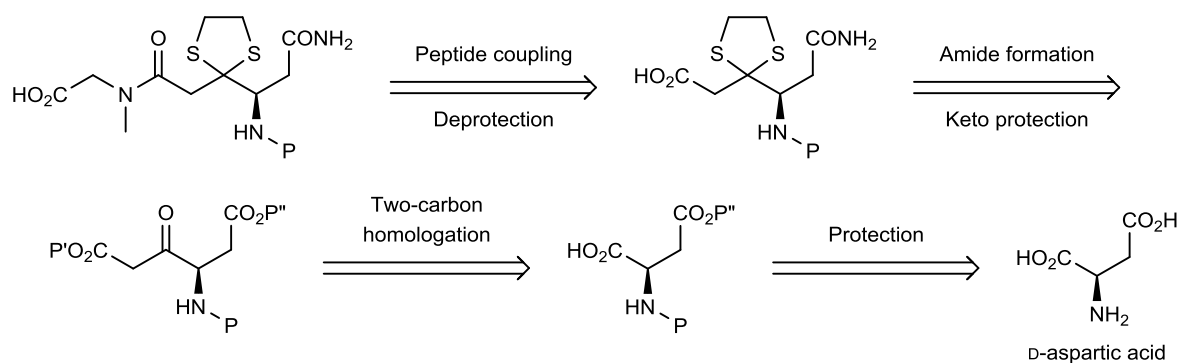


Figure 33: Choice of the keto protecting group

2. Synthetic strategy

Inspired by Shioiri's work,^{359,360} we set out to prepare a suitably functionalized derivative of mPyrAA from D-aspartic acid (Scheme 35). Thus, the dipeptide mPyrAA–Sar should be obtained by peptide coupling of a *N*-terminal protected mPyrAA derivative with sarcosine. This mPyrAA derivative should be obtained by transformation of the ester side chain into a primary amide and deprotection of the *C*-terminal ester group of an aminodiester derivative obtained by protection of the keto group as a dithioketal. The parent γ -amino- β -keto adipate should be obtained *via* a two-carbon homologation of an appropriately protected D-aspartic acid derivative following Masamune's procedure.³⁶⁶

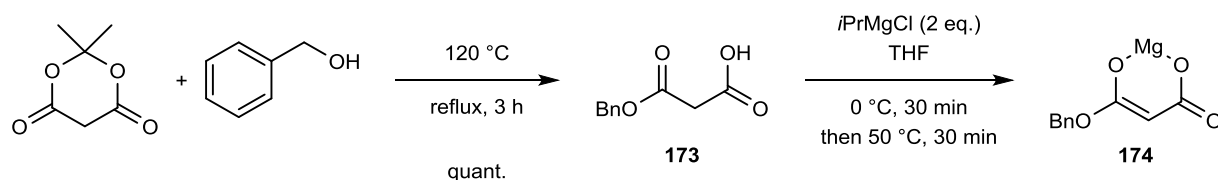


Scheme 35: Retrosynthetic analysis of the dipeptide mPyrAA–Sar

The proposed synthetic strategy excludes the use of certain protecting groups. Since formation of the dithioketal requires the use of Lewis acid, Boc and *t*-butyl ester which are removed in acidic medium can't be used. Moreover, since amide formation will be performed using ammonia, the Fmoc group is also excluded. Furthermore, orthogonal protecting groups for the two carboxylic acid functions are required. Taking into accounts all these parameters, our initial plan was to use a Cbz group to protect the amine function, a methyl ester for the aspartic acid side chain and a benzyl ester for second carboxylic acid function.

3. Synthesis of the *N*-Cbz protected pyrrolidinoacetic acid derivative

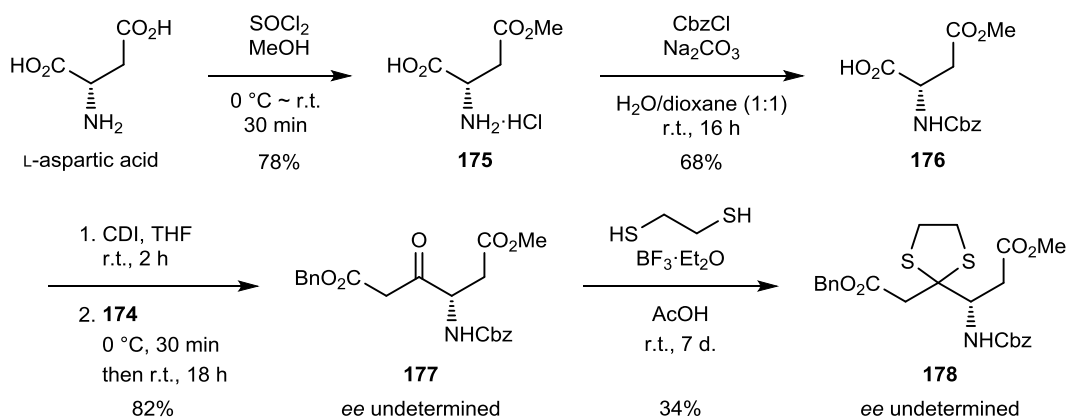
It was decided that the development of our synthetic strategy would be done using L-aspartic acid and once the synthesis had been optimized, the required pyrrolidinoacetic acid residue would be prepared from D-aspartic acid. As outlined above, the β -ketoester would be obtained *via* two-carbon homologation of an aspartic acid derivative under Masamune's conditions.³⁶⁶ This reaction employs the magnesium salt of a hemimalonate. Thus, monobenzylmalonate **173** was obtained quantitatively by treatment of Meldrum's acid with benzyl alcohol at 120 °C (Scheme 36).⁴⁷¹ The hemimalonate was then treated with 2 equivalents of isopropylmagnesium chloride to produce the corresponding magnesium enolate salt **174** which was used directly in the coupling reaction.⁴⁷²



Scheme 36: Preparation of the monobenzylmalonate magnesium salt

Regioselective esterification of the side chain of L-aspartic acid was performed by treatment of a suspension of this amino acid in methanol to give the methyl ester as the ammonium salt **175** in good yield (Scheme 37). Then the amino group was protected by treatment with benzyl chloroformate in the presence of a base to give the protected L-aspartic acid derivative **176** in reasonable yield.⁴⁷³ Activation of acid **176** using CDI followed by treatment with freshly prepared magnesium enolate **174** produced the γ -amino β -keto benzyl ester **177** in 82% yield (*ee* value undetermined). The next step consisted of the protection of the keto group as a dithioketal. We initially used classical conditions, using a slight excess of 1,2-ethanedithiol (1.5 eq.) and a catalytic amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.4 eq.) in dichloromethane.⁴⁷⁴ After some adaptations inspired by Fieser's conditions,^{475,476} we found that the reaction worked better in acetic acid as solvent, and the use of larger amounts of 1,2-ethanedithiol (3 eq.) and of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (5 eq.) added in 5 portions (every 2 days). Nevertheless, the reaction was sluggish and after one week at room temperature, the desired dithioketal derivative **178** was obtained in a poor 34% yield. All the starting material was consumed and we were able to detect about 40% yield of benzyl alcohol which clearly showed that extensive degradation occurred during the process. Heating the reaction mixture increased the degradation even over shorter reaction times. It appears that the Cbz group can also be deprotected under these conditions, in a similar way to the results of Thurston⁴⁷⁷ who reported the Cbz deprotection with ethanedithiol/ $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and Sánchez⁴⁷⁸ who observed the deprotection with $\text{Me}_2\text{S}/\text{BF}_3 \cdot \text{Et}_2\text{O}$ or 1,3-propanedithiol/ $\text{BF}_3 \cdot \text{Et}_2\text{O}$. Additionally, the keto group of the protected β -keto benzyl ester **177** is quite sterically hindered making its protection somewhat challenging.

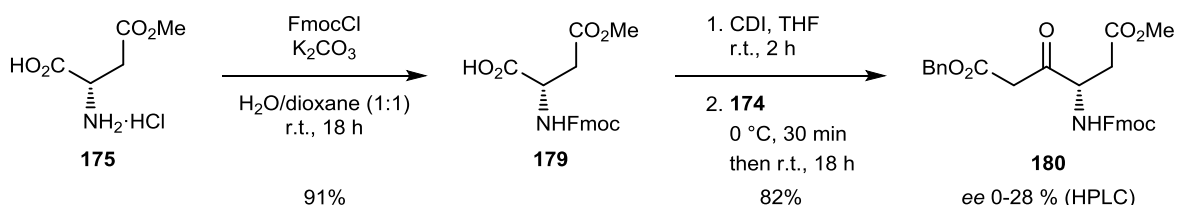
In summary, the use of the Cbz group to protect the amine function of aspartic acid was compromised due to its sensitivity to 1,2-ethanedithiol/ $\text{BF}_3 \cdot \text{Et}_2\text{O}$. Substrate **177** underwent extensive degradation and the desired dithioketal product was obtained only in low yield. It was decided to use a different protecting group.

Scheme 37: Preparation of *N*-Cbz protected dithioketal derivative

4. Synthesis of the *N*-Fmoc protected pyrrolidinoacetic acid derivative

4.1. Synthesis of the *N*-Fmoc- γ -amino- β -ketoester

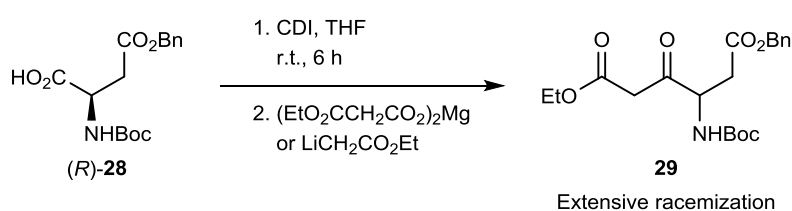
Since the Fmoc group is stable in acidic media and usually deprotected by organic bases (such as piperidine, pyridine, etc...), it should be stable under the dithioketal formation conditions (1,2-ethanedithiol/ $\text{BF}_3 \cdot \text{Et}_2\text{O}$). Thus, the L-aspartic acid derivative **175** was protected efficiently by a Fmoc group using FmocCl.⁴⁷⁹ The resulting protected amino acid **179**⁴⁸⁰ was submitted to the Masamune's procedure to form the γ -amino- β -ketoester **180** in 82% yield after optimization. Unfortunately, evaluation of the enantiomeric excess of this γ -amino- β -ketoester **180** by HPLC revealed an extensive racemization of the chiral center ($ee = 0\text{--}28\%$), and despite many attempts, we were not able to suppress the racemization phenomenon.

Scheme 38: Preparation of *N*-Fmoc γ -amino- β -ketoester

4.2. Origin of the racemization in the Masamune's protocol

Initially, this racemization was quite surprising since the Masamune's protocol has been the most commonly employed method for the synthesis of β -ketoesters, and among the thousands of papers and reports generated by many groups, no racemization was reported. In most cases, results were evaluated on the basis of NMR data, and sometimes optical rotation was measured, but no enantiomeric excess values were given. In the specific case of Shioiri's work dealing with the preparation of the pyrrolidinoacetic acid residue *via* Masamune's protocol there is no evidence of the obtention of optically pure benzyl β -ketoester.^{359,360} Moreover, in his work on the total synthesis of microsclerodermin E Ma mentioned that addition of an enolate to an aspartic acid derivative activated by *N,N'*-carbonyldiimidazole (CDI), *N*-hydroxysuccinimide (NHS) or pentafluorophenol (PFP) led to partial or full racemization.⁴²⁴ Thus, we came to the conclusion that the use of Masamune's protocol is not a reliable method for the preparation of optically pure β -ketoesters.

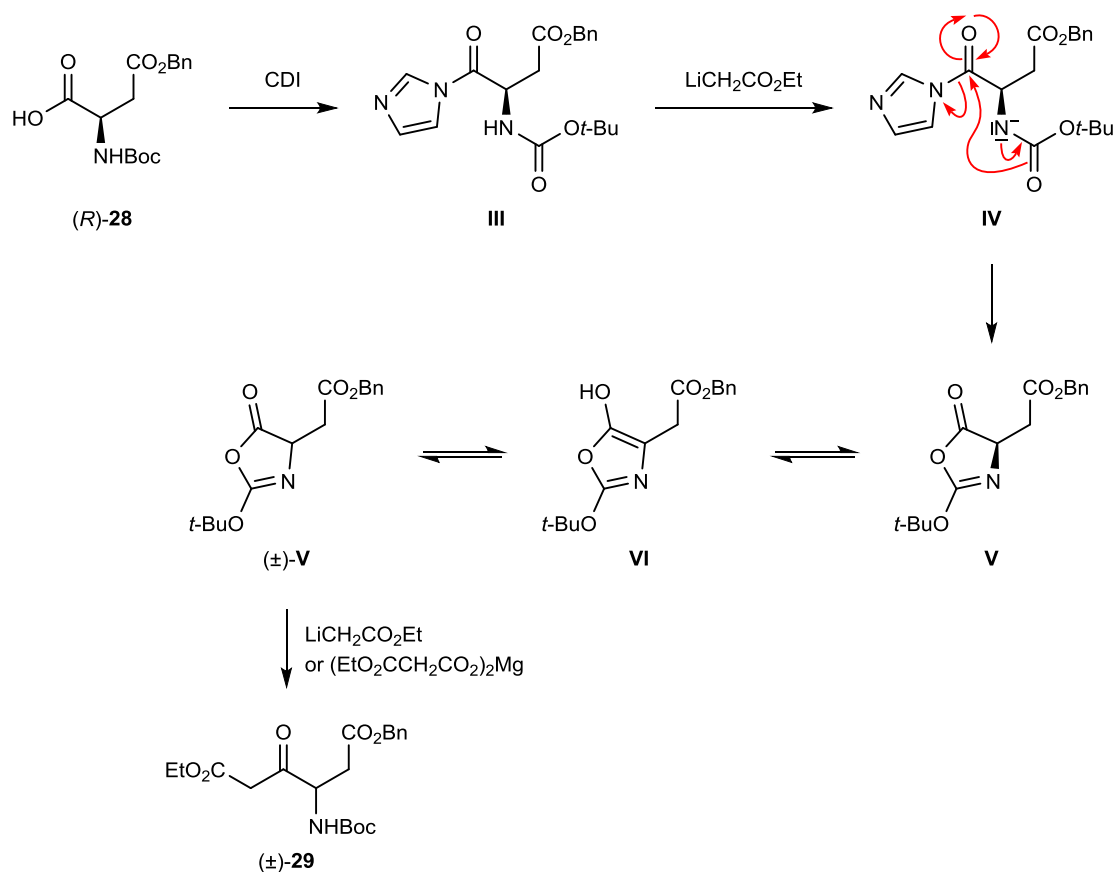
In Ma's published work,⁴²⁴ there are no details and no discussion on the reasons leading to partial or full racemization. However, Zhu's PhD manuscript⁴⁸¹ (Ma's PhD student working on the total synthesis of microsclerodermin E) was quite informative and revealed that they initially followed the work of Shioiri and thus used the Masamune's procedure. The acid was firstly activated by CDI, then treated with a magnesium hemimalonate or a lithium enolate reagent, and in all cases partially or fully racemic γ -amino- β -ketoester **29** was obtained after many tests (Equation 2).



Equation 2: Ma's preparation of γ -amino- β -ketoester *via* Masamune's protocol

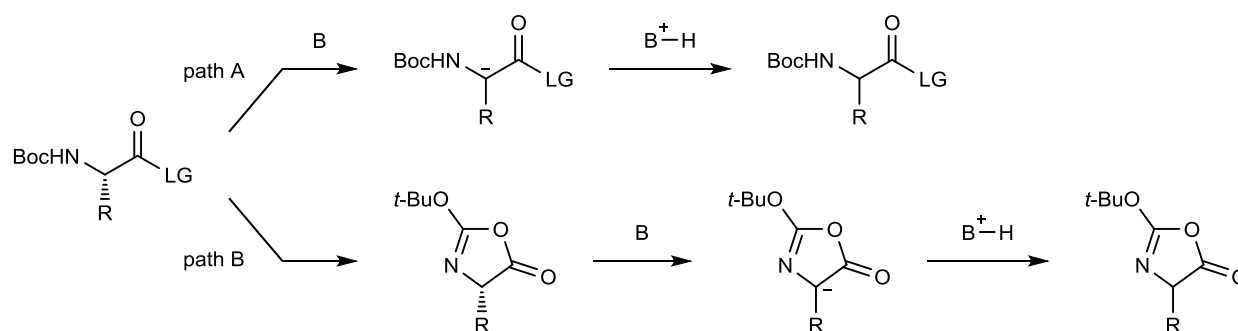
In his thesis, Zhu proposed a mechanism to explain this racemization (Scheme 39). Initially, activation of the *N*-Boc-D-aspartic acid derivative (*R*)-**28** by CDI gave the active *N*-acyl-imidazole intermediate **III**. The lithium enolate (or the magnesium hemimalonate) which was added was as a strong enough base to deprotonate the carbamate nitrogen to give the intermediate **IV**. This

deprotonation of the carbamate provokes the attack of the Boc group on the activated *N*-acyl-imidazole moiety to give the oxazolone **V**. Then enolization of this oxazolone into the oxazole **VI** occurred in the basic media and led to the loss of the stereogenic carbon. Finally, attack of the lithium enolate (or the magnesium hemimalonate) gave partially or fully racemic γ -amino- β -ketoester.



Scheme 39: Mechanism of the racemization during Masamune's procedure

Racemization of activated α -amino acids is a well-known problem in peptide chemistry and Goodman also proposed alternative pathways for the racemization *N*-Boc protected activated amino acids (Scheme 40).⁴⁸² Thus he proposed that the activated amino acid will be deprotonated in the α position by a base. Alternatively, an intramolecular reaction of the Boc group on the activated acid will result in the formation of an oxazolone that can be deprotonated by a base in the α position. In both cases reprotonation is not stereoselective and leads to racemization.

Scheme 40: Mechanism of racemization of activated α -amino acid

4.3. Synthesis of the masked PyrAA–Sar dipeptide

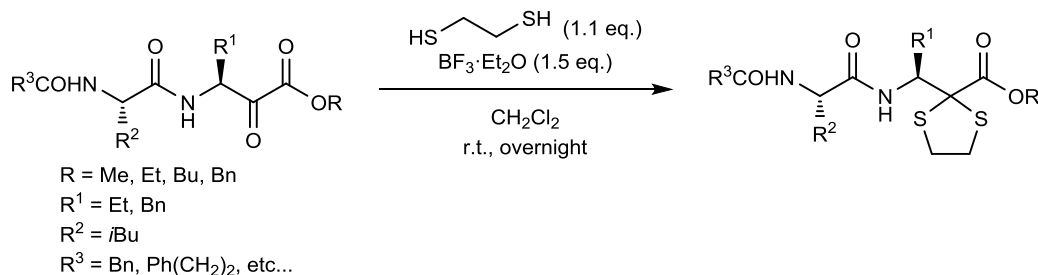
Although we were not able to access an enantiopure β -ketoester using Masamune's protocol, we decided to continue our development of this synthetic route to get the racemic dipeptide mPyrAA–Sar using partially racemized β -ketoester **180**. We reasoned that our strategy to install the hydroxypyrrolidinoacetic acid residue should be validated first, and if indeed this was the case. Of course, in the meantime we also set out to explore various possibilities to prepare the β -ketoester **180** in an enantioselective manner.

4.3.1. Dithioketal protection of the *N*-Fmoc protected benzyl β -ketoester

4.3.1.1. Dithioketal protection of ketones

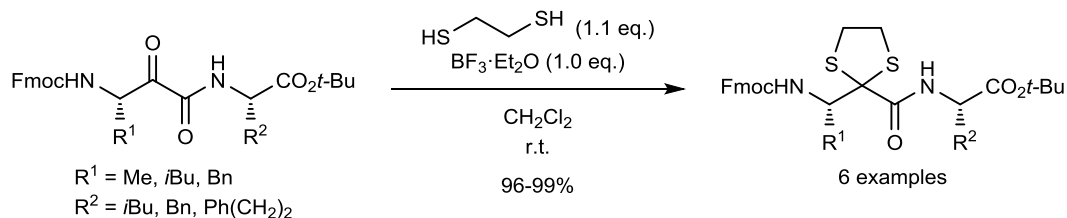
The dithioketal is a common protecting group for ketones. Since the 1950s, dithioketal protection of simple ketones was performed using 1,2-ethanedithiol/ $BF_3 \cdot Et_2O$ in acetic acid under Fieser's conditions,^{475,476} and it has been widely employed by many groups, such as Smith^{483,484} and Covey.⁴⁸⁵⁻⁴⁸⁷ It has also proved its efficiency for the protection of keto-peptides by Powers^{488,489} and Meldal.⁴⁹⁰ Dithioketal formation can be performed using various acid catalysts such as $BF_3 \cdot Et_2O$, *p*-TsOH, $SnCl_2$, $TiCl_4$, $Cu(OTf)_2$, $Sc(OTf)_3$ and others.

In one example, Powers^{488,489} reported a highly efficient conversion of α -ketoester dipeptides into dithioketals in excellent yield using 1,2-ethanedithiol in the presence of $BF_3 \cdot Et_2O$ in dichloromethane (Equation 3). These α -ketoesters dipeptides substrates appear to be really reactive, making the reaction efficient.



Equation 3: Powers's dithioketal protection of α -ketoesters dipeptides

In another example, Meldal⁴⁹⁰ reported a highly efficient conversion of α -ketoamide dipeptides into the corresponding dithioketals in excellent yield using 1,2-ethanedithiol in the presence of BF₃·Et₂O in dichloromethane (Equation 4).

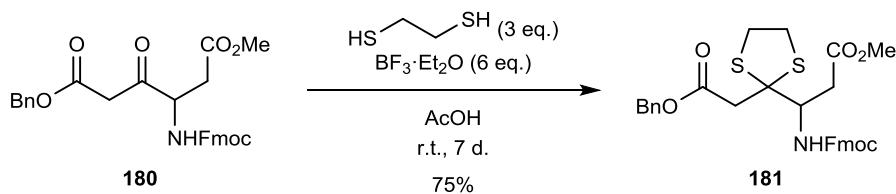


Equation 4: Meldal's dithioketal protection of α -ketoamides dipeptides

4.3.1.2. Protection of *N*-Fmoc protected benzyl β -ketoester

We studied the protection of the racemic β -ketoester **180** using 1,2-ethanedithiol. An initial experiment with a slight excess of 1,2-ethanedithiol (1.2 equivalent) and a catalytic amount of BF₃·Et₂O (0.5 eq.) in dichloromethane⁴⁷⁴ showed that the reaction was sluggish as it had been the case for the Cbz protected β -ketoester **177** and that although the desired product was observed, some degradation occurred. We varied the amount of 1,2-ethanedithiol and BF₃·Et₂O and the reaction temperature, but we obtained similar results. When the solvent was changed to acetic acid, we were able to obtain 50% yield of the expected dithioketal product **181** while 25% yield of starting material remained. In most cases, we often observed the formation of acetyl 1,2-ethanedithiol as a by-product. Further improvements were obtained by using a large amount of BF₃·Et₂O added in several portions, and finally we managed to get 75% yield of the product **181** by the use of larger excesses of 1,2-ethanedithiol (3 eq.) and of BF₃·Et₂O (6 eq.) added in 3 portions (every 2 days) (Equation 5). In this case almost all the starting material was consumed and less than 3% was detected by ¹H NMR. However, the reaction seemed to be difficult to reproduce and in

some cases the reaction just stopped, even when excess of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was added or after prolonged reaction time. Reaching a full conversion was really important since separation of the dithioketal **181** from the ketone **180** by column chromatography was extremely difficult.



Equation 5: Dithioketal protection of the *N*-Fmoc benzyl β -ketoester

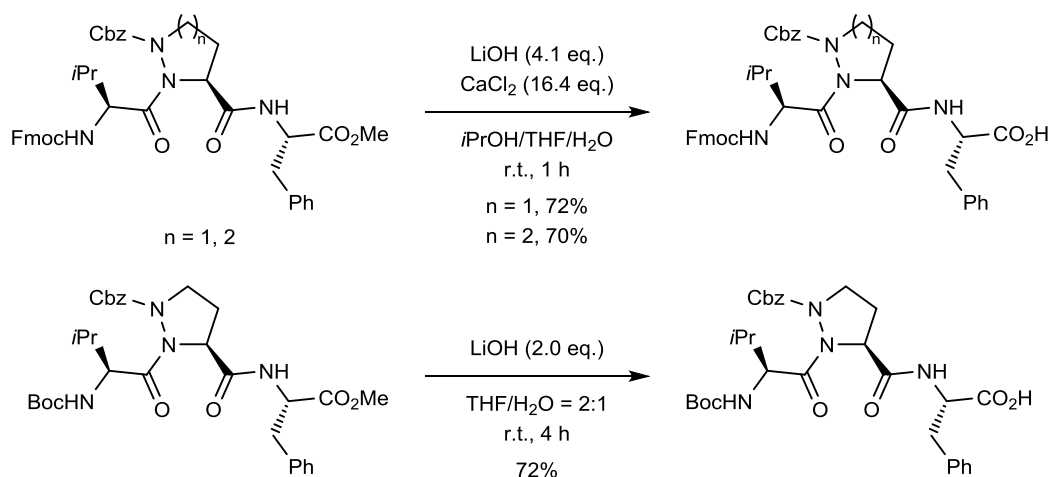
4.3.2. Access to the dipeptide mPyrAA–Sar

With dithioketal protected compound **181** in hand, access to the target dipeptide required a few more steps. First of all, the methyl ester should be transformed into a primary amide, the benzyl ester should then be deprotected to allow the final coupling with a protected derivative of sarcosine. Alternatively, the transformation of the methyl ester into the primary amide could be performed after peptide coupling.

4.3.2.1. Hydrolysis of methyl ester

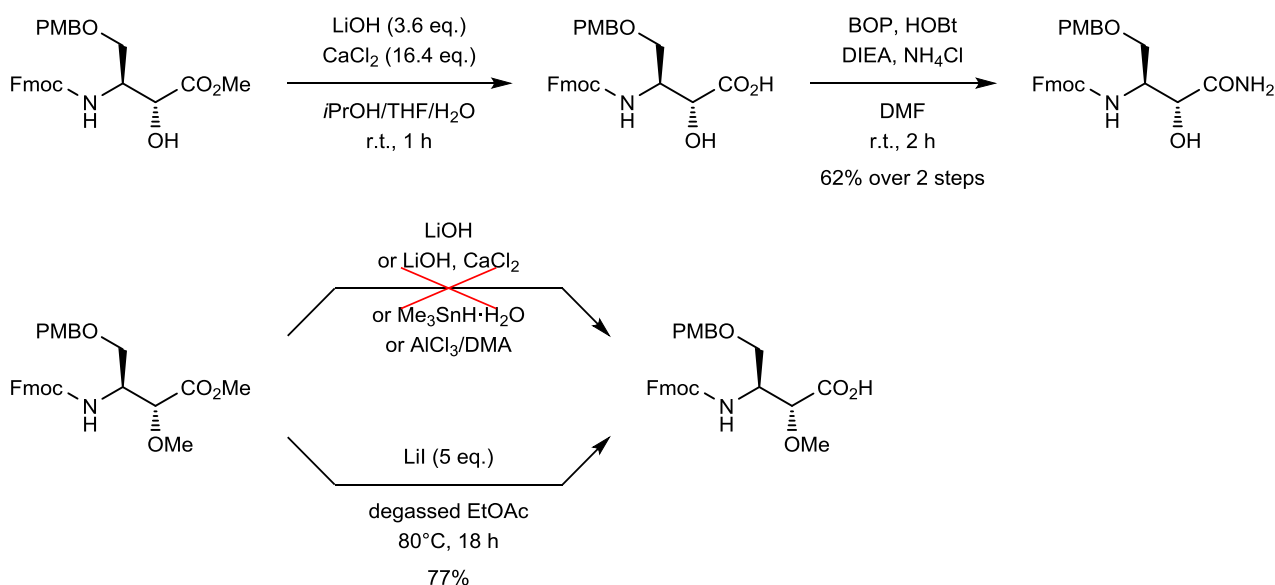
The success of the hydrolysis of the methyl ester depends on our ability to maintain the Fmoc protecting group. In 1998, Pascal⁴⁹¹ reported that *C*-terminal methyl esters could be easily removed without removing the Fmoc protecting group under alkaline conditions in the presence of CaCl_2 in an isopropanol/water mixture. The use of CaCl_2 dramatically increased the lifetime of the Fmoc protecting group and had little effect on the saponification processes with LiOH or NaOH.

This method was applied by Sinha⁴⁹² in 2016 to *N*-Fmoc protected tripeptide esters which were efficiently hydrolyzed with LiOH and concentrated CaCl_2 in an isopropanol/THF/water mixture (Scheme 41). As a comparison, treatment of the *N*-Boc analog with LiOH gave the acid in a similar yield, demonstrating the efficiency of the method developed by Pascal.



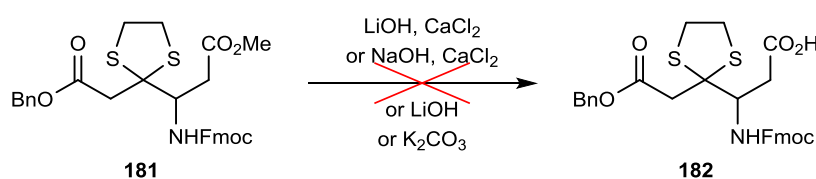
Scheme 41: Deprotection of methyl esters in the presence of a Fmoc group

In 2019, Taylor⁴⁹³ reported the sequential transformation of a methyl ester into a primary amide on a *N*-Fmoc protected substrate by saponification of the methyl ester with LiOH and concentrated CaCl₂ in an isopropanol/THF/water mixture followed by activation of the resulting acid using BOP/HOBt/DIEA, and treatment with NH₄Cl (Scheme 42). However, when the α -hydroxy group was replaced by a methoxy group, saponification of the methyl ester was very slow even at high CaCl₂ concentration, and did not work either with LiOH, trimethyltin hydroxide or AlCl₃/DMA. Efficient deprotection was achieved in good yield by lithium iodide mediated dealkylation *via* lithium ion coordination,⁴⁹⁴ in degassed ethyl acetate at 80 °C.



Scheme 42: Taylor's hydrolysis of *N*-Fmoc protected methyl esters

Based on Pascal's conditions⁴⁹¹ and Sinha's report,⁴⁹² the Fmoc protected substrate **181** was treated with LiOH in the presence of CaCl₂ but no saponification occurred. Most of the starting material was recovered and it failed to give the acid **182** (Equation 6). Replacing LiOH by NaOH gave the same results, and we observed complete degradation after prolonged reaction time. Even the use of LiOH without CaCl₂^{495,496} gave similar results. Seeking an alternative, we used a weak base, potassium carbonate in a THF/water mixture, but once again most of the starting material was recovered.



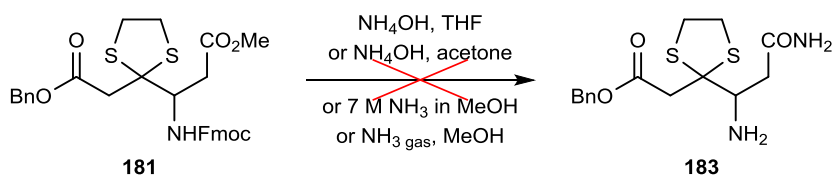
Equation 6: Methyl ester saponification attempts

The failure of the saponification reaction could be the result of a heterogeneous reaction mixture that impedes the reaction. Our substrate **181** possesses a large organic moiety that could considerably limit its solubility in an aqueous medium. Moreover, the methyl ester appears to be quite sterically hindered.

4.3.2.2. Conversion of the methyl ester into a primary amide

Since the hydrolysis of methyl ester **181** was unsuccessful, we then studied the direct conversion of the methyl ester into a primary amide. Direct ammonolysis of a methyl ester was usually achieved by treatment with NH₃, NH₄OH, or HCONH₄, but under these conditions the Fmoc group will also be deprotected.

To examine this eventuality, the methyl ester **181** was treated with 28% NH₄OH in THF or in acetone, with a solution of NH₃ in methanol or with gaseous ammonia (Equation 7). In all cases the starting material was completely consumed and we observed the deprotection of the Fmoc group (presence of DBF). However complex mixtures of products were obtained and we were not able to detect or isolate the expected primary amide **183**.

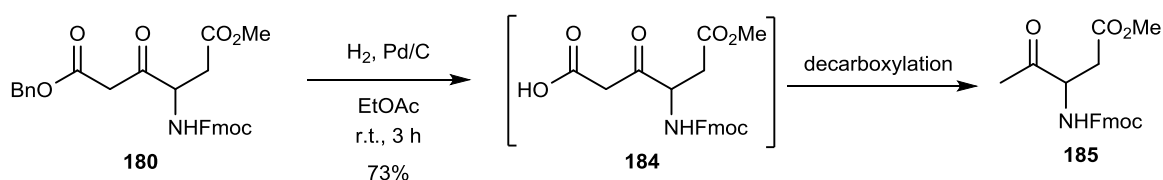


Equation 7: Direct conversion of the methyl ester into a primary amide

Since these results were not encouraging, we decided to modify our strategy and to install the primary amide at the dipeptide stage. This required the deprotection the benzyl ester before the peptide coupling.

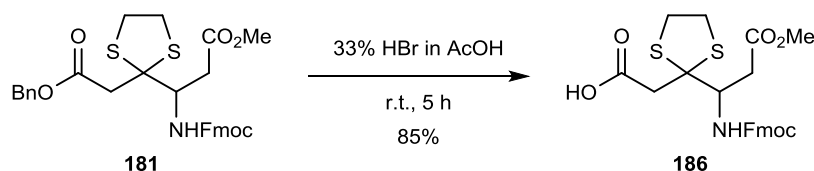
4.3.2.3. Deprotection of the benzyl ester

Since sulfur compounds often poison palladium catalysts, it was not reasonable to envisage the hydrogenolysis of the benzyl ester of dithioketal compound **181**. Thus, we examined the hydrogenolysis of the benzyl β -ketoester **180** over Pd/C. Unfortunately, we obtained the methyl ketone product **185** instead of the expected β -ketoacid **184** due to spontaneous decarboxylation (Scheme 43).



Scheme 43: Hydrogenolysis of the benzyl β -ketoester **180**

A literature search revealed that a benzyl ester can be deprotected using HBr in acetic acid.⁴⁹⁷ In the event, treatment of the *N*-Fmoc benzyl β -ketoester **181** using a 33% HBr solution in acetic acid produce 85% yield of *N*-Fmoc β -ketoacid **186** (Equation 8). The reaction had to be carefully controlled since both reaction time and substrate concentration affected the chemical selectivity between the benzyl ester and the methyl ester and traces of diacid by-product were often observed. Moreover, it should be noted that traces of ketone **180** as impurity in sample of **181** also gave some by-products that led to a difficult purification of **186**.



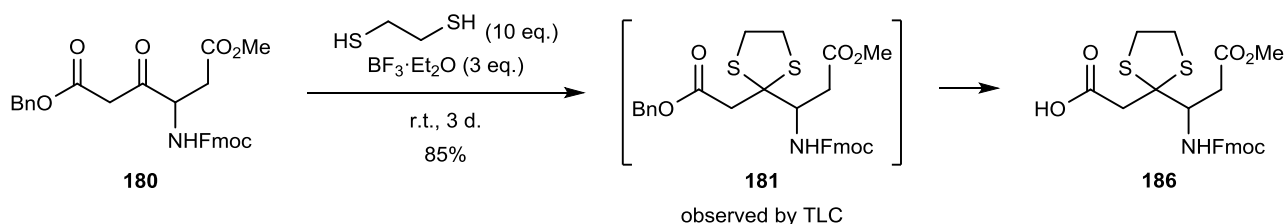
Equation 8: Deprotection of the benzyl ester using HBr in acetic acid

4.3.2.4. One-pot dithioketal formation and deprotection of the benzyl ester

While 2 sequential steps, dithioketal formation and benzyl ester deprotection with HBr, allowed the formation of the free acid **186** ready for coupling with sarcosine, the process presented different drawbacks:

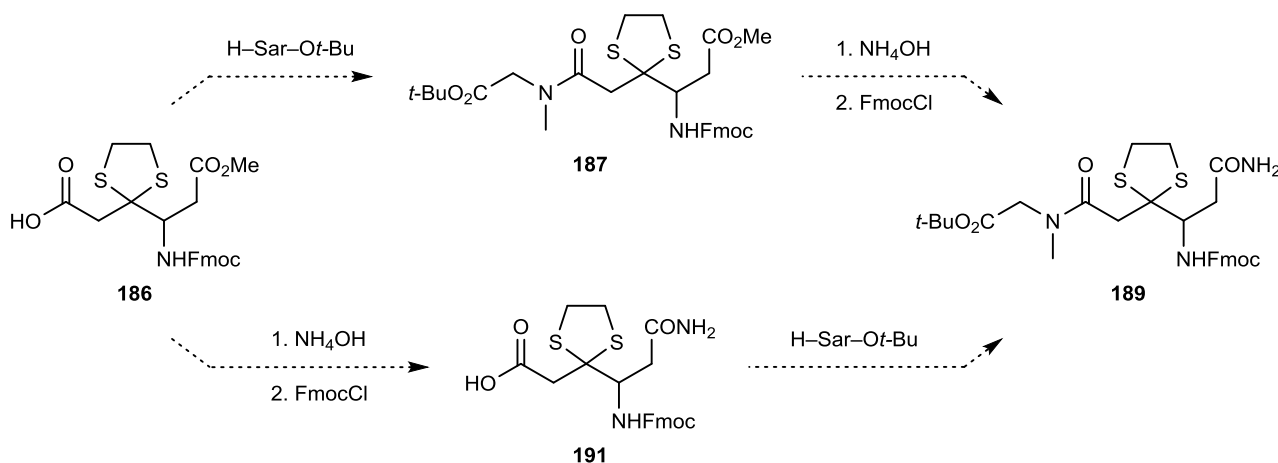
- the dithioketal formation generally requires 6 or 7 days to reach an acceptable conversion
- the dithioketal formation gave variable results and sometimes even the use of a larger excess of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or prolonged reaction time didn't allow full conversion, and the reaction stopped for no apparent reason.
- when the reaction was incomplete, the ketone **180** and the dithioketal **181** were very difficult to separate.
- traces of ketone **180** as impurity in sample of **181** gave some by-products during the benzyl deprotection

In order to address these problems, the dithioketal formation reaction was performed without solvent (Scheme 44). The use of a larger excess of 1,2-ethanedithiol (10 eq.) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (3 eq.) allowed us to obtain 85% yield of the *N*-Fmoc β -dithioketal acid **186** after only 3 days at room temperature. The reaction was followed by TLC and after 24 h we observed the formation of the intermediate dithioketal **181**, keto group protection therefore occurred before cleavage of the benzyl ester.



Scheme 44: One-pot dithioketal formation and benzyl deprotection

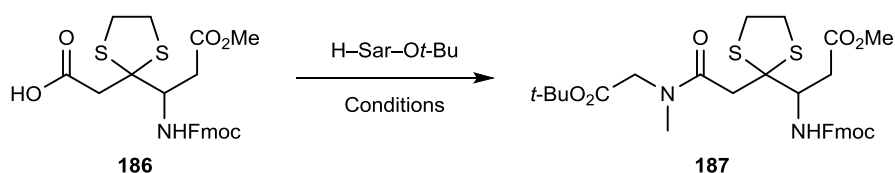
With *N*-Fmoc β -dithioketal acid **186** in hand, we continued our investigations to obtain the required mPyrAA–Sar dipeptide. The acid **186** can be engaged in the peptide coupling with sarcosine followed by installation of the primary amide or alternatively, the methyl ester could be converted into the primary amide before the coupling with sarcosine (Scheme 45).



Scheme 45: Alternative routes for the preparation of the mPyrAA–Sar dipeptide **189**

4.3.2.5. Peptide coupling and conversion of the methyl ester into a primary amide

Peptide coupling between acid **186** and *H*-Sar-*O*-*t*-Bu was examined using different coupling reagent (Table 4). When the coupling was operated using EDCI in the presence of DMAP, 60% yield of the expected dipeptide **187** was obtained (entry 1). However, when DIC was used instead of EDCI, the coupling gave only 40% yield of **187** together with diisopropylurea as an unseparable mixture (entry 2). Activation of the acid with HATU in the presence of DIEA gave 61% yield of the peptide **187** (entry 3) whereas the use of PyBOP in the presence of DMAP produced **187** in 69% yield (entry 4). Finally, the use of PyBroP in the presence of DIEA allowed the formation of the dipeptide **187** in an excellent 95% yield (entry 5).

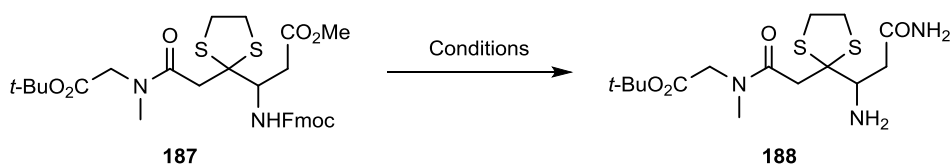


Entry	Conditions	Yield (%) ^a
1	EDCI (1.1 eq.), DMAP (3.0 eq.), CH ₂ Cl ₂ , r.t., 48 h	60%
2	DIC (1.1 eq.), NMM (2.0 eq.), CH ₂ Cl ₂ , r.t., 8 h	~40% ^b + Urea
3	HATU (1.5 eq.), DIEA (3.0 eq.), CH ₂ Cl ₂ /DMF, r.t., 8 h	61%
4	PyBOP (1.1 eq.), DMAP (3.0 eq.), CH ₂ Cl ₂ , r.t., 64 h	69%
5	PyBroP (1.1 eq.), DIEA (3.0 eq.), CH ₂ Cl ₂ , r.t., 20 h	95%

Notes: ^a Isolated yield; ^b Determined by ¹H NMR.

Table 4: Optimization of the peptide coupling between acid **186** with H-Sar-Ot-Bu

The next step was the conversion of the methyl ester into a primary amide. Dipeptide **187** was treated by various sources of ammonia (Table 5). In a first experiment (entry 1), the dipeptide **187** was treated with 28% NH₄OH in THF (1:1) and a very obvious phenomenon was observed at the beginning of the reaction (5-10 min): a white solid appeared at the surface of the solution, which we identified as dibenzofulvene (DBF). However, the reaction provided only unknown products along with 98% yield of DBF. Changing the solvent from THF to methanol (entries 2-3) allowed the formation of the amide in low yields after prolonged reaction times and increasing the proportion of methanol improved the yield. These reactions gave numerous unidentified by-products and the highly polar primary amide **188** was difficult to isolate in a pure form. Dipeptide **187** was then treated with an ammonia solution in methanol (entry 4) and after 5 days a complex mixture of products in which traces of amide **188** were observed by ¹H NMR. Using 28% NH₄OH in a THF/ethanol mixture (3:2) (entry 5) gave the 35% yield of the primary amide **188** after 4 days. In the last experiment, dipeptide **187** was treated sequentially with piperidine to first remove the Fmoc group, then 28% NH₄OH (entry 6), but once again only a complex mixture of products was obtained. Additionally, we observed that isolated sample of **188** underwent some degradation upon standing in CDCl₃ for NMR experiment recording. The amino primary amide **188** appears to be unstable, which partially explained the dirty reaction and low yields obtained for long reaction times. However, making a balance between conversion and degradation appears very difficult.

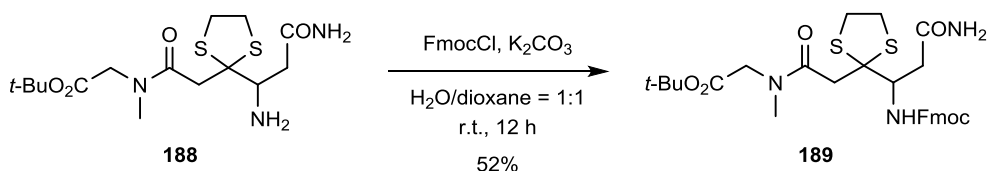


Entry	Conditions	Yield (%)	Results
1	28% NH ₄ OH/THF (1:1), r.t., 1 d.	–	Fmoc deprotection, unknown product
2	28% NH ₄ OH/MeOH (5:1), r.t., 4 d.	12	
3	28% NH ₄ OH/MeOH (3:2), r.t., 4 d.	17	
4	NH ₃ in MeOH, r.t., 5 d.	–	Fmoc deprotection, unknown product
5	28% NH ₄ OH/EtOH(3:2) r.t., 4 d.	35	
6	Piperidine, then 28% NH ₄ OH	–	Fmoc deprotection, complex mixture

Notes: ^a Isolated yield.

Table 5: Optimization of amide formation from dipeptide **187**

Since deprotection of the Fmoc group occurred during ammonolysis of the methyl ester, the dipeptide **188** was protected again using FmocCl in the presence of a base to give the protected dipeptide **189** in modest yield which was difficult to isolate in a pure form (Equation 9).

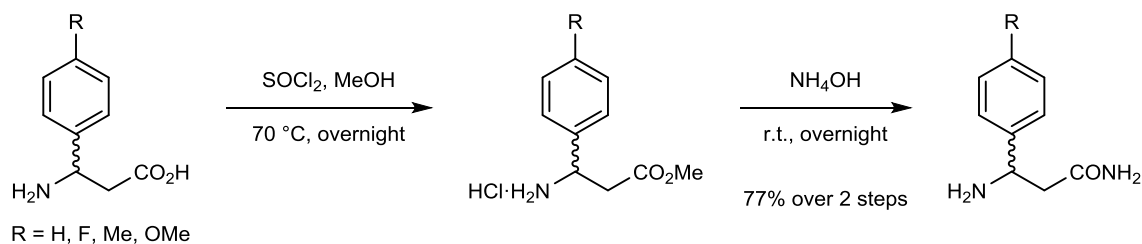


Equation 9: Protection of the aminodipeptide **188**

In summary, although coupling of **186** with sarcosine was successful, selective saponification of the methyl ester was not possible. Installation of the primary amide function by direct ammonolysis of **186** was accompanied by Fmoc deprotection, so a re-protection step was required. Thus, we were able to obtain the key dipeptide **189** in its racemic form in a rather low yield of 6.2% over 8 steps from aspartic acid. The last two steps are really limiting, characterized by poor yields, messy reaction and arduous purification.

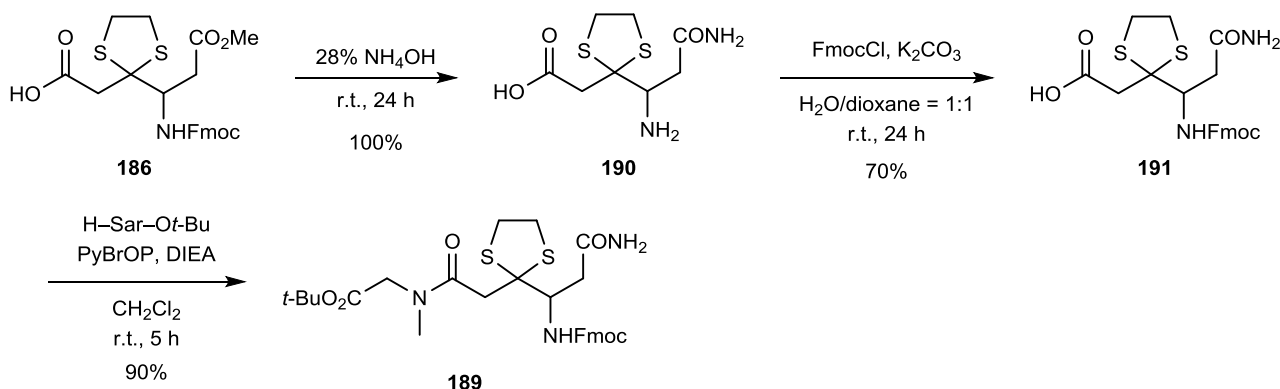
4.3.2.6. Conversion of the methyl ester into a primary amide and peptide coupling

The difficulties encountered during the formation of the primary amide at the dipeptide stage led us to reexamine the transformation of a methyl ester into a primary amide. In the literature, we noticed a facile synthesis of β -amino primary amides in good yield reported by Kim⁴⁹⁸ in which the hydrochloride salts of β -amino methyl esters were treated directly with NH_4OH (Scheme 46). We supposed that the reaction was facilitated by a good solubility of the substrate in NH_4OH .



Scheme 46: Kim's conversion of methyl esters into primary amides

Inspired by Kim's results, we considered the ammonolysis of the acid **186** (Scheme 47). Treatment of this compound with 28% NH_4OH gave the expected primary amide **190** in quantitative yield. The Fmoc group was then reinstalled under standard conditions and the resulting protected amino acid **191** was then coupled with sarcosine using PyBroP in the presence of DIEA to produce the key dipeptide **189** in excellent yield.



Scheme 47: Synthesis of key dipeptide **189** by ammonolysis followed by peptide coupling

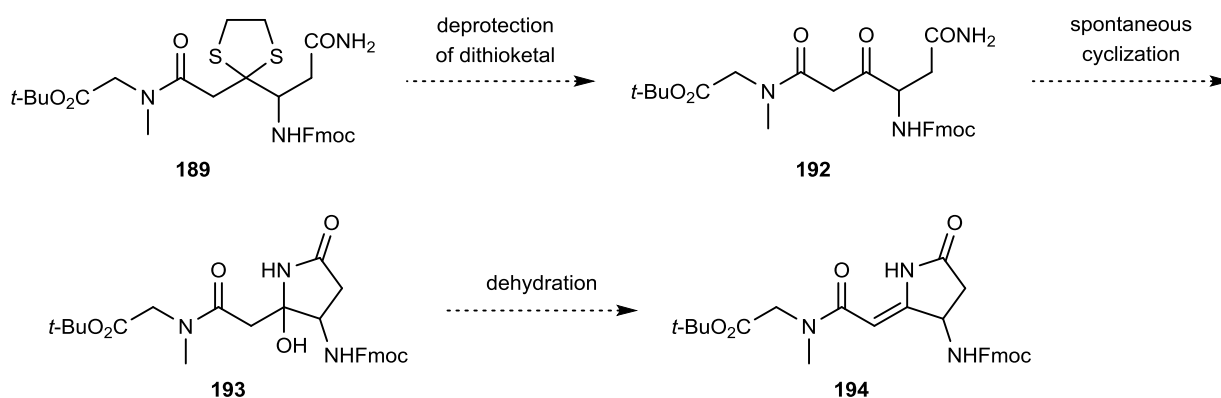
In summary, ammonolysis could be performed efficiently on the acid **186** and thus, after Fmoc re-protection, we were able to obtain the key dipeptide **189** in its racemic form in 22.6% yield over 8 steps from aspartic acid.

4.4. Deprotection of the dithioketal and spontaneous cyclization

Methods for the deprotection of thioketals into the corresponding carbonyl compounds have been extensively reviewed.⁴⁹⁹⁻⁵⁰⁵ The deprotection of a dithioketal can be achieved by three main pathways:

- acidic or transition metal ions hydrolysis (such as Hg^{+2} , Ti^{+4} , Ag^+ , Ce^{+4} , Cd^{+2})
- oxidative hydrolysis (NBS, PIFA, H_5IO_6 , I_2 , H_2O_2)
- alkylative hydrolysis (MeI, MeSO_3F)

With racemic key dipeptide **189** in hand, we were able to evaluate our proposed strategy for the installation of the PyrAA residue of microsclerodermin D (Scheme 48, Table 6). We expected that deprotection of the dithioketal of **189** would produce the intermediate γ -ketoamide **192** which should then cyclize spontaneously to give the hydroxypyrrolidone product **193**. Ideally, dehydration of compound **193** into the dehydrated dipeptide **194** should not occur.



Scheme 48: Overview of the deprotection followed by spontaneous cyclization strategy

First, some common conditions were attempted for deprotection of the dithioketal **189** (Table 6): the use of CAN (entry 1), iodine in the presence of NaHCO_3 (entry 2)^{506,507} and PIFA (entry 3)⁵⁰⁸ lead to extensive degradation and complex mixtures of unidentified compounds. We then turn our attention to use the mixture of mercury salts. The first report of the deprotection of a dithioketal into a carbonyl group using a mercury salt was presented by Fisher in 1894 in his work on sugars,⁵⁰⁹ and remains the most common method, partially due to its low cost and wide versatility. The reaction requires exactly 1.0 equivalent of Hg^{2+} per sulfur atom (*i.e.* 2 equivalent of HgCl_2 for the dithioketal), any less amount would not allow a complete reaction, whereas an excess

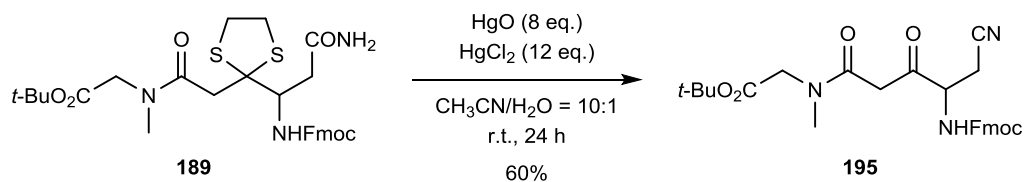
could lead to undesired solvent-mercuriation formation.⁵⁰⁵ Typically, the reaction is run in the presence of an excess of a mild base such as HgO or CaCO₃, in order to neutralize the HCl formed during hydrolysis.⁵⁰² The commonly used solvent medium is a mixture of acetonitrile or THF and water, but numerous early works reported the use of methanol and water.^{510,511} When dipeptide **189** was treated with HgO (3 eq.) and HgCl₂ (2 eq.) in a mixture of methanol and water (9:1) for 5 days, only the starting material **189** was recovered (entry 4). When larger amount of HgO (8 eq.) and HgCl₂ (12 eq.) were used 5 days, some degradation was observed but 60% of the starting material **189** remained intact (entry 5).^{499,510,511} Additionally, the reaction was also run in THF and water (8:2) for 24 h, and 93% of the starting material **189** was recovered (entry 6). We attributed the failure of the use of mercury salts to a strong affinity of primary amide with mercury ion, which has been explained and evidenced by Leopold⁵¹² and Sease.⁵¹³ This strong affinity probably led to the formation of a Hg-amide complex that precipitate resulting in no reaction. However, interestingly, when changing the solvent for a mixture of acetonitrile and water, the reaction provided 10% yield of the dehydrated compound **194** and 60% of a by-product, the nitrile **195**, after 24 h (entry 7) (Equation 10). We proposed that the formation of **195** resulted from the dehydration of the primary amide catalyzed by HgCl₂ similarly to the PdCl₂ catalyzed dehydration of primary amides in aqueous acetonitrile proposed by Maffioli in 2005.⁵¹⁴ Subsequently, NBS was used for the deprotection of dithioketal. When dipeptide **189** was treated with NBS in the presence of AgNO₃ and Na₂CO₃ in a mixture of acetonitrile and water (entry 8)⁵¹⁵ no starting material was observed but an unidentified product was obtained. We supposed that a Hofmann rearrangement⁵¹⁶ of the amide occurred because of the presence of water in a weakly basic medium since Ivanović has recently reported a NBS-mediated Hofmann rearrangement of carboxamides.⁵¹⁷ Then, treatment with NBS alone in acetone followed by quenching with water and purification on a very short chromatography gave 44% of the γ -ketoamide **192** accompanied with 5% of the dehydrated dipeptide **194** (entry 9).⁵⁰⁶ This result was encouraging since the formation of compound **194** indicated that deprotection of the dithioketal and cyclization occurred indeed, but slowly. This NBS procedure was repeated and a solution of the crude product mixture was stirred in the presence of silica gel for 24 h to provide gratifyingly the desired PyrAA dipeptide **193** in 33% yield along with 5% of the dehydrated dipeptide **194** (entry 10). ROESY NMR experiment revealed a *cis* relationship between the carbamate and hydroxyl substituents in position 4 and 5 of the pyrrolidinone ring as observed by Dohonoe in 2017.⁴³⁹ This NBS procedure was repeated again and the crude product mixture was

eluted through a neutral alumina column, this time providing the desired PyrAA dipeptide **193** in 29% yield accompanied by only traces of dehydrated dipeptide **194** (entry 11). In order to obtain sufficient quantities of reference material, a sample of crude NBS reaction product was treated with 4 M HCl in acetone for 24 h furnishing 40% yield of the dehydrated dipeptide **194** as the main product (entry 12).

Entry	Conditions	Results/Yield ^a
1	CAN (4.0 eq.), CH ₃ CN/H ₂ O (4:1) r.t., 3 h	Degradation Fmoc deprotection
2	I ₂ (7.0 eq.), NaHCO ₃ (8.5 eq.), acetone/H ₂ O (5:1) r.t., 48 h	Complex mixture Traces of 189
3	PIFA (3.0 eq.), CH ₃ CN/H ₂ O (10:1) r.t., 15 min	Degradation
4	HgO (3 eq.), HgCl ₂ (2 eq.), CH ₃ OH/H ₂ O (9:1) r.t., 5 d.	No reaction 189 recovered
5	HgO (8 eq.), HgCl ₂ (12 eq.), CH ₃ OH/H ₂ O (9:1) r.t., 5 d.	Some degradation 189 60%
6	HgO (8 eq.), HgCl ₂ (12 eq.), THF/H ₂ O (8:2) r.t., 24 h.	No reaction 189 93%
7	HgO (8 eq.), HgCl ₂ (12 eq.), CH ₃ CN/H ₂ O (10:1) r.t., 24 h	194 10% 195 60%
8	NBS, AgNO ₃ /Na ₂ CO ₃ , CH ₃ CN/H ₂ O (8:2) 0 °C, 10 min	Unknown product
9	1. NBS, acetone, 0 °C, 40 min, then H ₂ O 2. Very short flash on silica	192 44% 194 5%
10	1. NBS, acetone, 0 °C, 40 min, then H ₂ O 2. Silica, MeOH, r.t., 24 h	193 33% 194 5%
11	1. NBS, acetone, 0 °C, 40 min, then H ₂ O 2. Neutral aluminum chromatography	193 29% 194 traces
12	1. NBS, acetone, 0 °C, 40 min, then H ₂ O; 2. 4 M HCl, acetone, r.t., 24 h	194 40%

Notes: ^a Isolated yield.

Table 6: Deprotection of dithioketal and spontaneous cyclization

Equation 10: Dithioacetal deprotection with HgO/HgCl₂ in aqueous acetonitrile

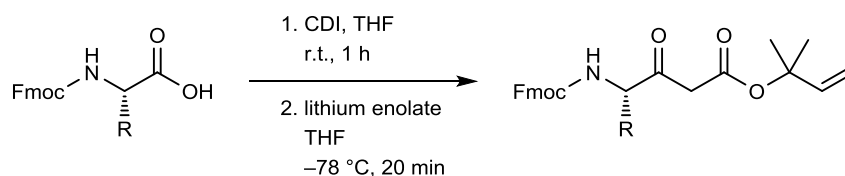
Herein, the deprotection of dithioacetal then cyclization sequence was successfully validated by treatment of dipeptide **189** with NBS. This encouraging result confirmed the potential of our proposed strategy to install the hydroxypyrrolidinoneacetic acid residue for the total synthesis of microsclerodermin D by the deprotection of dithioacetal then cyclization sequence.

4.5. Access to optically pure β-ketoester

Since we had successfully validated our mPyrAA strategy using a model substrate, we returned to solve the problem of the preparation of β-ketoester **180** as enantiomerically pure material. Racemization occurred during the Masamune's procedure between the activated aspartic acid derivative and the magnesium hemimalonate although this latter reagent was reported to be neutral.

Racemization of α-amino acids derivative is a common issue in peptide synthesis and can occur in the presence of various activating reagents, such as SOCl₂, CDI, NHS, PFP, IPCF, DIC, DCC and even HATU, HBTU. However, in many cases the racemization can be controlled.

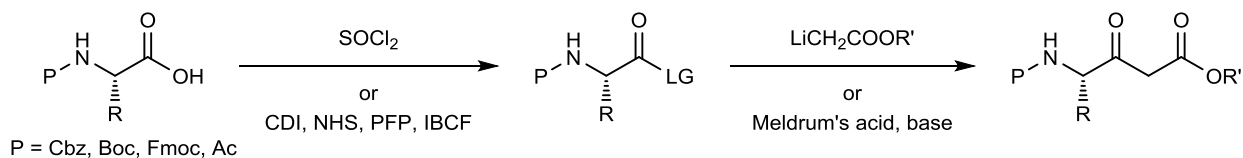
β-Ketoesters are commonly obtained *via* cross-Claisen condensation on *N*-Boc or *N*-Cbz protected amino acids, or by addition of a lithium enolate (or a magnesium hemimalonate) on *N*-Fmoc-amino acid derivatives.^{518,519} In 2015 Maillard developed a short route to heterocyclic γ-amino acids from *N*-Fmoc protected γ-amino-β-ketoesters which were obtained *via* cross-Claisen condensation of lithium enolates on *N*-Fmoc-amino acids (Table 7).⁵²⁰ Compared to neutral magnesium hemimalonates, lithium enolates are more basic, and thus more likely to induce racemization of α-amino acid derivatives.



Entry	Fmoc-AA-OH	γ -amino- β -ketoester yield (%)
1	Fmoc-L-Leu-OH	73
2	Fmoc-Gly-OH	59
3	Fmoc-L-Ala-OH	80
4	Fmoc-L-Phe-OH	66
5	Fmoc-L-Lys(Boc)-OH	55
6	Fmoc-L-Glu(<i>t</i> -Bu)-OH	53
7	Fmoc-L-Aps(<i>t</i> -Bu)-OH	72
8	Fmoc-L-Cys(Trt)-OH	45
9	Fmoc-L-Trp(Boc)-OH	49
10	Fmoc-L-Arg(Pbf)-OH	34

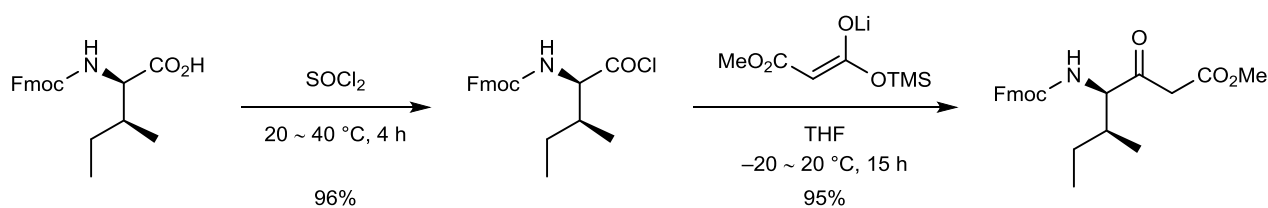
Table 7: Maillard's preparation of *N*-Fmoc protected γ -amino- β -ketoesters

Since Claisen condensation⁵²¹ was discovered more than a century ago, β -ketoesters have become a very significant class of intermediates in organic synthesis. To date, cross-Claisen condensations of activated carboxylic acids (or esters) with a lithium enolate or Meldrum's acid is still a classic and common pathway to generate β -ketoesters and γ -amino- β -ketoesters (Scheme 49).^{518,520,522,523}

Scheme 49: Common approaches to β -ketoester *via* activation of α -amino acids

The *N*-Fmoc protected amino acids are of increasing importance in peptide synthesis, especially solid-phase peptide synthesis.^{520,524-529} In his work on the total synthesis of didemmins, Schmidt^{530,531} claimed that treatment of Fmoc-alloisoleucine chloride with the lithium enolate of methyl trimethylsilylmalonate furnished the corresponding enantiopure *N*-Fmoc protected

β -ketoester, which was based on Carpino's results (Scheme 50).⁵³² However, only optical rotation data was provided, and the enantiomeric excess was not reported.



Scheme 50: Schmidt's preparation of *N*-Fmoc protected β -ketoesters

Several methods for preparation of the *N*-Fmoc β -ketoester **180** in its optically pure form were systematically explored in order to secure an alternative to the Masamune's procedure, as we presented below.

4.5.1. Direct condensation of a Weinreb amide with a lithium enolate

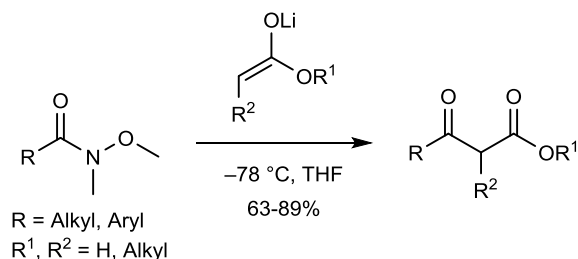
Historically, Weinreb amides have been used for synthesis of ketones through treatment with a Grignard reagent (or an alkyllithium or a lithium enolate), and few examples of the preparation of β -ketoesters have been reported. The two common approaches to convert Weinreb amides into ketones are:

- reduction of Weinreb amides into aldehydes with LiAlH_4 ,⁵³³⁻⁵³⁷ followed by treatment with a lithium enolate or a Grignard reagent, and final oxidation^{538,539}
- direct displacement using an alkyllithium reagent⁵³⁴ or a Grignard reagent^{540,541}

In our case, since we required to keep the methyl ester on the side chain, reduction of the corresponding Weinreb amide into an aldehyde with LiAlH_4 seemed likely to pose the problem of selectivity between Weinreb amide and methyl ester. Thus, direct displacement by treatment with a lithium reagent or a Grignard reagent appeared to be a more promising approach.

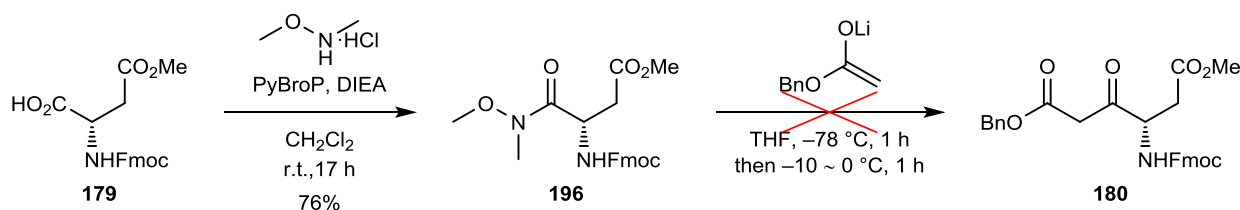
After perusal of literatures, we found that most Weinreb amides derived from *N*-Cbz, *N*-Boc or *N*-Ac α -amino acids^{534,541-544} were used to provide ketones by treatment with Grignard or alkyllithium reagents. In 1989, Turner⁵⁴⁵ reported an effective synthesis of β -ketoesters by treatment of Weinreb amides of simple carboxylic acids with lithium enolates (Equation 11). However there

are no cases of the preparation of β -ketoesters by treatment of Weinreb amides derived from *N*-protected α -amino acids with lithium enolates. A few cases of Weinreb amides derived from *N*-Fmoc α -amino acids were found to have applications in solid-phase reactions.⁵²⁶⁻⁵²⁸



Equation 11: Conversion of Weinreb amides into β -ketoesters

The protected amino acid derivative **179** was converted into the corresponding Weinreb amide **196** by treatment with *N,O*-dimethylamine hydrochloride using PyBroP in the presence of DIEA (Scheme 51).⁵³⁷ Treatment of this Weinreb amide with the lithium enolate of benzyl acetate gave a complex mixture of unidentified products, but cleavage of the Fmoc group was observed.

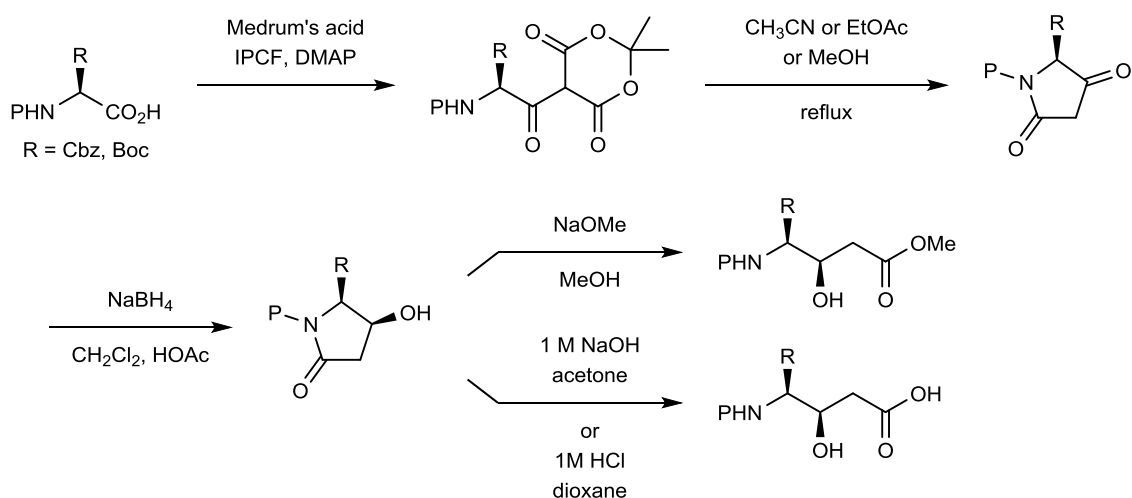


Scheme 51: Attempt of the preparation of β -ketoester by addition of an enolate on a Weinreb amide

4.5.2. Coupling with Meldrum's acid followed by treatment with benzyl alcohol

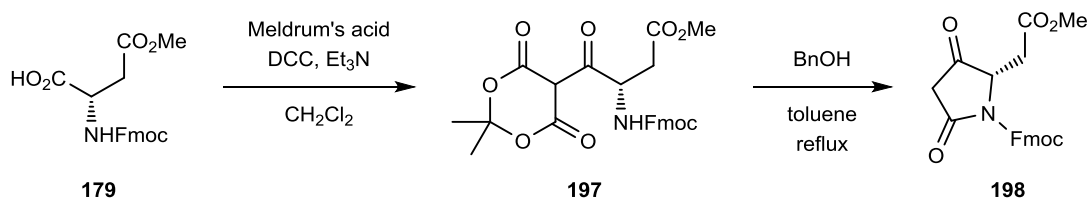
Early in 1982, Yonemitsu⁵⁴⁶ reported that acylation of Meldrum's acid derivatives could be used for the synthesis of β -ketoesters by condensation of acid chlorides. In 1987, Jouin⁵⁴⁷ reported a facile approach to *N*-protected (Cbz or Boc) statines and their analogues *via* chiral tetramic acid derivatives (Scheme 52). The main step consisted in the condensation of α -amino acids with Meldrum's acid using IPCF in the presence of DMAP. The unstable intermediate thus obtained underwent decarboxylation and cyclization in refluxing acetonitrile or ethyl acetate, and even in methanol to give the cyclic tetramic acid derivatives instead of the expected γ -amino- β -ketoesters.

Thus, reduction of the keto group followed by methanolysis or hydrolysis produced the corresponding γ -amino- β -hydroxyesters or γ -amino- β -ketoesters.



Scheme 52: Jouin's condensation of α -amino acids with Meldrum's acid

Based on the above results, we explored the preparation of the β -ketoester **180** via the Meldrum's acid route. Since activation of α -amino acids using CDI led to partial racemization, we preferred the use of other coupling reagents to perform the coupling the aspartic acid derivative **179** with Meldrum's acid. In a first experiment using EDCI in the presence of trimethylamine, we observed only degradation and some cleavage of the Fmoc group. Changing EDCI for DCC gave the unstable intermediate **197** (mixed with DCU) which was not purified and then treated directly with benzyl alcohol in refluxing toluene (Scheme 53). Unfortunately, we only obtained the unwanted tetramic acid derivative **198** as the side product instead of the expected benzyl γ -amino- β -ketoester. The formation of this cyclization product was not a surprise and corresponds to the results reported previously by different research groups.⁵⁴⁷⁻⁵⁵¹

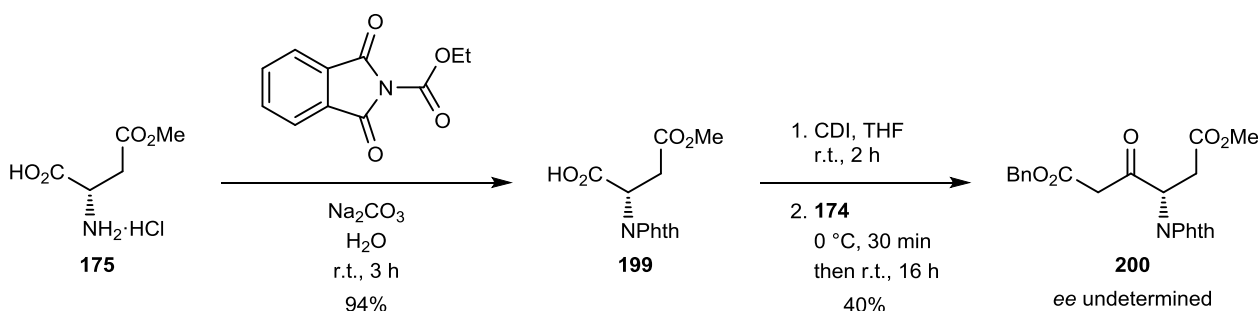


Scheme 53: Attempt of the preparation of β -ketoester by coupling with Meldrum's acid

4.5.3. Use of *N*-Phth protected substrate in the Masamune's procedure

In his total synthesis of microsclerodermin E, Ma attributed the low enantiomeric excess of the γ -amino- β -ketoester prepared *via* the Masamune's procedure on the CDI activated Boc-amino acid to the presence of a free proton on the carbamate, which led to racemization in basic medium.⁴²⁴ To preclude this process, we envisaged the protection of the amino group of aspartic acid as a phthalimide.

The aspartic acid derivative **175** was treated with *N*-carbethoxyphthalimide to produce the phthalimido derivative **199** in excellent yield (Scheme 54).⁵⁵² Then Masamune's reaction of **199** with magnesium enolate **174** gave the β -keto- γ -phthalimidoester **200** in modest yield.⁵⁵³ The racemic material was also prepared *via* the same synthetic route.⁵⁵⁴ However, we were unable to achieve the separation of the enantiomers upon chiral HPLC analysis of the racemic material (\pm)-**200** and therefore we were unable to evaluate a possible racemization in sample **200** prepared from non-racemic **175**.

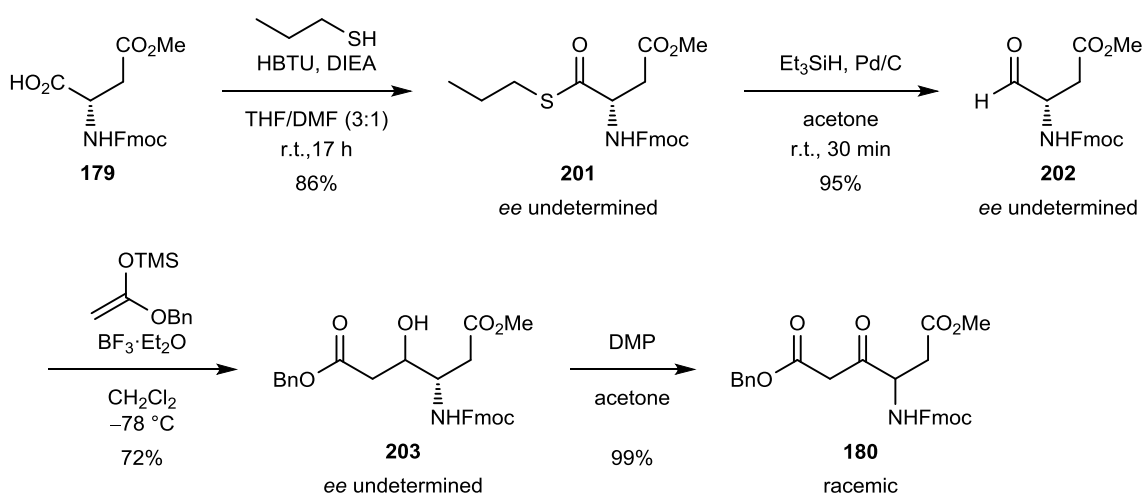


Scheme 54: Use of a *N*-Phth protected substrate for the preparation of benzyl β -ketoester

4.5.4. Through Mukaiyama aldol condensation followed by oxidation

Alternatively, the β -ketoester could be installed by oxidation of the corresponding β -hydroxyester. Thus, a possible pathway would be the reduction of the acid into an aldehyde followed by an aldol condensation then oxidation of the alcohol into a ketone. α -Amino aldehydes are prone to racemization and the method to prepare them is really important, among the various methods developed to avoid epimerization, two possibilities emerge: reduction of a Weinreb amide with LiAlH_4 or Fukuyama reduction of a thioester with triethylsilane in the presence of palladium.

The aspartic acid derivative **179** was coupled with propanethiol using HATU in the presence of DIEA to give the protected thioester **201** in good yield (Scheme 55).⁵⁵⁵ Fukuyama reduction⁵⁵⁶⁻⁵⁶² of the thioester **201** was performed with Et₃SiH over Pd/C produced the aldehyde **202** in excellent yield (*ee* undetermined). This aldehyde was then submitted to a Mukaiyama aldol reaction⁵⁶³⁻⁵⁶⁹ to provide the γ -amino- β -hydroxyester **203** in 72% yield (*ee* undetermined)⁵⁷⁰ which was then submitted to Dess-Martin oxidation^{383,571} to furnish the desired benzyl γ -amino- β -ketoester **180** near-quantitatively.⁵⁷² However, chiral HPLC analysis revealed that complete racemization had occurred.



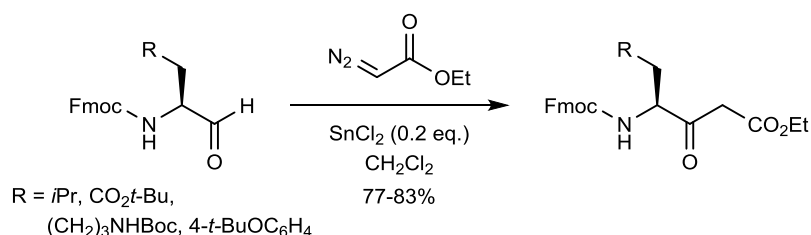
Scheme 55: Preparation of benzyl γ -amino- β -ketoester through a thioester

Both the purified aldehyde and crude aldehyde **202** were submitted to the Mukaiyama aldol reaction, with the same racemization results. Since the enantiomeric excess of the intermediates **201**, **202** and **203** were not evaluated we can't be sure at which step racemization happened. We suspect that it occurred during the Mukaiyama aldol reaction, since the aldehyde **202** was activated by BF₃·Et₂O and this coordination probably led to enolization and further epimerization.

4.5.5. Homologation of an aldehyde through the Roskamp reaction

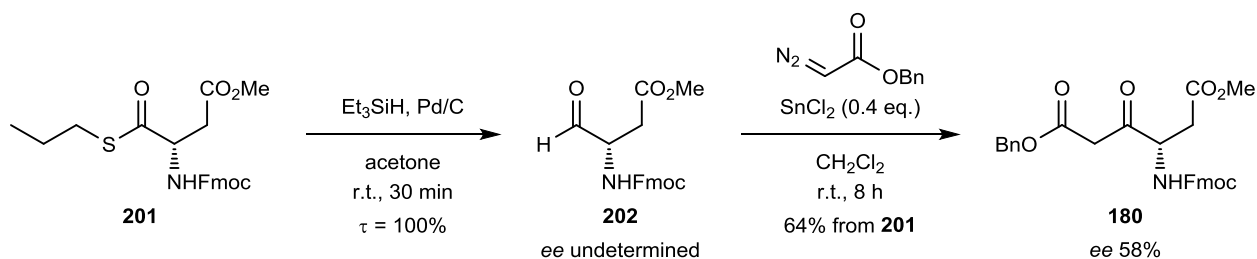
The Roskamp reaction⁵⁷³ consists of a double homologation of an aldehyde with a diazo compound in the presence of a Lewis acid that generates a ketone. It has already been applied for the synthesis of γ -amino- β -ketoesters.⁵⁷⁴⁻⁵⁸¹ Notably, Gopi reported a synthesis of *N*-protected γ -amino- β -ketoesters through the Roskamp reaction using Tin (II) chloride.⁵⁷⁴ Interestingly, it was

claimed that several examples of *N*-Fmoc protected α -amino aldehydes were used to give optically pure γ -amino- β -ketoesters (based on the optical rotation) (Scheme 56).



Scheme 56: Preparation of *N*-Fmoc γ -amino- β -ketoesters using Roskamp's procedure

Thus, *N*-Fmoc protected aldehyde **202** was prepared once again by Fukuyama reduction and treated with benzyl diazoacetate in the presence of SnCl_2 to furnish the desired benzyl γ -amino- β -ketoester **180** in 64% over 2 steps (Scheme 57). In order to minimize the possibility of racemization, the crude aldehyde **202** was used in this procedure without purification. Chiral HPLC analysis revealed that compound **180** was obtained with an enantiomeric ratio of 79:21. We supposed that the partial racemization could be the result of enolization of aldehyde **202** promoted by SnCl_2 .

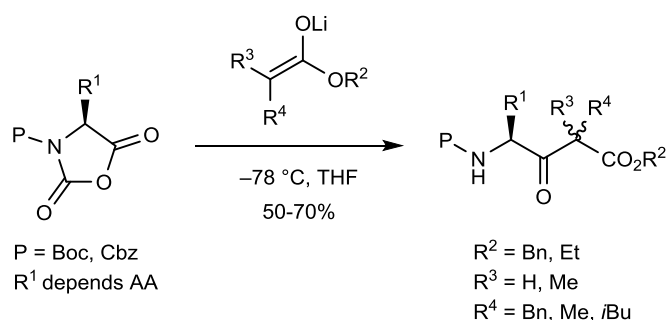


Scheme 57: Preparation of benzyl γ -amino- β -ketoester **180** through the Roskamp's procedure

4.5.6. Condensation of *N*-Fmoc protected UNCA with magnesium hemimalonate and silyl enolether

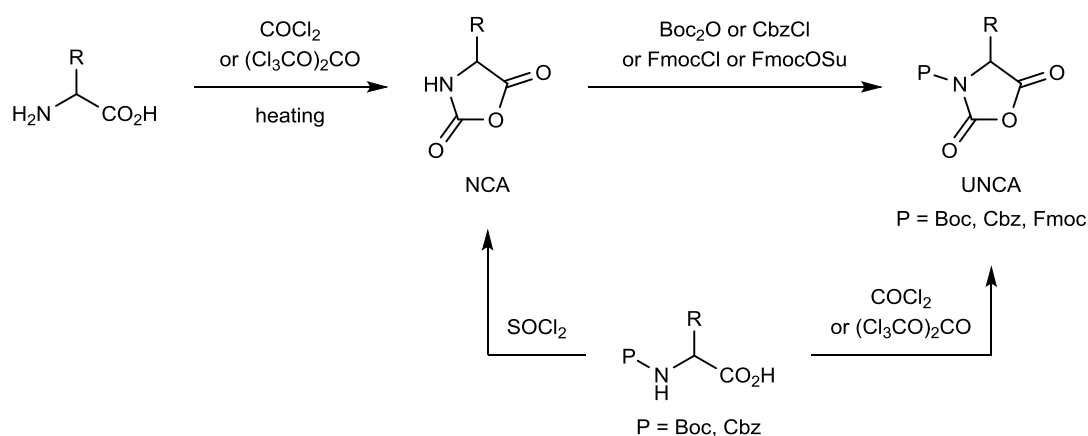
α -Amino acid *N*-carboxyanhydrides (NCAs, Leuchs's anhydrides,⁵⁸²⁻⁵⁸⁵) first report in 1906, and their corresponding urethane *N*-carboxyanhydrides (UNCAs) represent both protected and activated derivatives of α -amino acids. They are important monomers in peptide and polypeptide synthesis, and are useful intermediates in the preparation of γ -amino- β -ketoesters or tetramic acid derivatives.⁵⁸⁶⁻⁵⁸⁹ To date, thousands of reports and applications of Boc- and Cbz-UNCAs have been

described over the decades.^{429,482,587,590-599} There are only a few reports about *N*-Fmoc protected UNCAs (Fmoc-UNCAs). One example was the preparation of chiral urethane *N*-alkoxycarbonyl tetramic acids by condensation of UNCAs with Meldrum's acid in the presence of a tertiary amine, and subsequent cyclization supplied tetramic acid derivatives.⁵⁹² Martinez and his colleagues have reported an interesting example of the use of UNCAs for the synthesis of Cbz and Boc protected γ -amino- β -ketoesters (Equation 12).⁴²⁹ However Fmoc-UNCAs were not used probably because this protecting group was incompatible with the strongly basic lithium enolates.



Equation 12: Preparation of γ -amino- β -ketoesters from Boc- and Cbz-UNCA

The most common approach to UNCAs is the direct phosgenation of free amino acids to produce NCAs (Fuchs-Farthing synthesis)⁶⁰⁰⁻⁶⁰⁴ followed by the protection of the free nitrogen by alkoxylation (Scheme 58).⁵⁹⁴ Alternatively, Boc or Cbz protected amino acids can be treated by thionyl chloride to give NCAs (Leuch's method), or by phosgene or triphosgene to give directly the UNCAs. However, there is no report about direct phosgenation of Fmoc-amino acids into UNCAs. The main application of UNCAs is peptide coupling but they can react with a broad



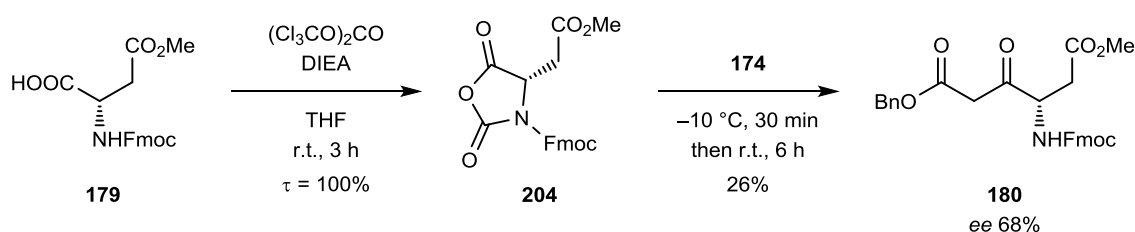
Scheme 58: Common methods for the preparation of UNCAs and NCAs

range of nucleophiles. Racemization of UNCAs happens only by the direct enolization through abstraction of the α proton. However, NCAs and UNCAs are sensitive and difficult to purify because of their high reactivity^{601,605-607} leading to various side reactions including polymerization.^{596,598,599,608,609}

In light of the interesting reactivity of UNCAs, we decided to study the reaction of magnesium hemimalonates and silyl enolether which are less basic than lithium enolates with the Fmoc-UNCA derived from aspartic acid as the activated amino acid derivative in order to access optically pure benzyl γ -amino- β -ketoester **180**

We embarked on the preparation of the Fmoc-UNCA **204** by phosgenation of the Fmoc protected aspartic acid derivative **179** using triphosgene in the presence of an HCl trapping reagent such as α -pinene, TEA, DIEA or NMM.^{610,611} In a first experiment the Fmoc amino acid **179** was treated with triphosgene (1.2 eq.) in the presence of α -pinene (2.5 eq.) in THF. After 6 h at 45 °C, the mixture was poured in *n*-hexane to crystallize the UNCA, but the sticky semi-solid obtained after filtration was only starting material (94% was recovered). Increasing the amount of α -pinene (5.0 eq.) and refluxing the reaction mixture for 18 h had no effect on the conversion and even when more α -pinene was added, this still had no use. We supposed that α -pinene was not strong enough to motivate the UNCA formation. When α -pinene was replaced by DIEA (2.0 eq.) and after 16 h of reaction at 60 °C the expected Fmoc-UNCA **204** was observed, as well as the starting Fmoc amino acid **179**. However, we also noticed the presence of dibenzofulvene which indicated that partial Fmoc deprotection had occurred. Moreover, UNCAs are not especially stable and heating the reaction might be deleterious to UNCA formation. The reaction was repeated at room temperature and after 3 h, some starting material was still present (determined by TLC). Additional triphosgene (0.15 eq.) and DIEA (0.5 eq.) were added and after an additional 3 h at room temperature, the mixture was poured into *n*-hexane to crystallize the UNCA. ¹H NMR analysis of the crude product showed an incomplete reaction and partial Fmoc deprotection, but about 40% yield of the desired UNCA **204** was observed. The crude sticky solid obtained was therefore treated directly in one case with magnesium hemimalonate **174** and in another case with the trimethylsilyl enol ether of benzyl acetate. Treatment with the magnesium hemimalonate **174** for 1 h produced 11% yield of the benzyl γ -amino- β -ketoester **180** over 2 steps with an enantiomeric ratio of 67:33, whereas treatment with

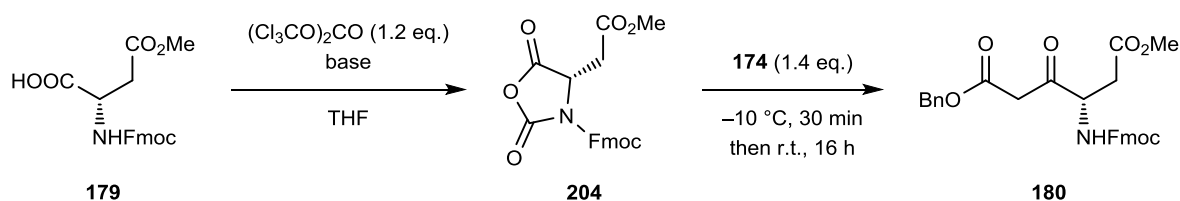
the silyl enolether for 16 h gave only a complex intractable mixture. The preparation of Fmoc-UNCA **204** was considerably improved by addition of a solution of triphosgene (1.2 eq.) in THF over 30 min to a solution of the Fmoc amino acid **179** and DIEA (2.4 eq.) in THF. After 3 h at room temperature, almost 100% conversion was observed by ^1H NMR (Scheme 59). Since the crude Fmoc-UNCA appeared to be steadily decomposed during work-up and crystallization,⁵⁹⁴ we decided to limit the treatment to the strict minimum. The diisopropylethylammonium salt precipitated was filtered off and the filtrate (containing traces of the ammonium salt) was used directly in the condensation step with the magnesium hemimalonate **174**. After 6 h the expected benzyl γ -amino- β -ketoester **180** was obtained in 26% yield with an enantiomeric ratio of 84:16.



Scheme 59: Sequential Fmoc-UNCA formation and condensation with magnesium hemimalonate

This very encouraging result in term of enantiomeric excess prompted us to continue our investigations on the use of Fmoc-UNCA. Although DIEA is a good promotor for the formation of the UNCA, unfortunately it is also a strong enough base that leads to Fmoc-deprotection and partial racemization. Moreover, the presence of traces of diisopropylethylammonium salt in the solution of Fmoc-UNCA seemed to affect the condensation of the magnesium hemimalonate and thus we decided to explore over bases (Table 8). Replacing DIEA by *N*-methylmorpholine (NMM) (entry 1) for the formation of the UNCA in the conditions described above gave 56% yield of the γ -amino- β -ketoester **180** with an enantiomeric ratio of 94:6, which was a significant improvement. However, when the UNCA formation was performed at $0\text{ }^\circ\text{C}$ for 3 h (entry 2), after treatment with the magnesium hemimalonate only the starting material **179** was observed (90% were recovered). When the amount of NMM was reduced and added over a shorter period of time (entry 3), we obtained 44% yield of the γ -amino- β -ketoester **180** with a slightly reduced enantiomeric ratio of 93:7. It was deduced that a slow addition of the base over 30 min at room temperature appeared the most appropriate conditions. Using these conditions, other bases were tested. When 2,6-lutidine was used (entry 4), 41% yield of the product **180** was obtained with an enantiomeric ratio of 96:4. With

sym-collidine (entry 5), full conversion of the Fmoc- amino acid **179** was observed and 42% yield of the γ -amino- β -ketoester **180** was obtained with an enantiomeric ratio of 96:4. When DTBMP was used (entry 6), reaction was slower and some starting material was observed. Although the intermediate Fmoc-UNCA was formed, no condensation product was obtained.



Entry	UNCA formation		Condensation	
	Conditions	Results	Yield (%)	<i>ee</i> (%)
1	Solution of NMM (2.2 eq.) in 0.5 mL of THF added at r.t. over 30 min then r.t., 2.5 h	$\tau \approx 100\%$ UNCA observed	56	88
2 ^a	Solution of NMM (2.2 eq.) in 0.5 mL of THF added at 0 °C over 30 min then 0 °C, 2.5 h	$\tau > 95\%$ UNCA observed	no product, 90% yield of 179 recovered	
3	Solution of NMM (2 eq.) in 0.5 mL of THF added at 0 °C over 5 min then r.t., 1.5 h	$\tau \approx 90\%$ UNCA observed	44	84
4	Solution of 2,6-lutidine (2.2 eq.) in 0.5 mL of THF added at r.t. over 30 min then r.t., 2.5 h	$\tau > 98\%$ UNCA observed	41	92
5	Solution of <i>sym</i> -collidine (2.2 eq.) in 0.5 mL of THF added at r.t. over 30 min then r.t., 2.5 h	$\tau \approx 100\%$ UNCA observed	42	92
6	Solution of DTBMP (2.2 eq.) in 0.5 mL of THF added at r.t. over 30 min then r.t., 4 h	$\tau \approx 90\%$ UNCA observed	no product, some SM	

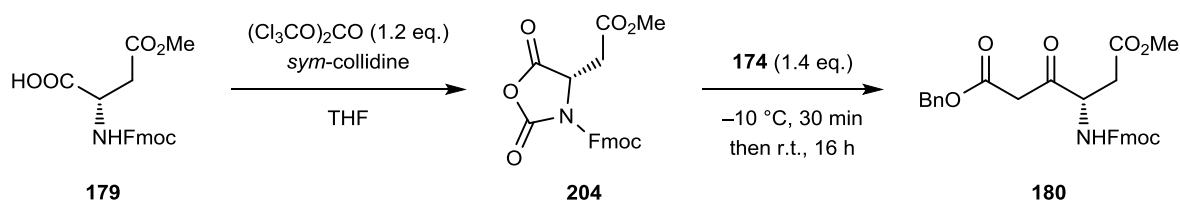
Notes: ^a Addition performed at -20 °C.

Table 8: Base screening for the preparation of the Fmoc-UNCA **204**

On the basis of these results above, *sym*-collidine was selected for further optimization (Table 9). When the solution of base was added at 0 °C over 30 min and the reaction mixture maintained at this temperature for 1 h (entry 1), the reaction seemed to slow down considerably, thus additional triphosgene was added and the mixture was the stirred for 4 h at room temperature.

The precipitate was filtered off and the filtrate, a solution of UNCA was split in two parts. On the first part, the addition of the magnesium hemimalonate was performed at $-10\text{ }^{\circ}\text{C}$ to provide 39% of the γ -amino- β -ketoester **180** with an enantiomeric ratio of 98:2. On the second part, the addition of the magnesium hemimalonate was performed at $0\text{ }^{\circ}\text{C}$ to give 40% of the γ -amino- β -ketoester **180** with an enantiomeric ratio of 97:3. In order to improve the reaction rate, half of the solution of *sym*-collidine was added directly at $0\text{ }^{\circ}\text{C}$ and the second half was then added over 30 min at room temperature (entry 2). Work-up after 1.5 h followed by condensation gave 53% of the γ -amino- β -ketoester **180** with an enantiomeric ratio of 95:5. When the solution of *sym*-collidine in THF was added all at once at room temperature and the stirring maintained for 1.5 h, we observed a slight decrease in yield and enantiomeric ratio (entry 3). Using a slight excess of *sym*-collidine (2.2 eq.) provoked a partial deprotection of the Fmoc group, revealed by the presence of DBF (entry 4). Consequently, after condensation, only 26% of the product was obtained with a similar enantiomeric ratio. We then tried to add some FmocCl to compensate for Fmoc deprotection (entry 5), however we noticed that the reaction slowed down considerably and more triphosgene and *sym*-collidine were added. Finally after a total of 6 h for the formation of the UNCA, work-up and condensation with magnesium hemimalonate, we obtained 52% yield of the expected product with an enantiomeric ratio of 95:5. The speed of addition of *sym*-collidine seemed to influence the yield and thus a solution of *sym*-collidine in THF was added at $0\text{ }^{\circ}\text{C}$ over 5 min (entry 6). Finally, after 1.5 h reaction time, work-up and condensation, 36% yield of the γ -amino- β -ketoester **180** was obtained with an enantiomeric ratio of 95:5. To test the impact of the temperature, the solution of *sym*-collidine in THF was added at $0\text{ }^{\circ}\text{C}$ over 20 min and the mixture was then stirred at $0\text{ }^{\circ}\text{C}$ for 40 min and then at r.t. for 2 h (entry 7). After work-up and condensation we obtained only 36% yield of the expected product with a slightly reduced enantiomeric ratio of 93:7. In conclusion, we successfully achieved the preparation of benzyl γ -amino- β -ketoester **180** in acceptable yield over 2 sequential steps and good enantiomeric excess.

The limitation of the yield was attributed to incomplete conversion of the starting material, whose consumption was difficult to be followed by TLC, and to polymerization of the NCA resulting from partial deprotection of the Fmoc group. Nonetheless, the optimization efforts were considered to be a success.



Entry	UNCA formation		Condensation	
	Conditions	Results	Yield (%)	<i>ee</i> (%)
1 ^a	Solution of <i>sym</i> -collidine (2.2 eq.) in 0.5 mL of THF added at $0\text{ }^\circ\text{C}$ over 30 min then $0\text{ }^\circ\text{C}$ for 1 h, then r.t. for 3 h	$\tau > 95\%$ UNCA observed	39 ^b	96
	additional triphosgene (0.15 eq.), r.t. 1.5 h		40 ^c	94
2	Solution of <i>sym</i> -collidine (2.0 eq.) in 0.5 mL of THF added in two parts: 0.25 mL in one portion at $0\text{ }^\circ\text{C}$ and 0.25 mL at r.t. over 30 min, then r.t., 1.5 h	$\tau > 95\%$ UNCA observed	53	90
3	Solution of <i>sym</i> -collidine (2.0 eq.) in 0.5 mL of THF added in one portion at r.t. then r.t., 1.5 h	$\tau > 95\%$ UNCA observed	49	88
4	Solution of <i>sym</i> -collidine (2.2 eq.) in 0.5 mL of THF added at r.t. over 30 min then r.t., 1.5 h	$\tau \approx 90\%$ DBF UNCA observed	26	90
5	<i>sym</i> -collidine (2.0 eq.), FmocCl (0.1 eq.), r.t., 3 h (no reaction) then additional triphosgene (0.3 eq.), collidine (0.2 eq.), 3 h	$\tau > 95\%$ UNCA observed	52	90
6	Solution of <i>sym</i> -collidine (2.0 eq.) in 0.5 mL of THF added at $0\text{ }^\circ\text{C}$ over 5 min then r.t., 1.5 h	$\tau \approx 90\%$ UNCA observed	36	90
7	Solution of <i>sym</i> -collidine (2.0 eq.) in 0.5 mL of THF added at $0\text{ }^\circ\text{C}$ during 20 min then $0\text{ }^\circ\text{C}$, 40 min, then r.t., 2 h	$\tau \approx 90\%$ UNCA observed	36	86

Notes: ^a Solution of UNCA in THF was split in two part to run two condensation with magnesium hemimalonate. ^b Addition performed at $-10\text{ }^\circ\text{C}$. ^c Addition performed at $0\text{ }^\circ\text{C}$.

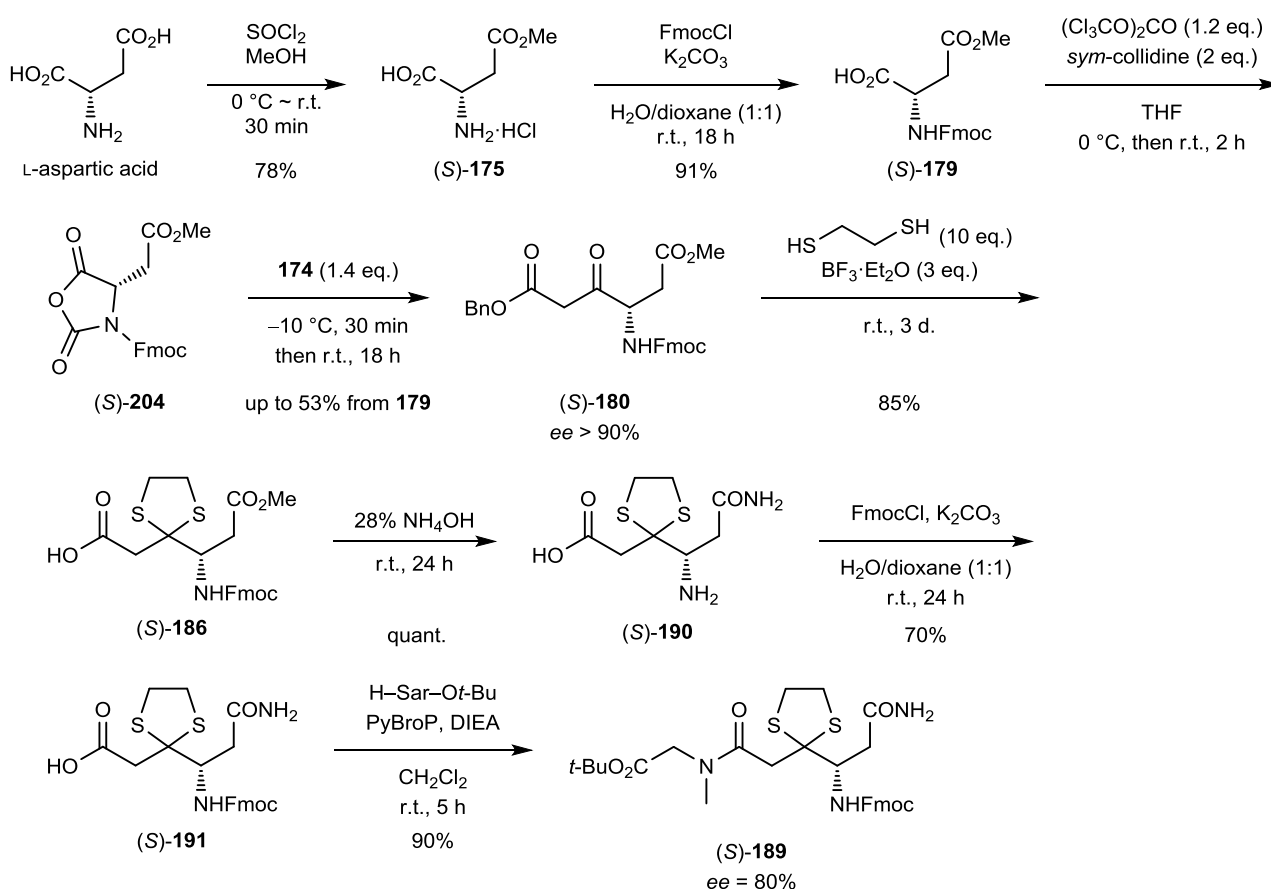
Table 9: Optimization of the preparation of the Fmoc-UNCA **204** and condensation

Retrospectively, in our results on the use of Fmoc-UNCA in the Masamune's procedure, and compared with the racemization results (See Chapter 2, §4.1., Scheme 38), it seems clear that racemization occurs during the activation stage with CDI in contrast to what was proposed by Ma and Zhu (See Chapter 2, §4.2., Scheme 39).⁴⁸¹

5. Conclusions

5.1. Final synthesis of the key dipeptide: (*S*)-mPyrAA–Sar

In summary, the (*S*)-mPyrAA–Sar dipeptide (**S-189**) was obtained in 20.1% yield over 8 steps through the synthesis developed (Scheme 60). Notably, from (*S*)-**180** to (*S*)-**189** over 4 steps, an erosion of 10% *ee* occurred. Optimization of the condensation of the magnesium hemimalonate to the Fmoc-UNCA derivative of L-aspartic acid allow the preparation of the key benzyl γ -amino- β -ketoester (*S*)-**180** with a good enantiomeric excess above 90%.

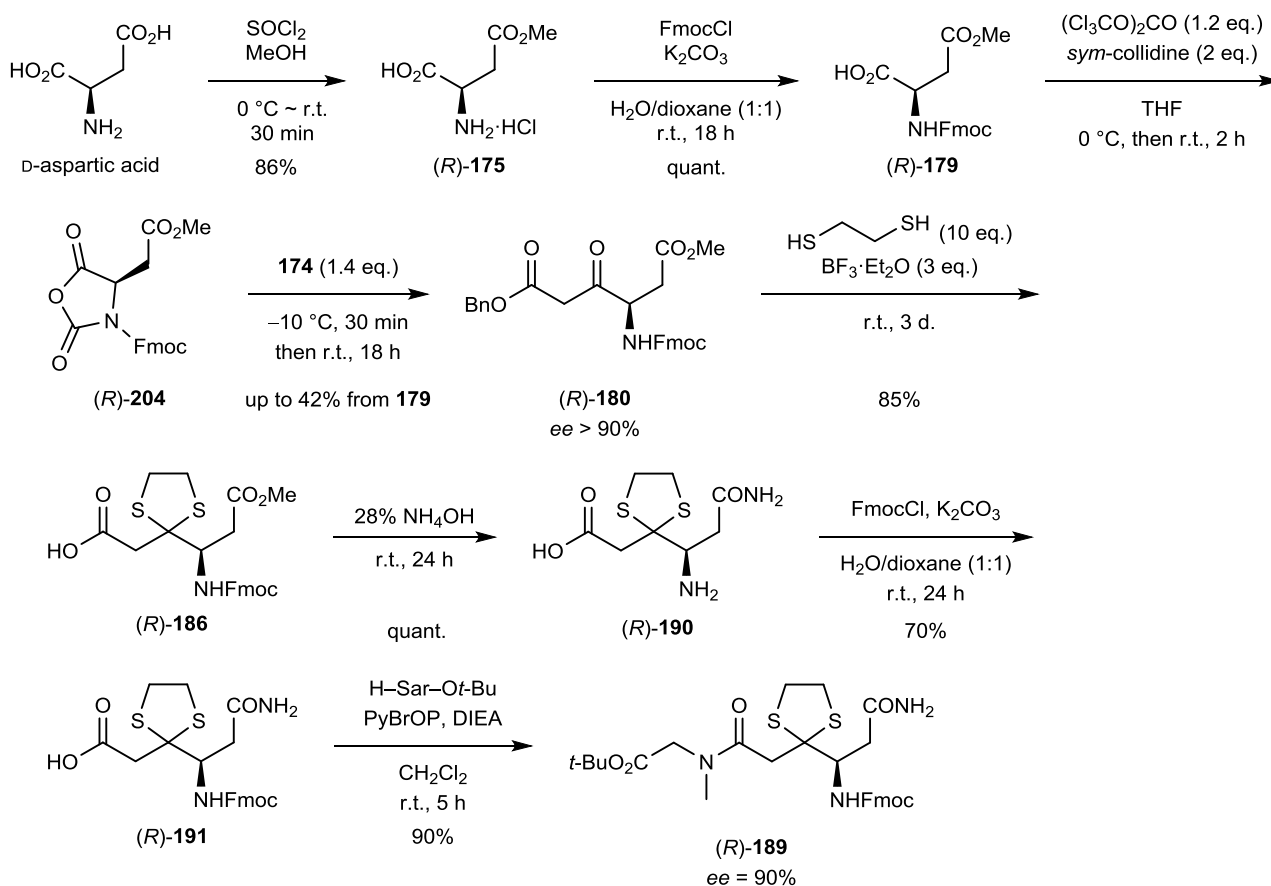


Scheme 60: Synthesis of the (*S*)-mPyrAA–Sar from L-aspartic acid

5.2. Final synthesis of the key dipeptide: (*R*)-mPyrAA–Sar

Since D-aspartic acid (*R*-configuration) was required for the total synthesis of microsclerodermin D, the same synthetic route was then applied to prepare the (*R*)-mPyrAA–Sar dipeptide (*R*)-**189** from D-aspartic acid in 19.3% yield over 8 steps (Scheme 61). Notably, from

(*S*)-**180** to (*S*)-**189** over 4 steps, no erosion occurred. Similarly, to the (*S*)-derivative, the key benzyl γ -amino- β -ketoester (*R*)-**180** was obtained with a good enantiomeric excess above 90%.



Scheme 61: Synthesis of the (*R*)-mPyrAA–Sar from D-aspartic acid

CHAPTER 3

SYNTHEIS OF DIPEPTIDE Trp(6-Cl)–Gly

1. Introduction

1.1. Target structure

According to our proposed strategy, the second target required for the total synthesis of microsclerdermin D, is the dipeptide D-Trp(6-Cl)-Gly (Figure 34). The uncommon D-6-chlorotryptophan residue also exists in microsclerdermin L and pedein A, while differently modified tryptophan derivatives exist in the other members of the microsclerdermin family: microsclerdermins F, H, J, K, M and pedein B present the D-tryptophan, which is commercially available; microsclerdermins G and I present dehydrotryptophan; microsclerdermins A, B, E, N and O present D-2-carboxytryptophan; microsclerdermin C is the only family member bearing D-*N*-formamidotryptophan.

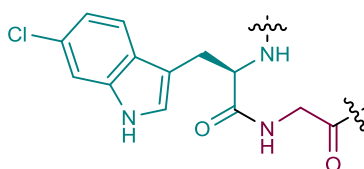


Figure 34: Dipeptide D-Trp(6-Cl)-Gly fragment present in microsclerdermin D

1.2. Synthesis of tryptophan derivatives

L-Tryptophan (Trp), the only proteingenic amino acid with an indole ring, is one of the essential amino acids for animals.⁶¹² It is not synthesized by the human body but ingested from diets such as meat, fish, eggs, fruit, vegetables, nuts, etc... and it plays a significant role in the synthesis of proteins and muscle tissues. It also serves as a precursor of key functional biomolecules such as tryptamine, quinolinic acid, nicotinamide, serotonin and others.⁶¹³ Besides, Tryptophan is the precursor of indole-3-acetic acid, the most abundant auxin in higher plants (Figure 35).⁶¹⁴

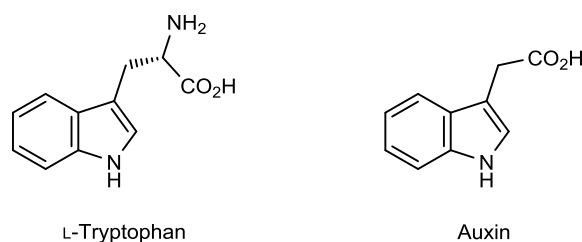
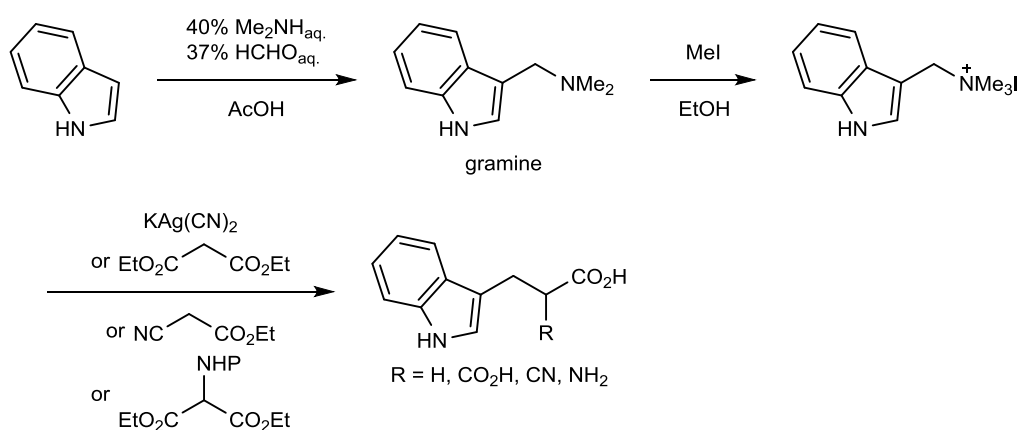


Figure 35: L-Tryptophan and Auxin

Earlier in 1944, Snyder reported the first synthetic approach to 3-indolemethylene derivatives using quaternary ammonium salts (methiodide of gramine) as alkylating agent. It was discovered that quaternary ammonium salts could generate a benzyl type radical.⁶¹⁵ Afterwards, this method was used for the synthesis of DL-tryptophan and its analogues.⁶¹⁶⁻⁶¹⁸ Interestingly, Albertson *et al.* reported the synthesis of tryptophan from gramine at the same time.^{619,620} Alkylation of the methiodide of gramine, obtained in a 3-component Mannich reaction between indole, formaldehyde and dimethylamine by Kuhn's procedure,⁶²¹ was performed with various reagents: sodium enolates of acetoacetates or cyanoacetates, potassium silver cyanide dialkyl aminomalonate (Scheme 62).⁶¹⁵⁻⁶¹⁷



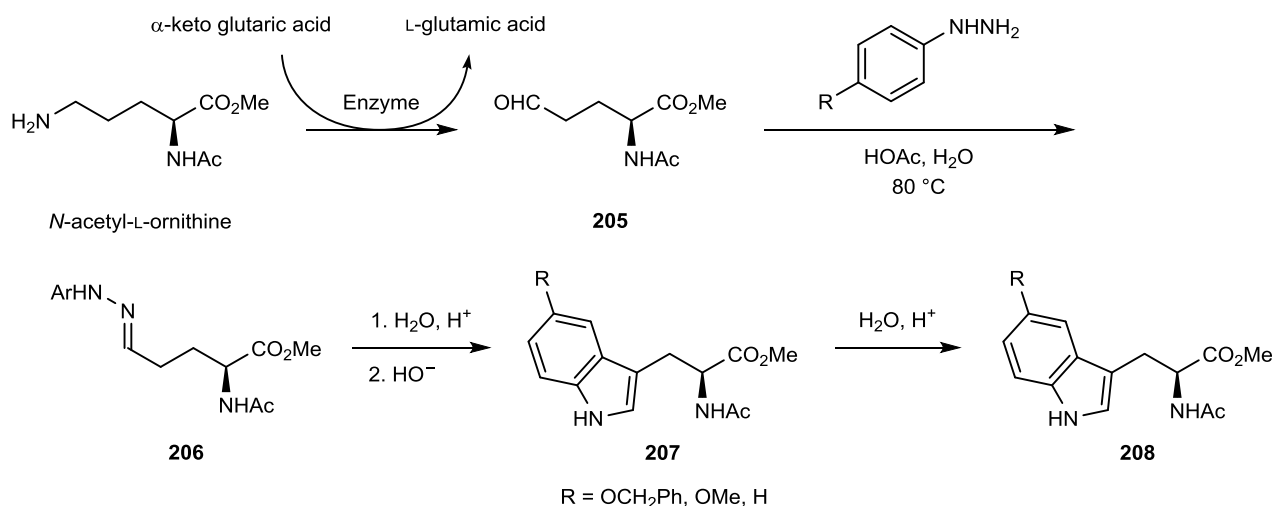
Scheme 62: Snyder's synthesis of tryptophan derivatives

Current methods employed for the synthesis of tryptophan derivatives mainly rely on either chemical or enzymatic approaches, as well as biosynthesis:

- chemical synthesis approaches including stepwise functional group conversion,^{616-619,622-645} phase-transfer catalytic alkylation,^{633,646} and metal-catalysis^{460,625,647,648}
- enzymatic synthesis⁶⁴⁹⁻⁶⁵³ (tryptophan synthase such as TrpB2, *N*-acylase enzymes)
- biocatalytic platform⁶⁵³⁻⁶⁶⁴ using bacteria, protozoa, neurospora, RNA or cells

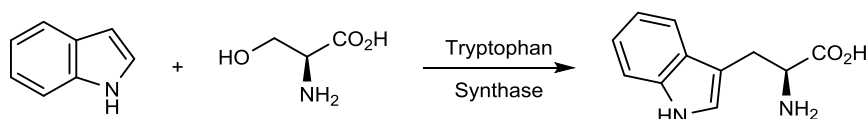
Historically, multistep syntheses of racemic tryptophan have been reported by many groups including those of Snyder,⁶¹⁵⁻⁶¹⁸ Albertson,^{619,620} Rinderknecht,⁶³⁵ Hellmann,^{632,665} Kornfeld,⁶⁴¹ McLaughlin⁶²² and recently Fuller.⁶⁶⁶ To date, numerous asymmetric synthetic methods for chiral tryptophan derivatives have also been reported by many groups, which could be classified in two categories: use of chiral starting materials and use of chiral auxiliary or chiral ligands.

Early in 1957, Yamada *et al.* reported the enzymatic resolution of acetyl-DL-tryptophan with mold acylase,⁶⁶⁷ which could be the first report about optically pure tryptophan. Additionally, 5-hydroxy-L-tryptophan was obtained by optical resolution of *N*-acyl-5-benzyloxy-DL-tryptophan by Armstrong⁶⁶⁸ and Rinderknecht,⁶⁶⁹ as well as by oxidation of 2,3-dihydro-L-tryptophan by Sato.⁶⁷⁰ In 1978, Tsuchihashi described the first synthesis of 5-hydroxy-L-tryptophan from enzymatically prepared *N*-acetyl-L-glutamic- γ -semialdehyde **205** with α -keto glutaric acid in the presence of aminotransferase followed by a Fischer indole synthesis through intermediate **206** to provide 5-substituted-L-tryptophan derivatives **207**, further transformed into 5-hydroxy-L-tryptophan **208** (Scheme 63).⁶³⁶ Similarly, Masumi and Yamada⁶³⁸ also disclosed two approaches to L-tryptophan from L-glutamic acid derivatives with almost no racemization using Fischer indole synthesis. This method was also used for syntheses of D- and L-tryptophan, as well as substituted tryptophan derivatives by Irie in 1984.⁶³⁴



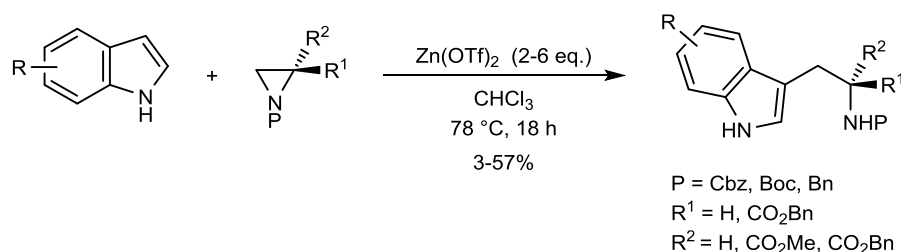
Scheme 63: Tsuchihashi's first synthesis of 5-hydroxy-L-tryptophan

The shortest synthesis of tryptophan consists of the direct coupling of the C³-position of indole with serine or its equivalents mediated by an enzyme such as tryptophan synthase (TrpB2, *N*-acylase enzymes) (Equation 13).^{650-653,671-673}



Equation 13: Synthesis of L-tryptophan using tryptophan synthase

Various strategies have been developed to mimic synthetic pathways without enzymes. An example was the ring opening of aziridines derived from serine with 3-*H*-indoles to prepare various tryptophan derivatives (Equation 14).⁶⁷⁴ However, the yields were unsatisfactory arranging from 3% to 57% after optimization, especially with lower yields for substituted indoles.

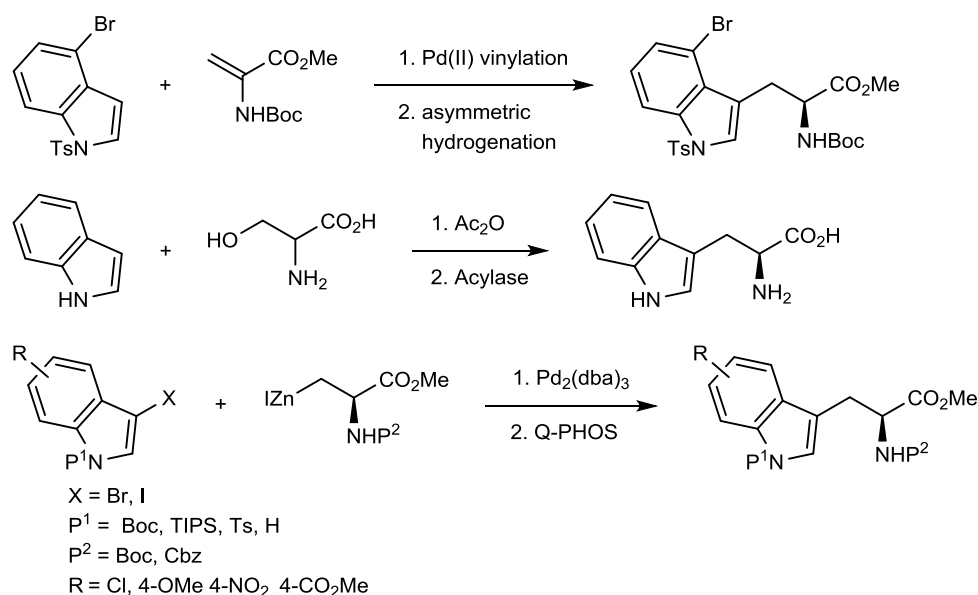


Equation 14: Synthesis of tryptophan derivatives by ring-opening of aziridines

In 1989, Jackson reported the use of Negishi cross-coupling for the synthesis of enantiomerically pure protected β -aryl-alanines from aryl halides and readily available organozinc reagents of iodoalanine (derived from serine),⁶⁷⁵ and for the preparation of enantiomerically pure protected γ -keto- α -amino acids from acyl chlorides and readily available organozinc reagent of iodoalanine.⁶⁷⁶ Although numerous applications of the synthesis of various chiral aromatic amino acids have been reported. Only a few have reported the synthesis of tryptophan using this method. For example, Rainier prepared the tryptophan unit of kapakahine E and F following this method to complete their total synthesis.^{677,678} Kalesse reported a selective Pd-catalyzed vinylation of 4-bromoindole with dehydroalanine, followed by enantioselective hydrogenation of olefin in the presence of DuanPhos ligand, to synthesize the tryptophan derivative unit to complete the total synthesis of argyrin F.⁶⁷⁹ Yokoyama explored various asymmetric synthesis of substituted tryptophan derivatives (Scheme 64):

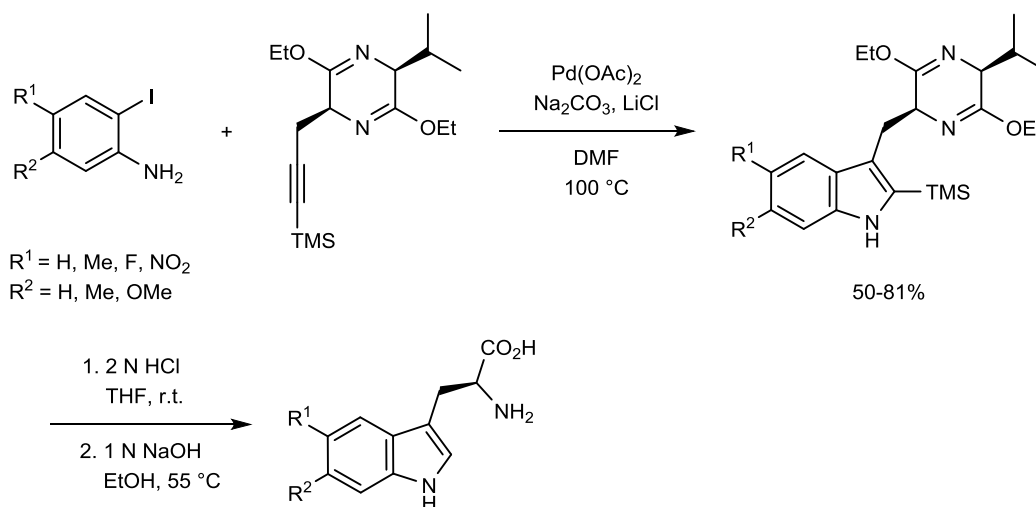
- selective Pd-catalyzed vinylation of 4-bromoindole with dehydroalanine, followed by asymmetric hydrogenation⁶⁸⁰⁻⁶⁸⁴
- one-step synthesis of *N*-acetyltryptophan from indole and serine in the presence of acetic anhydride using kinetic resolution with acylase^{685,686}
- using Negishi cross-coupling reaction of iodoalanine with 3-haloindole without loss of enantiomeric purity after optimization. The best result was obtained when the reaction of

N-tosyl-3-bromoindole with *N*-Cbz-iodoalanine methyl ester was carried out in the presence of Pd₂(dba)₃ and the sterically hindered ferrocenyl ligand Q-PHOS.⁴⁶⁰



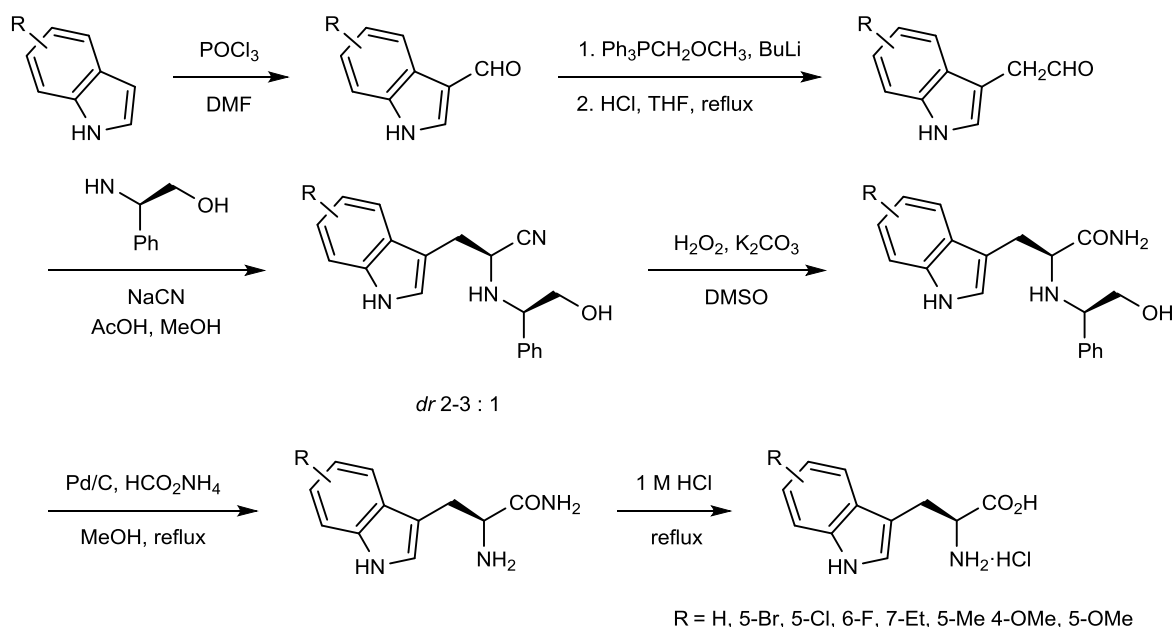
Scheme 64: Yokoyama's asymmetric synthesis of substituted tryptophan derivatives

A short, practical and versatile synthesis of optically active substituted tryptophan derivatives from a variety of iodoanilines, *via* a palladium-mediated heteroannulation reaction with a chiral alkyne obtained by diastereoselective alkylation of the Schölkopf chiral auxiliary,⁶⁸⁷ was developed by Cook (Scheme 65).⁶⁸⁸ This method have been applied by many groups, such as Cook,^{625,647} Castle,⁶⁸⁹ Björn,⁶⁹⁰ and Hecht.⁶²⁶



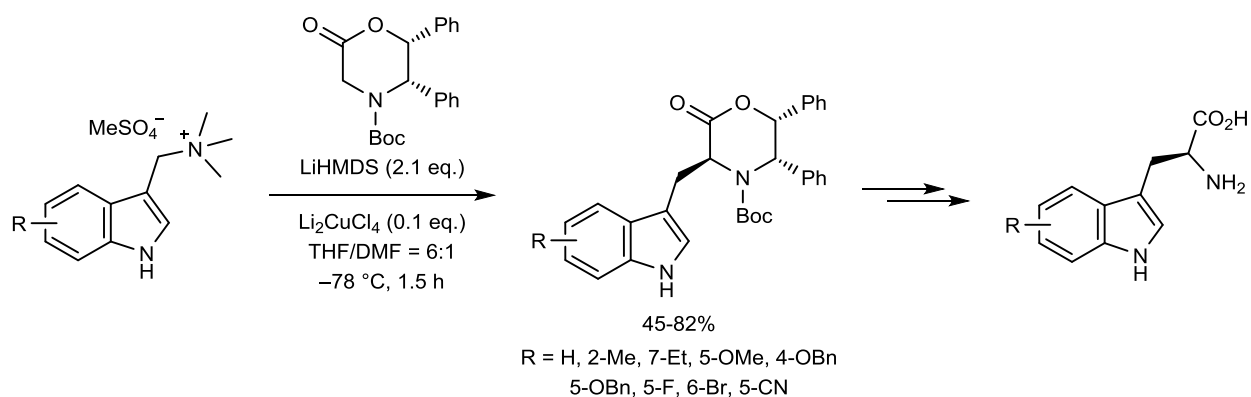
Scheme 65: Synthesis of substituted tryptophan derivatives through heteroannulation

Chan established a synthesis of ring-substituted (*S*)-tryptophan derivatives from the corresponding indoles, using a chiral auxiliary-facilitated Strecker amino acid synthesis⁶⁹¹ strategy (Scheme 66).⁶²⁹ Using this method, eight optically pure (*S*)-tryptophan analogues were synthesized, and subsequently used for the total synthesis of argyrin A and its analogues.



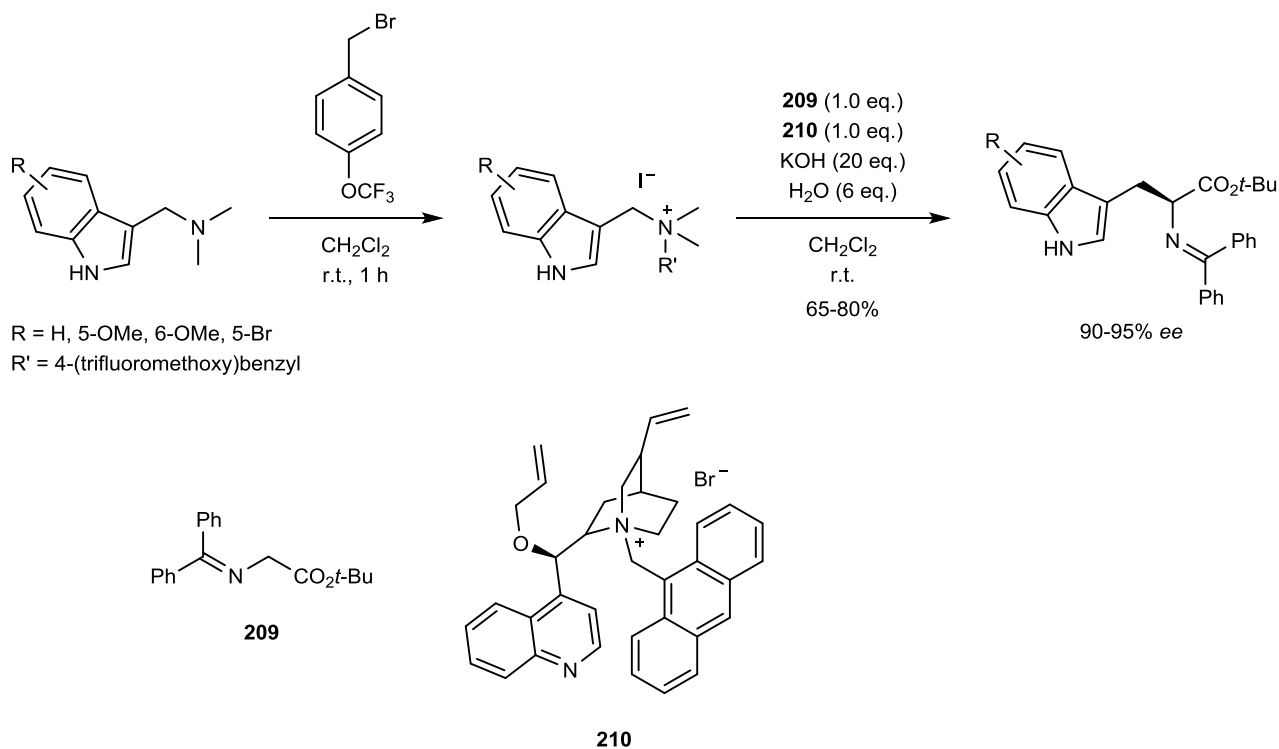
Scheme 66: Synthesis of optically active substituted tryptophan derivatives

Recently Katkevics reported a general method for the diastereoselective synthesis of substituted tryptophan derivatives by alkylation of William's morpholinone chiral auxiliary with quaternary gramines as alkylating agents with good overall yields (Scheme 67).⁶⁹²



Scheme 67: Katkevics's diastereoselective synthesis of substituted tryptophan derivatives

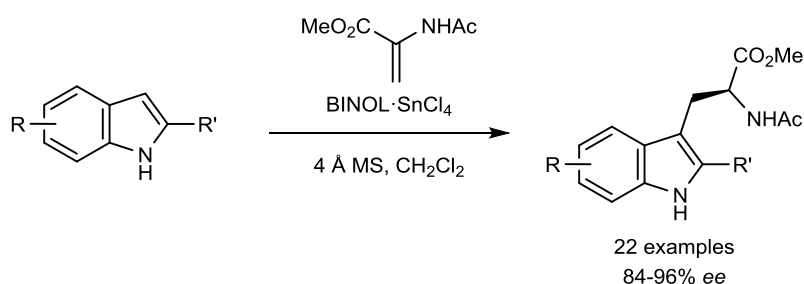
Asymmetric phase-transfer catalytic alkylation of glycine imine derivative **209** using the cinchona-derived catalyst **210** was reported by Hossain for the preparation of substituted tryptophan derivatives with *ee* up to 95% (Scheme 68).⁶³³ A similar method was also used by Maruoka for the enantioselective synthesis of α,α -dialkyl- α -amino acids by chiral phase-transfer catalysis from the Schiff base of **209**, including the preparation of a *N*⁷-Boc protected D-tryptophan derivative in 78% yield and 91% *ee*.⁶⁴⁶



Scheme 68: Enantioselective synthesis of tryptophan derivatives by asymmetric phase transfer catalysis

A widely used method for the enantioselective preparation of tryptophan derivatives consists of a tandem Friedel-Crafts/conjugate addition of substituted indoles to dehydroalanines. For example, Reisman reported the reaction of 2-substituted indoles with methyl 2-acetamidoacrylate catalyzed by a BINOL·SnCl₄ complex to prepared synthetic tryptophan derivatives in good yields and high level of enantioselectivity (Equation 15).⁶²⁸ In a similar manner, Chen described the reaction of indoles with nitroacrylates catalyzed by the chiral complex (4*R*,5*S*)-DiPh-BOX-Cu(OTf)₂.⁶²³ Besides, a convenient synthesis of constrained β -substituted tryptophans by asymmetric catalytic reaction of glycine derivatives with sulfonylindoles using a

catalyst derived from AgCl and a commercially available chiral monodentate phosphoramidite ligand was developed by Hou.⁶⁹³



Equation 15: Reisman's diastereoselective synthesis of substituted tryptophan derivatives

2. Synthesis of Trp–Gly

2.1. Alkylation of chiral glycine imine derivatives

Asymmetric synthesis of α -amino acids by alkylation of the glycine *tert*-butyl ester Schiff base derived from 2-hydroxypinanone is a well-known methodology, firstly reported by Yamada in 1976,⁶⁹⁴ and widely applied by many groups.^{361,362,695-712} However, only a few applications to the enantioselective synthesis of tryptophan derivatives have been described.^{359,360} The origin of stereoselectivity of this reaction was explored in details by different groups (Figure 36):

- a possible transition state was proposed by Soladié-Cavallo who postulated a dimeric aggregate based on literature X-ray crystallographic data early in 1993⁷¹³⁻⁷¹⁵
- Seebach described the formation of dimers and even higher aggregates in 1988 when reviewing the structure and reactivity of lithium enolates⁷¹⁶
- computational studies were used by Matsumoto to propose a *meso*-dimer type model on half of the dimeric enolate in 1996^{699,700}
- Haufe suggested the formation of aggregates of intermediary enolates in solution and diastereomeric interactions of the enantiomers in 2000⁷⁰⁴

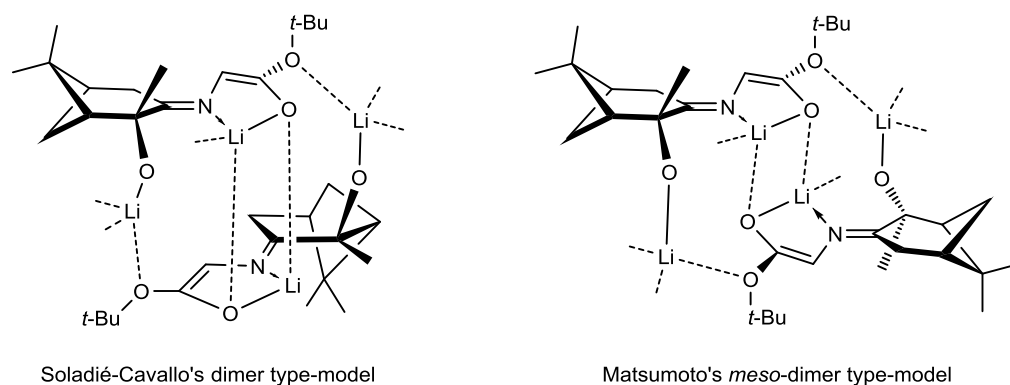


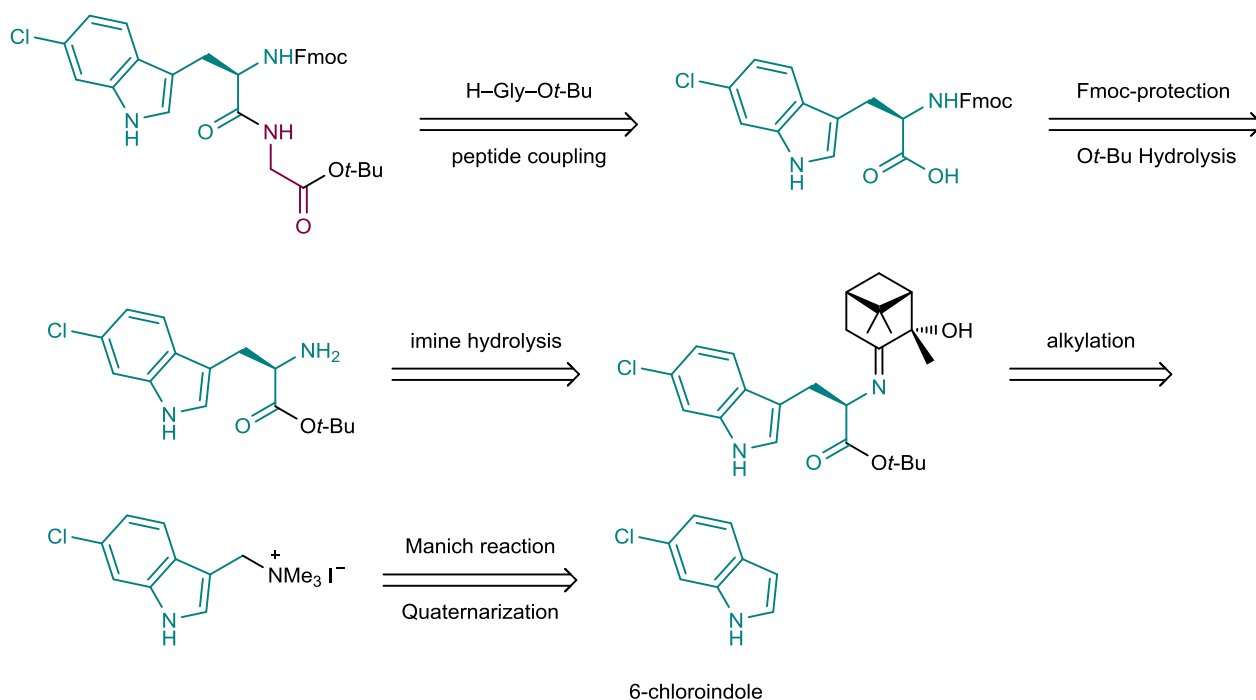
Figure 36: Proposed transition state type-model of alkylation of 2-hydroxypinanone glycine imine using lithium enolates

2.2. Strategy

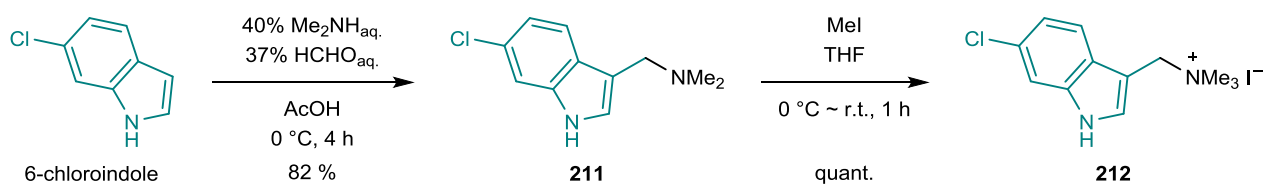
Based on the work of Shiori,^{359,360} we proposed the preparation of the Trp(6-Cl) residue through alkylation of a 2-hydroxypinanone glycine imine derivative. This method presents the advantage of allowing access to either enantiomers depending on the stereochemistry of the chosen 2-hydroxypinanone. To fit with our overall plan for the preparation of microsclerodermin D, a Fmoc group and a *t*-butyl ester were chosen to protect the amine and the acid functions, respectively. The target dipeptide would be obtained by coupling of Fmoc-Trp(6-Cl)-OH with *t*-butyl glycinate (Scheme 69). The appropriately protected 6-chloroindole would be prepared by alkylation of the 2-hydroxypinanone glycine imine with an ammonium salt derived from 6-chloroamine which would be obtained from 6-chloroindole through a Mannich reaction followed by quaternarization.

2.3. Synthesis of H-[(*R*)-Trp(6-Cl)]-Gly-O*t*-Bu

The quaternary ammonium salt **211** was prepared efficiently in two steps from 6-chloroindole (Scheme 70). This latter was engaged in a 3-component Mannich reaction with dimethylamine and formaldehyde to provide the gramine derivative **211** in 82% yield. Then treatment with methyl iodide allows quaternarization to produce the ammonium salt **212** in quantitative yield following Sun's procedure.⁷¹⁷



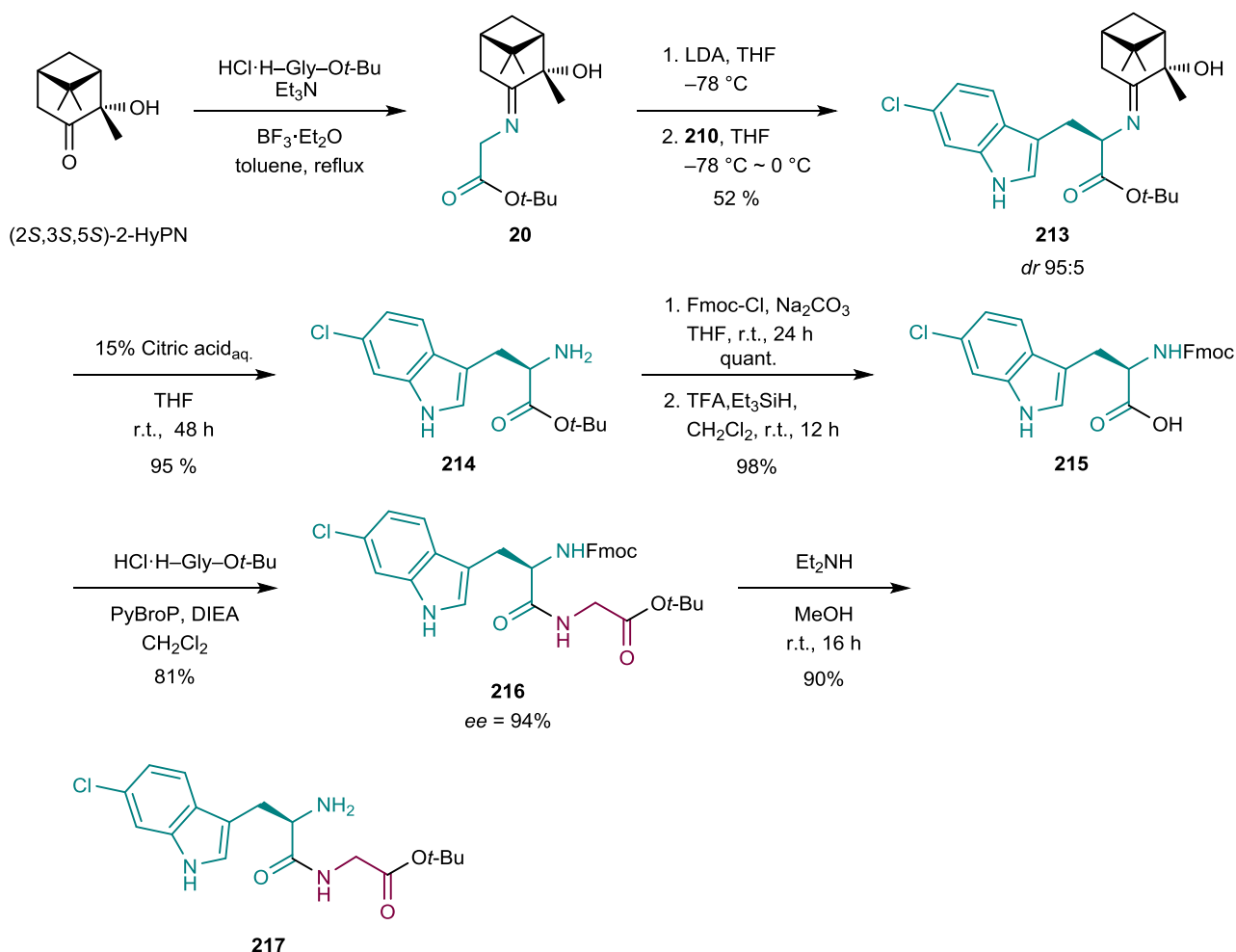
Scheme 69: Retrosynthetic analysis of dipeptide modified 6-Cl-Trp-Gly



Scheme 70: Preparation of the ammonium salt derived from 6-chloroindole

Subsequently, the chiral Schiff base of glycine *t*-butyl ester **20** was prepared by treatment of glycine *t*-butyl ester with optically pure (1*S*,2*S*,5*S*)-(+)-2-hydroxy-3-pinanone (HyPN) in the presence of catalytic $\text{BF}_3 \cdot \text{Et}_2\text{O}$ refluxing in toluene (Scheme 71). Then, deprotonation of the chiral imine **20** with LDA provided an enolate which was treated with the quaternary ammonium salt **212** to provide the imine **213** in 52% yield and a diastereoisomeric ratio of 95:5 (after chromatography purification, the ratio improved above 97:3). It appeared that the hydrolysis of imine **213** required care to avoid racemization; thus, upon treatment with 15% citric acid, we were able to obtain 95% yield of the α -amino ester **214**. Afterwards, protection of the amine with a Fmoc group followed by TFA-mediated hydrolysis of the *t*-butyl ester gave the *N*-Fmoc-Trp(6-Cl) derivative **215** in excellent yield over 2 steps. Interestingly, when hydrolysis of the *t*-butyl ester was performed in the absence of triethylsilane, the reaction was dirty with lower yield and the product was difficult to purify. Peptide coupling of **215** with glycine *t*-butyl ester with PyBOP in the presence of DIEA, gave the

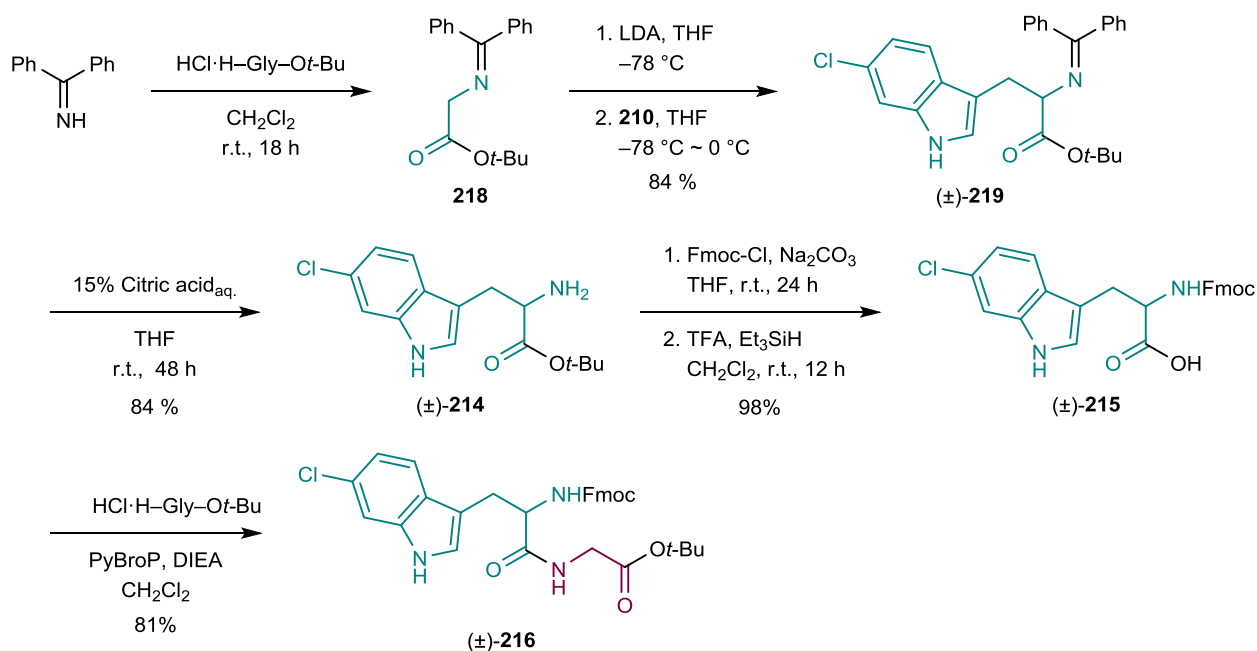
dipeptide Fmoc-*Trp(6-Cl)-Gly-Ot-Bu* **216** in 67% yield; the efficiency was then improved by replacing PyBOP with PyBroP which gave 81% yield of the dipeptide **216**. Chiral HPLC analysis of **216** revealed an enantiomeric excess of 94%. Final deprotection of the Fmoc group was initially performed under the common conditions using piperidine in dichloromethane, but it gave a modest 50% yield as impure product. Alternative conditions were sought. Treatment of **216** with TBAF in the presence of benzylmercaptan in THF and 28% NH_4OH in THF (1:1), gave 80% and 81% yield of the product **217**, respectively. The best result was obtained by treatment with Et_2NH (40 eq.) in MeOH which gave an excellent 90% yield of **217**. Under these conditions, no degradation, no polymer of DBF and no adduct of DBF with Et_2NH were formed and only DBF by-product was observed.



Scheme 71: Enantioselective synthesis of dipeptide H-*Trp(6-Cl)-Gly-Ot-Bu*

In order to evaluate the enantiomeric excess of **216**, the racemic material was also prepared according to a similar strategy, but the chiral Schiff base was replaced by the benzophenone imine

derivative **218** (Scheme 72). Thus, condensation of glycine *t*-butyl ester with benzophenone imine gave the Schiff base **218** quantitatively.^{718,719} This compound was deprotonated and treated with the quaternary ammonium salt **212** to provide the imine (\pm)-**219**. After hydrolysis of the imine, protecting group manipulation and peptide coupling, the racemic dipeptide (\pm)-**216** was obtained in good yield and used to establish a chiral HPLC analysis protocol to evaluate the enantiomeric excess.



Scheme 72: Racemic synthesis of dipeptide Fmoc-Trp(6-Cl)-Gly-Ot-Bu

3. Conclusion

We successfully synthesized the Fmoc-Trp(6-Cl)-Gly-Ot-Bu dipeptide fragment in 32.2% yield over 7 steps with an enantiomeric excess of 94%, starting from 6-chloroindole. The chiral center was constructed by a classic strategy for chiral α -amino acids preparation based on the diastereoselective alkylation of the chiral Schiff base derived from 2-hydroxypinanone and glycine *t*-butyl ester with a gramine type of ammonium salt.

CHAPTER 4

SYNTHESIS OF DIPEPTIDE GABOB-APTO

1. Introduction

According to our proposed strategy, GABOB–APTO (Figure 37) is the third dipeptide fragment required for the total synthesis of microsclerodermin D. It is also found in microsclerodermins C and L. This fragment is composed of (*R*)- γ -aminobutyric acid (GABOB) which is present in all the microsclerodermin family members, and of APTO, a polyhydroxylated β -amino acid residue containing four contiguous stereogenic centers. Across the microsclerodermin family, the polyhydroxylated β -amino acid unit presents some variations, and other residues like AETD, AMMTD, AMPTD, which contains four or five contiguous stereogenic centers and various styrene moiety can be encountered.

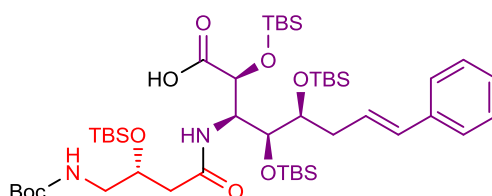


Figure 37: Dipeptide Boc–GABOB–APTO–OH

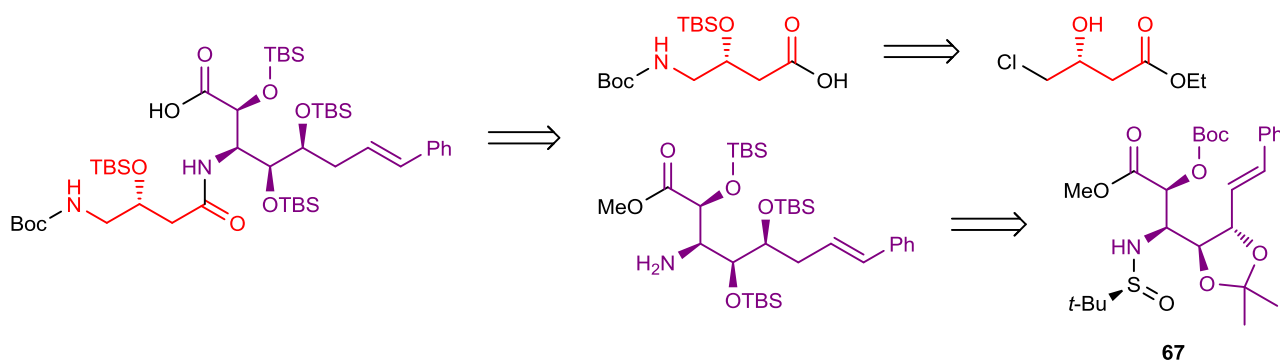
GABOB is a relatively common γ -amino acid whose preparation is well documented^{468-470,720,721} and it is easily accessible. Several groups have reported the preparation of protected derivatives of APTO, including McLeod³⁸⁰ in 2007, Aitken³⁸⁷ in 2008, Dauban and Dodd³⁹⁸ in 2009 and Davies⁴¹⁸ in 2013 (See Chapter 1, §4.).

2. Synthesis of GABOB–APTO

2.1. Strategy

We proposed to prepare the APTO fragment through the in-house strategy³⁸⁷ (See Chapter 1, § 4.2.3.) and to install appropriate protecting groups on the hydroxy groups, and to synthesize the protected GABOB from ethyl (*R*)-4-chloro-3-hydroxybutanoate according to Hayashi's procedures^{469,721} (Scheme 73). To fit with our proposed total synthesis strategy, the amino group of GABOB would be protected by a Boc group, and all the hydroxyl groups would be protected by a TBS group, with the intention of performing a single deprotection operation at the appropriate moment. Functional group modification of the known fully-protected APTO derivative **67** would

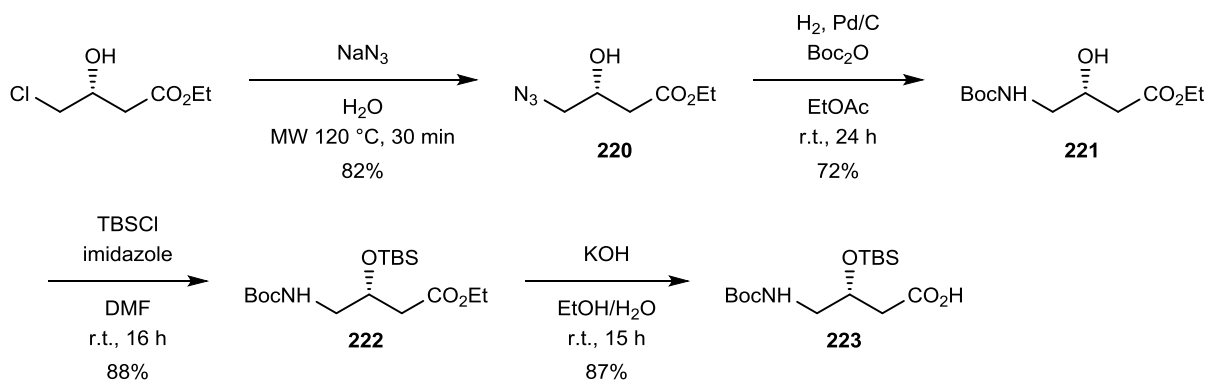
require the cleavage of sulfinyl, acetonide and *O*-Boc groups in acidic medium, followed by Fmoc protection of amine and *O*-TBS protection of all the free hydroxyl groups, and final Fmoc deprotection. After coupling with protected GABOB, the methyl ester would be hydrolyzed in order to be ready for further coupling.



Scheme 73: Retrosynthetic analysis of the dipeptide GABOB–APTO derivative

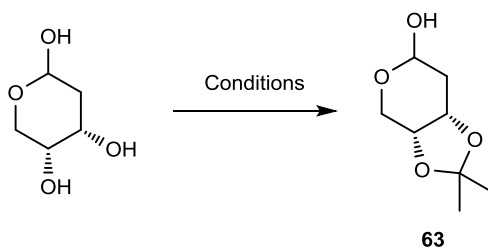
2.2. Synthesis of the protected GABOB

The preparation of GABOB started with azidation of commercially available ethyl (*R*)-4-chloro-3-hydroxybutanoate according to Hayashi's procedures (Scheme 74).^{469,721} In a first experiment the chloro ester was treated with sodium azide (1 eq.) at 90 °C in DMF for 48 h to give the azido ester derivative **220**. Although complete conversion was observed, only 66% yield of the product was obtained, and we suspected that the prolonged reaction time at high temperature could be the cause. To reduce reaction time we turned to microwave activation.⁷²² Thus the chloroester was treated with sodium azide (1.3 eq.) in water under microwave irradiation at 120 °C for 30 min. Unfortunately, the reaction was not complete and about 15% yield of starting material was observed. Increasing the quantity of sodium azide (2.5 eq.) in the same conditions allowed a complete conversion and furnished 82% yield of the azido ester **220** which could be used without purification. In a single procedure, the azide was reduced into an amine which was directly protected by a Boc group, by hydrogenolysis over Pd/C in the presence of Boc₂O to give the amino ester derivative **221** in good yield. Subsequently, the free alcohol was protected as a TBS ether under standard conditions to give the fully protected GABOB derivative **222** efficiently. Finally, saponification of the ethyl ester using potassium hydroxide gave the target protected (*R*)-GABOB **223** derivative in 87% yield. The (*R*)-GABOB **223** ready for coupling was prepared in overall 45.2% yield over 4 steps from ethyl (*R*)-4-chloro-3-hydroxybutanoate.

Scheme 74: Synthesis of the protected (*R*)-GABOB derivative **223**

2.3. Synthesis of protected APTO

The protected ATPO derivative was then prepared from 2-deoxy-D-ribose according to the procedure developed by Aitken's group.³⁸⁷ We began by preparing 2-deoxy-D-ribose acetonide **63** following Horton's conditions and procedures (Table 10, entry 1).³⁸⁸ Unfortunately, the reaction was sluggish and hardly gave the desired acetonide **63** when conducted under various common



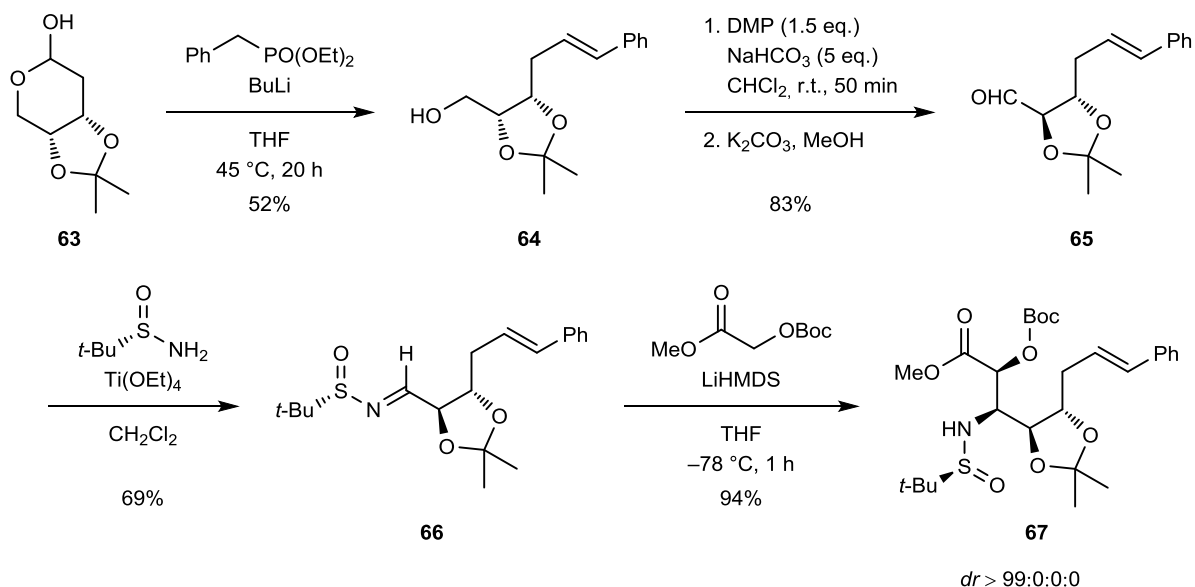
Entry	Conditions ^a	Results ^b
1	Sikkon CaSO ₄ , 2-MP (2.0 eq.), <i>p</i> -TsOH·H ₂ O (0.1 eq.), DMF, 0 °C, > 3 h	No reaction
2	2,2-DMP/ <i>p</i> -TsOH·H ₂ O (0.1 eq.), DMF, -10 °C, overnight	No reaction
3	2-MP (1.3 eq.), PPTS·H ₂ O (0.1 eq.), EtOAc, -10 °C, > 6 h	No reaction
4	CaSO ₄ , 2-MP (1.3 eq.), PPTS·H ₂ O (0.1 eq.), EtOAc, -10 °C, > 6 h	No reaction
5 ^c	2,2-DMP (1.3 eq.), PPTS·H ₂ O (0.1 eq.), EtOAc, -10 °C, > 6 h	Complex
6 ^d	2-MP (1.3 eq.), PPTS (0.1 eq.), EtOAc, -10 °C, > 6 h	66%
7 ^d	2-MP (1.5 eq.), PPTS (0.1 eq.), EtOAc, -10 °C, > 6 h	62%

Notes: ^a Conditions: dried DMF and EtOAc under argon; ^b Isolated yield or checked by TLC and ¹H NMR; ^c EtOAc not distilled; ^d PPTS was recrystallized in acetone.

Table 10: Ketal protection of 2-deoxy-D-ribose

conditions such as 2,2-dimethoxypropane/*p*-TsOH·H₂O,⁷²³ 2-methoxypropene/PPTS·H₂O,⁷²⁴ CaSO₄/2-methoxypropene/*p*-TsOH·H₂O were tested with no more success (entries 2-6).⁷²⁵ Finally, the use of 2-methoxypropene in the presence of anhydrous PPTS in dried ethyl acetate according to Robertson's conditions⁷²⁶ allowed the preparation of the expected acetonide **63** in 66% yield.

With 2-deoxy-D-ribose acetonide **63** in hand, we followed the synthetic route as previously described.³⁸⁷ The acetonide was treated with a phosphonate-stabilized carbanion obtained by deprotonation of benzyl diethylphosphonate with BuLi, to furnish the pure *E*-alkene **64** in moderate yield (Scheme 75). In our hands Swern oxidation of alcohol **64** was inefficient and we thus decided to turn to Dess-Martin oxidation. The alcohol **64** was oxidized quantitatively into an aldehyde by treatment with Dess-Martin periodinane in the presence of sodium bicarbonate.^{109,727} This aldehyde was then epimerized at the α -position by treatment with K₂CO₃ in MeOH³⁹³ to give aldehyde **65**. Condensation of this aldehyde with (*S*)-(-)-*tert*-butanesulfinamide in the presence of Ti(OEt)₄ gave the chiral sulfinimine **66** in 69% yield,³⁹⁴ which was then treated with the lithium enolate of *O*-Boc methyl glycolate to produce the protected APTO derivative **67** in excellent yield and complete diastereochemical control (*dr* > 99:0:0:0).

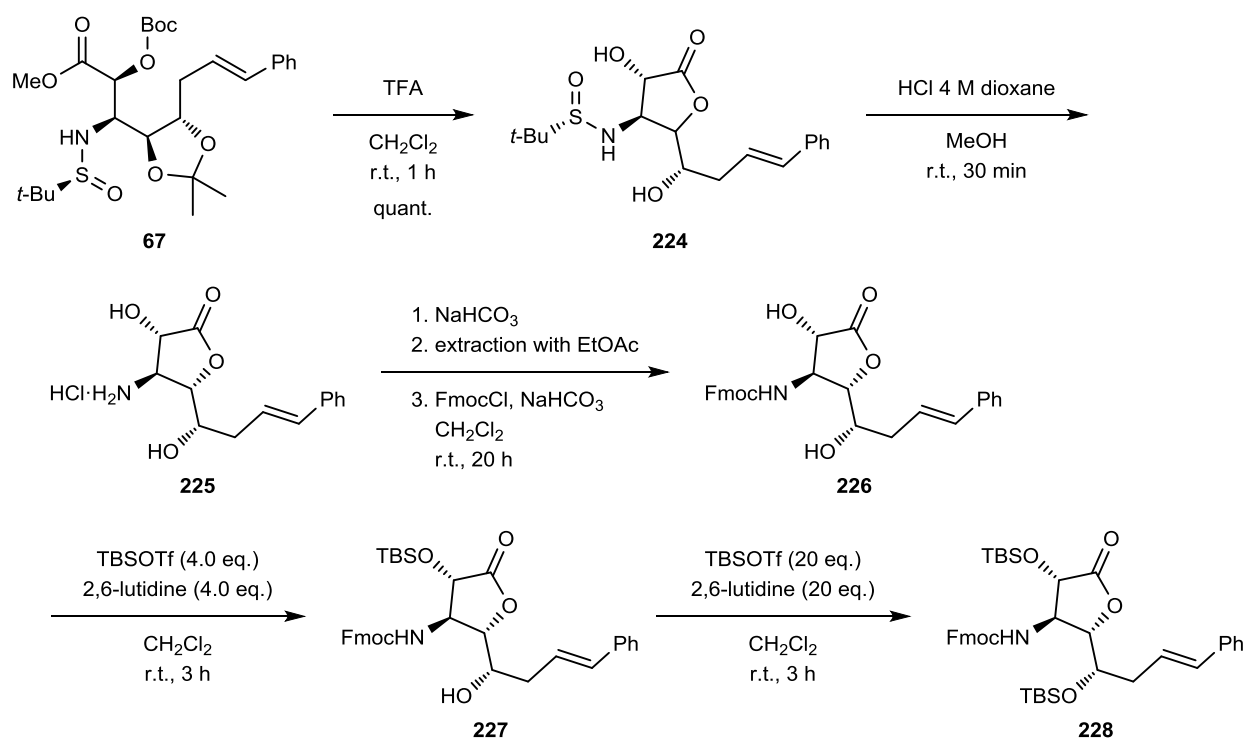


Scheme 75: Synthesis of a protected APTO derivative

With the protected APTO derivative secured, we needed to adapt the protecting group pattern to fit with our proposed total synthesis strategy. Thus, all the hydroxyl groups should be

protected as TBS ether and the amino group should be protected by a Fmoc group. Since the *tert*-butanesulfinyl, the acetonide and the *O*-Boc group are all acid labile, we decide to try to perform a complete deprotection through the action of TFA.

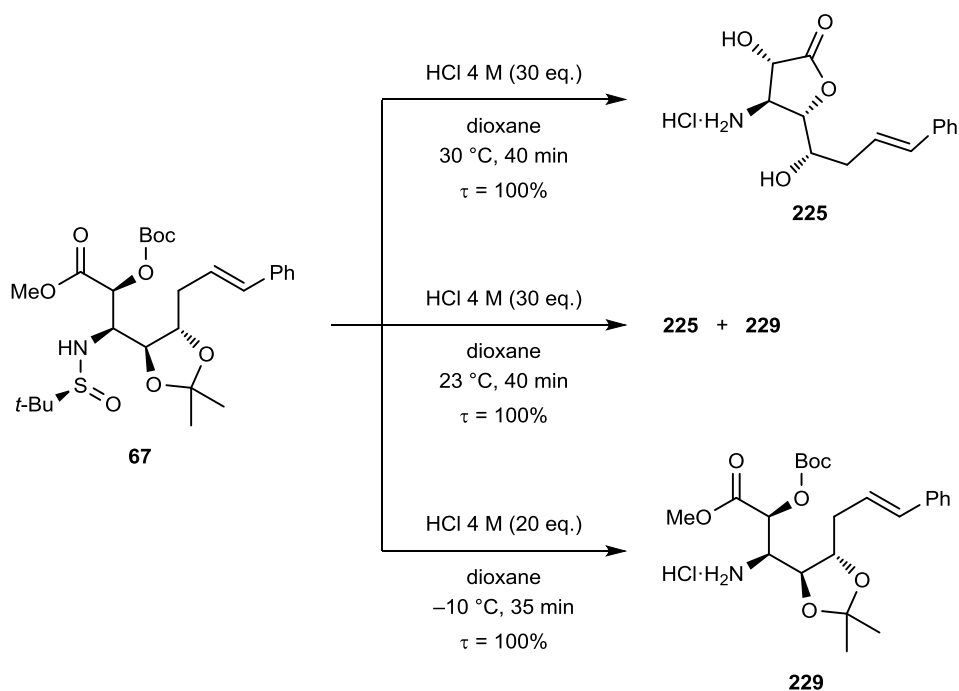
Thus, compound **67** was treated with TFA in dichloromethane (20% v/v) to give the lactone derivative **224** quantitatively, in which the *tert*-butanesulfinyl group remained, and subsequential treatment with 4 M solution of HCl in dioxane gave the ammonium salt **225** (Scheme 76). Obtention of this lactone was not a surprising result since it has been also observed by Donohoe⁴³⁸ and Davies.⁴¹⁸ Then treatment of **224** with a 4 M solution of HCl in dioxane and methanol for 1.5 h produced the ammonium salt **225** quantitatively. Moreover, when treated with a 4 M solution of HCl in dioxane and methanol for 1.5 h at room temperature, the *tert*-butanesulfinyl, *O*-Boc and acetonide groups of compound **67** were all fully removed, and only traces of residual acetonide were observed, directly giving the the ammonium salt **225**. The salt was directly treated with FmocCl in the presence of NaHCO₃ to give the Fmoc protected lactone **226**. Protection of the free hydroxyl groups using TBSOTf in the presence of 2,6-lutidine gave only the mono protected compound **227**. Further treatment with large amount of TBSOTf and 2,6-lutidine was performed, but we were unable to confirm the formation of compound **228** bearing two TBS groups.



Scheme 76: Deprotection of the APTO derivative **67** with TFA or HCl

These results indicated that both the *O*-Boc group and the acetonide can be removed easily with TFA or HCl, whereas removal of the *tert*-butylsulfinyl group required the use of HCl. With HCl, all protecting groups can be removed in a single operation to provide the ammonium salt **225**. Moreover, it seemed difficult to install more than one TBS on the free hydroxyl groups, probably because of steric hindrance.

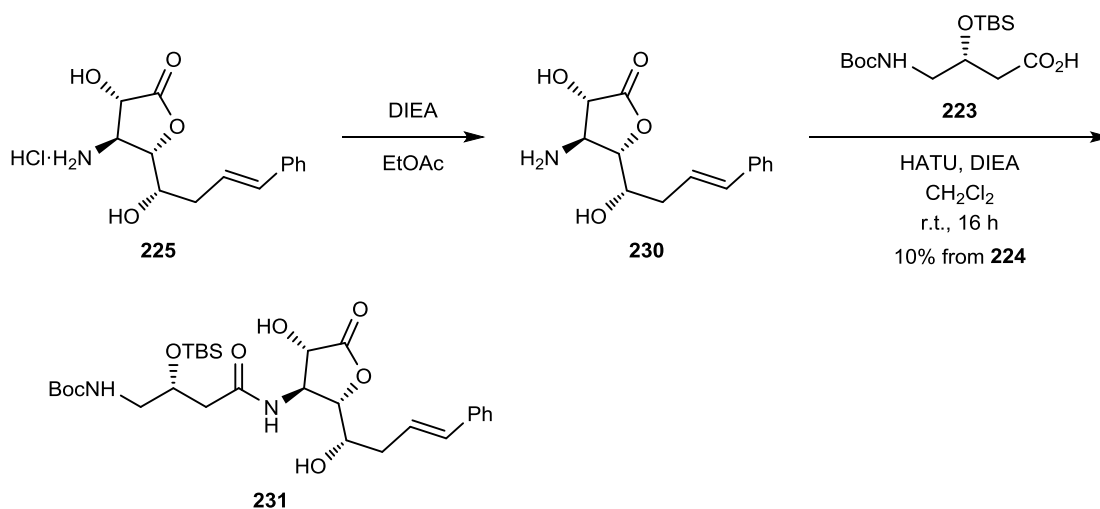
In the literature, the selectivity difference between TFA and HCl in the deprotection of some substrates with both acetonide and *tert*-butylsulfinyl, or with Boc and *tert*-butylsulfinyl has been reported by several groups.^{728,729} We reasoned that it should be possible to selectively remove the *tert*-butylsulfinyl group of APTO derivative **67** using a 4 M solution of HCl in dioxane. In the course of our studies on the deprotection of compound **67** with HCl, we observed that the selectivity was highly dependent on the temperature (Scheme 77). Warm conditions resulted in the formation of the fully-deprotected lactone product **225**, whereas ambient temperature allowed partial removal of the *tert*-butylsulfinyl group. Thus, when the reaction was performed at $-10\text{ }^{\circ}\text{C}$, we were able to obtain the free amine APTO derivative **229** in a completely selective transformation and in quantitative yield.



Scheme 77: Deprotection of the APTO derivative **67** with HCl in dioxane

2.4. Coupling of APTO derivatives with GABOB

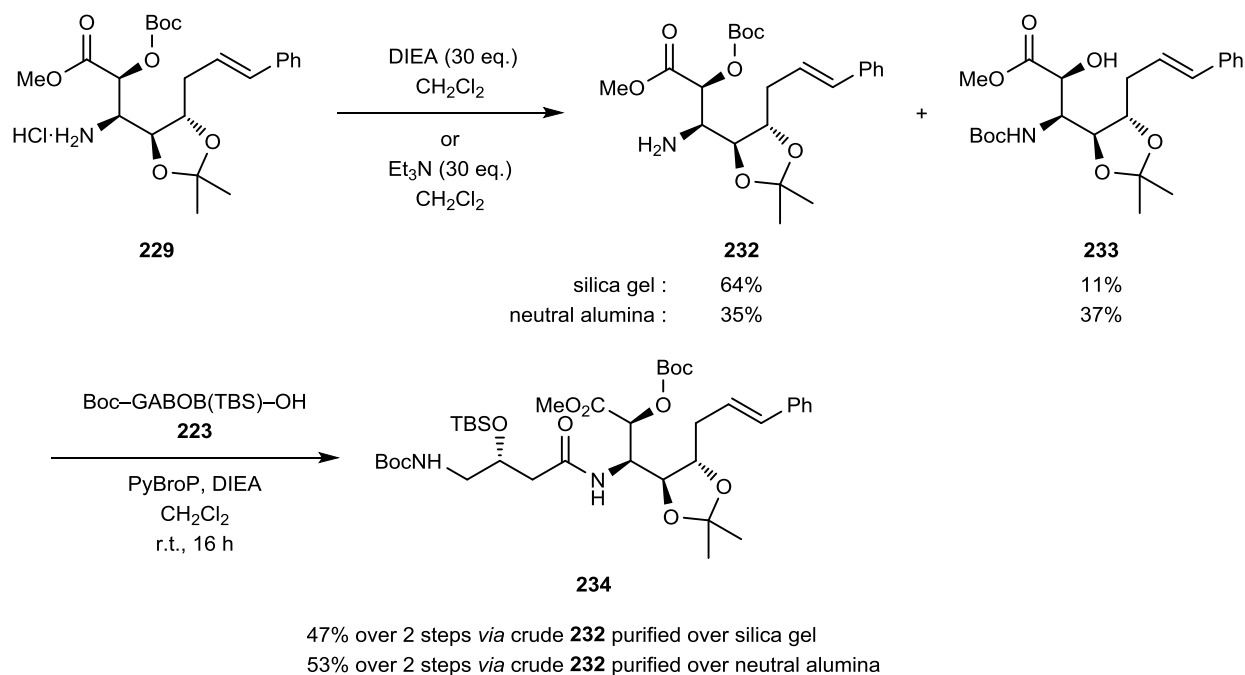
The final stage of the dipeptide synthesis consisted of the coupling of the two protected APTO and GABOB derivatives. We first envisaged the use of the lactone derivative of ammonium salt **225** as a protected APTO derivative in the final steps of our synthesis (Scheme 78). Thus compound **225** was first neutralized with DIEA to give free amine **230**, then engaged in a coupling with the protected GABOB derivative **223** using HATU in the presence of DIEA to produce dipeptide **231** in 10% yield. The low yield may have been the results of the polymerization of the aminolactone and also a second coupling of GABOB with the double hydroxyl groups of **230** or **231**.



Scheme 78: Coupling of APTO lactone derivative with protected GABOB

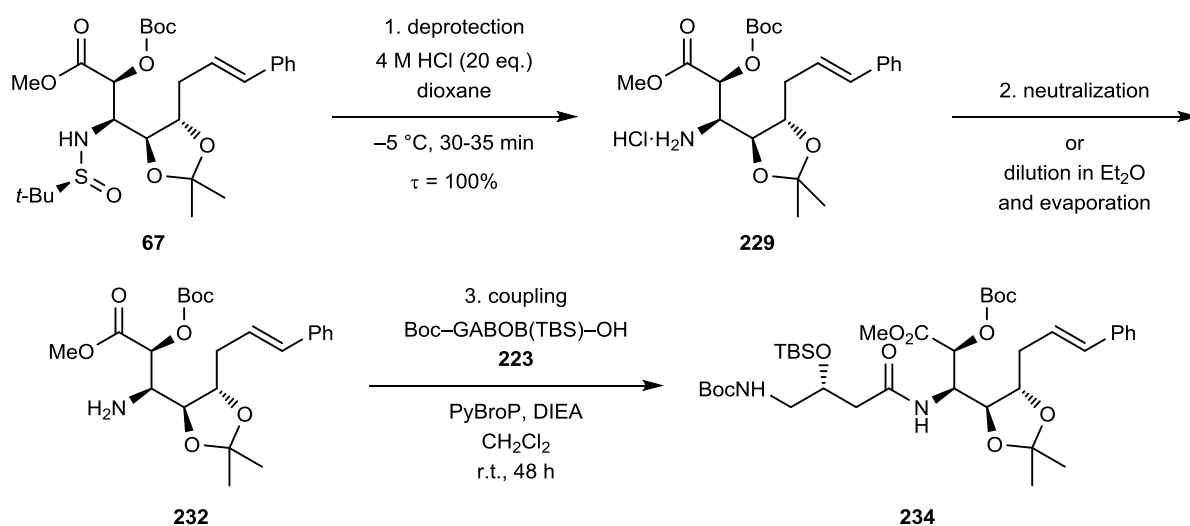
It seemed that we had difficulties to employ lactone derivative of ammonium salt **225**. Thus, we turned to the use of APTO derivative **229** for coupling with GABOB, and after neutralization that give free amine **232** which was very clean when checked by ¹H NMR (Scheme 79). However, in a first experiment, after purification by chromatography over silica gel, we obtained 64% of the desired free amine **232** and 11% yield of the unwanted Boc-migration product **233**. When compound **232** was used for coupling with the GABOB derivative **223** using PyBroP in the presence of DIEA, we were able to obtain 47% of the desired Boc–GABOB–APTO–OMe dipeptide **234**. In order to minimize the Boc-migration process, the crude **232** was purified by chromatography over neutral alumina in a second experiment. Unfortunately results were worse

since we obtained 35% of the free amine **232** and 37% of the Boc-migration product **233**. Coupling of this free amine **232** with GABOB **223** under the same conditions gave 53% of dipeptide **234**.



Scheme 79: Coupling of APTO derivative of free amine **232** with protected GABOB

We confirmed that the point was that the purification by chromatography of free amine **232** was detrimental. Thus, we considered the use of the ammonium salt **229** without purification by chromatography. The crude ammonium salt **229** was rapidly purified by dilution with diethyl ether and evaporated carefully in order to avoid further removal of *O*-Boc and acetonide groups. During this step, the excess of HCl and most of the *t*-butanesulfinyl chloride produced during the deprotection were removed.⁷³⁰ After coupling with GABOB, we were able to obtain up to 72% of the dipeptide **234** (Table 11, entries 1-2). Additionally, a one-pot reaction was also attempted, whereby the ammonium salt obtained by treatment with 4 M HCl was neutralized with DIEA, and Boc-GABOB(TBS)-OH and PyBroP were added to give 53% of the expected dipeptide **234** (entry 3). Finally, when amine **232** was isolated by simple extraction and used directly in the coupling with GABOB, the dipeptide **234** was obtained in 68% yield (entry 4).



Entry	Step 2: Conditions	234 ^a
1 ^b	dilution in Et ₂ O, evaporation	66%
2 ^c	dilution in Et ₂ O, evaporation	72%
3	One-pot reaction 2. DIEA (30 eq.), CH ₂ Cl ₂ , -5 °C 3. 223 , PyBroP, CH ₂ Cl ₂ , r.t., 48 h	53%
4	DIEA (30 eq.), CH ₂ Cl ₂ , -5 °C wash with water and dried over MgSO ₄	68%

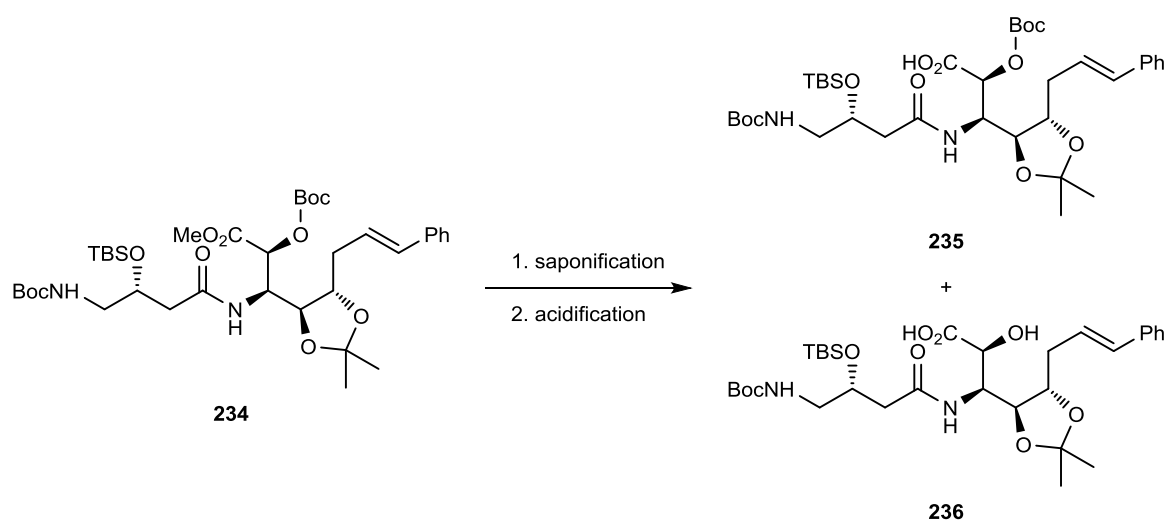
Notes: ^a Isolated yield. ^b 0.1 mmol scale. ^c 0.2 mmol scale

Table 11 Coupling of APTO derivative with GABOB

2.5. Saponification of Boc–GABOB–APTO–OMe

With the dipeptide derivative GABOB–APTO **234** in hand, we undertook the saponification of the methyl ester in order to make this dipeptide ready for peptide coupling (Table 12). Initially, dipeptide **234** was treated with LiOH (4 eq.) at 0 °C and slowly warmed to room temperature for 4 h, but no reaction was observed and the starting material was recovered quantitatively (entry 1). When the reaction was performed with a large excess of LiOH (10 eq.) at room temperature for 16 h, followed by treatment with 10% citric acid at 0 °C until pH = 2-3, the desired dipeptide acid **235** was obtained in 71% yield, accompanied by traces of the alcohol **236** (entry 2). However, when the treatment with 10% citric acid until pH = 2-3 was performed at 5-10 °C, the alcohol **236** was obtained in 80% yield as a single product (entry 3). Since the *O*-Boc group is very sensitive to acidic conditions we tried to control the quenching conditions. Thus, the treatment was performed with a limited amount of citric acid (15 eq.) at -10 °C but 54% of dipeptide acid **235** and 38% of

alcohol **236** were obtained (entry 4). An attempt to re-install the Boc group on alcohol **236** using Boc_2O in the presence of DMAP failed and gave only a mixture of undefined products.



Entry	conditions	235	236
1	1. LiOH (4 equiv.), MeOH/THF/H ₂ O (0.2/0.2/0.3 mL), 0 °C ~ r.t., 4 h 2. 10% citric acid until pH = 2-3 at 0 °C	No reaction	
2	1. LiOH (10 eq.), MeOH/THF/H ₂ O (0.2/0.2/0.3 mL), r.t., 16 h 2. 10% citric acid until pH = 2-3 at 0 °C	71%	trace
3	1. LiOH (10 eq.), MeOH/THF/H ₂ O (0.2/0.2/0.3 mL), r.t., 16 h 2. 10% citric acid until pH = 2-3 at 5~10 °C	0%	80%
4	1. LiOH (10 eq.), MeOH/THF/H ₂ O (0.2/0.2/0.3 mL), r.t., 16 h 2. citric acid (15 eq.) until pH = 3-4 at -10 °C	54%	38%

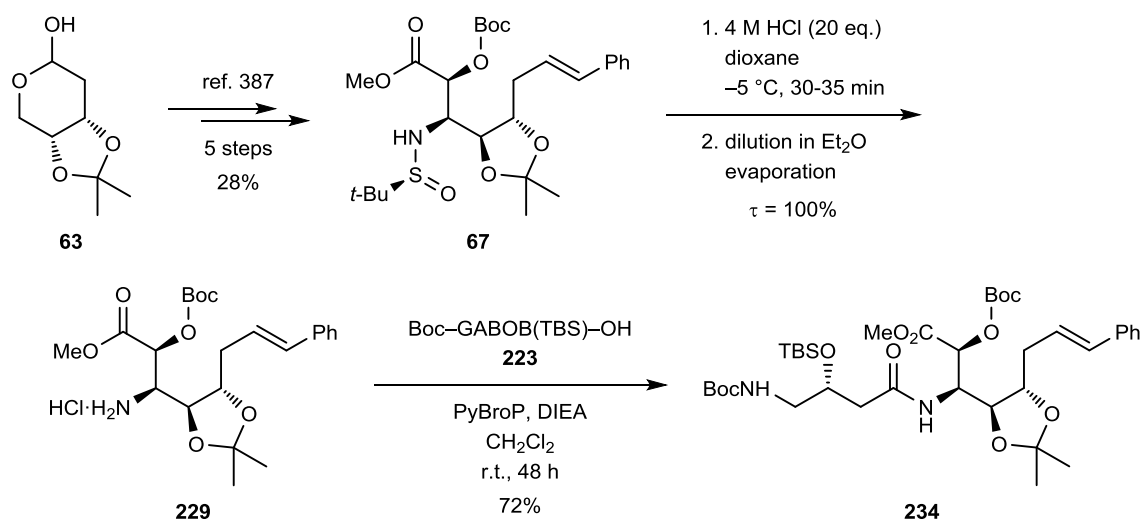
Table 12: Saponification of GABOB–APTO methyl ester with LiOH

4. Conclusion

In summary, starting from acetonide **63**, we were able to prepare the third dipeptide derivative **234** required for the proposed total synthesis of microsclerodermin D in 20.2 % yield over 7 steps and assumed to be enantiomerically pure (Scheme 80).

Key transformations were the completely diastereoselective addition of the lithium enolate of *O*-Boc methyl glycolate on a chiral sulfinimine derived from 2-deoxy-D-ribose which provided the fully protected APTO as a single diastereomer in 94% yield, and selective deprotection of the *tert*-butylsulfinyl group was ensured by the use of 4 M HCl in dioxane at low temperature. The

ammonium salt **228** was directly engaged in the coupling with GABOB to give the dipeptide **234** in an excellent 72% yield over 2 steps avoiding an unwanted Boc migration process.



Scheme 80: Synthesis of the dipeptide Boc–GABOB–APTO–OMe from 2-dexoy-D-ribose

CHAPTER 5

MACROCYCLIC PEPTIDE ASSEMBLY:

PEPTIDE COUPLING

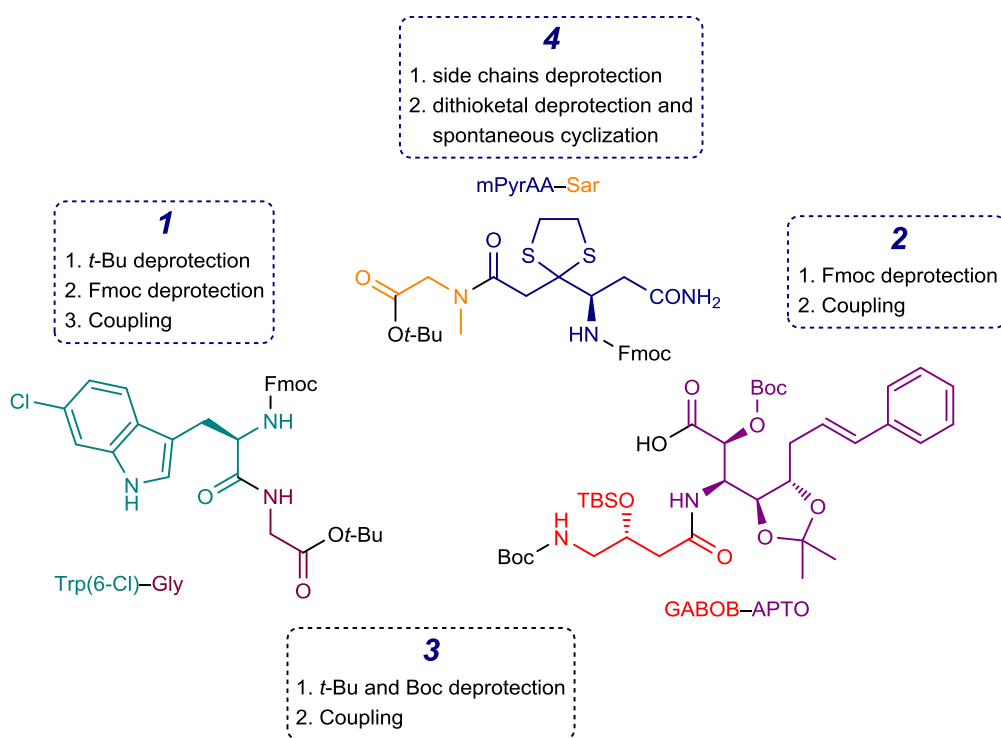
AND

MACROCYCLIZATION

1. Introduction - Strategy

Our objective was to develop a convergent synthesis of microsclerodermin D, using the three dipeptides described in the previous chapters: Fmoc-mPyrAA-Sar-Ot-Bu (*R*)-**189** (Chapter 2), Fmoc-[D-Trp(6-Cl)]-Gly-Ot-Bu **216** (Chapter 3) and Boc-GABOB(TBS)-APTO-OH **235** (Chapter 4). We proposed to assemble first a tetrapeptide, then a hexapeptide, then perform a macrocyclization and finally reveal the PyrAA unit by unmasking the mPyrAA.

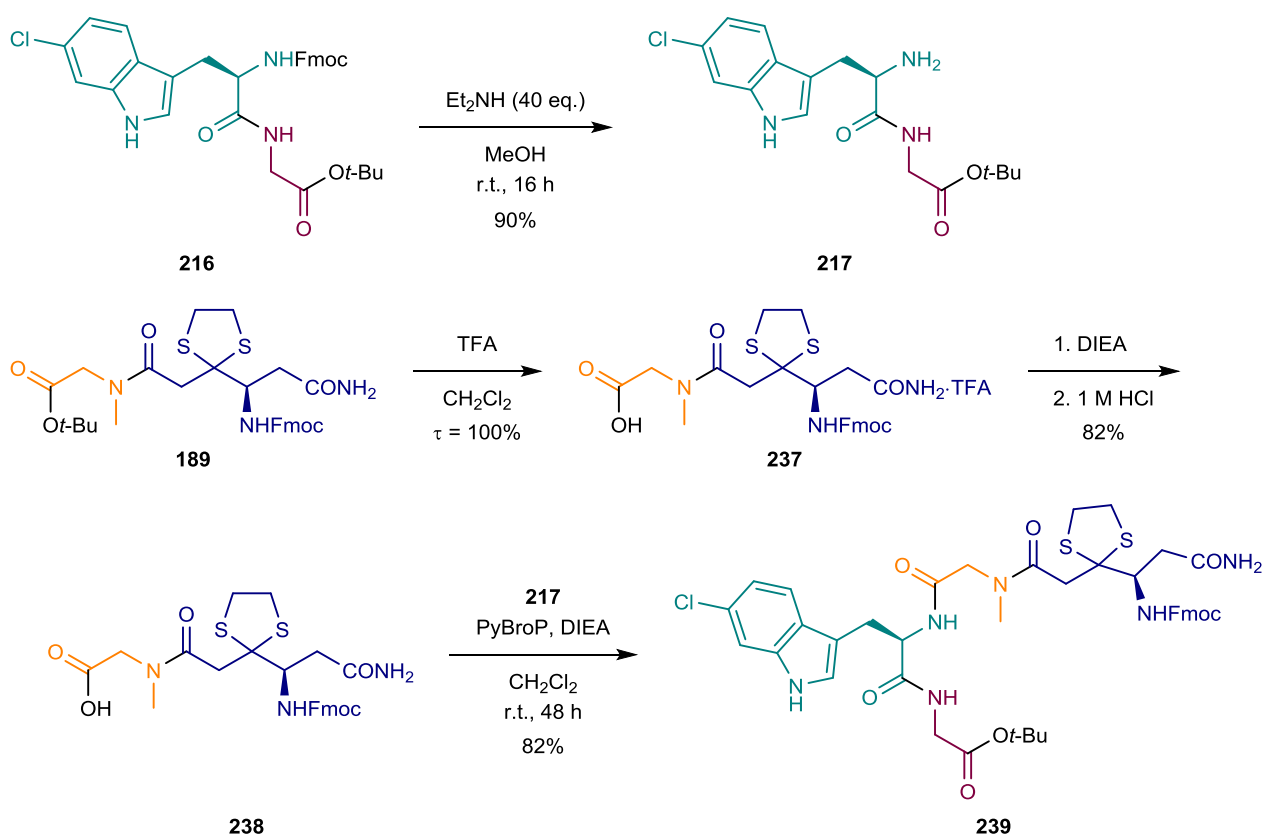
It was proposed that the macrocyclic assembly would start with deprotection of Fmoc-mPyrAA-Sar-Ot-Bu (*R*)-**189** and Fmoc-[D-Trp(6-Cl)]-Gly-Ot-Bu **216** followed by their coupling (Scheme 81). The resulting tetrapeptide Fmoc-mPyrAA-Sar-[D-Trp(6-Cl)]-Gly-Ot-Bu would be deprotected on the *N*-terminal and then coupled to the third dipeptide Boc-GABOB(TBS)-APTO-OH **235**. The linear hexapeptide thus obtained would be deprotected on the *C* and *N*-terminal before macrocyclization. Then the side chains will be deprotected and the dithioacetal group should be removed to liberate the γ -ketoamide which will cyclize spontaneously to install the pyrrolidinoacetic acid residue.



Scheme 81: Macrocyclic peptide assembly and final deprotection

2. Hexapeptide assembly

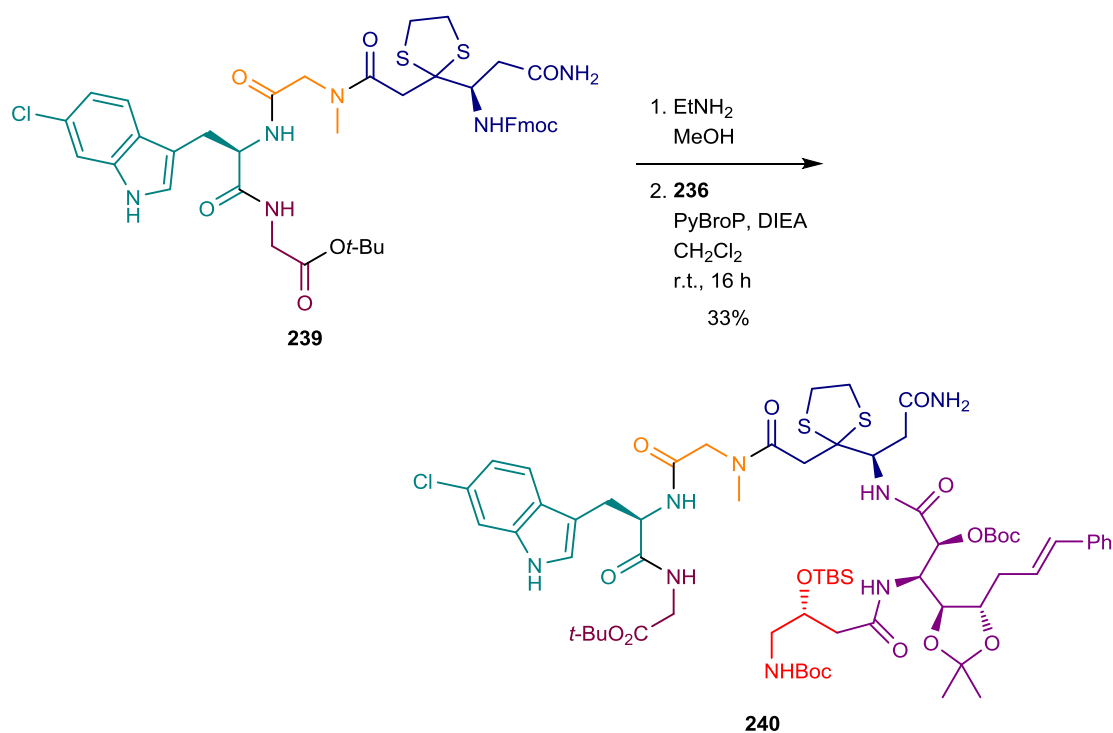
Preparation of the tetrapeptide required the deprotection of the tryptophan residue of **216** and the sarcosine residue of **189** (Scheme 82). The Fmoc group of **216** was first removed by treatment with diethylamine (40 eq.) in methanol overnight to give the dipeptide **217** according to the optimized conditions (See Chapter 3, § 2.3, Scheme 71). In parallel, Deprotection of *t*-butyl ester of **189** was efficiently performed using TFA (40 eq.) in dichloromethane at room temperature to produce the dipeptide acid **237** in a quantitative manner. The product **237** seems to be a complex with TFA as evidence by ^{19}F NMR. Thus, neutralization using DIEA and re-acidified with 1 M HCl, gave the free dipeptide acid **238** in good yield. Finally, peptide coupling of these two dipeptides **238** and **217** using PyBroP in the presence of DIEA gave the corresponding tetrapeptide **239** in 82% yield.



Scheme 82: Preparation of the tetrapeptide **239**

Fmoc deprotection of tetrapeptide **239** was also performed using diethylamine in methanol to give the corresponding free amine quantitatively (Scheme 83). Considering its very likely

instability, it was directly engaged in the coupling with the GABOB–APTO derivative **236**, successfully providing the desired hexapeptide **240** in 33% yield over 2 steps.



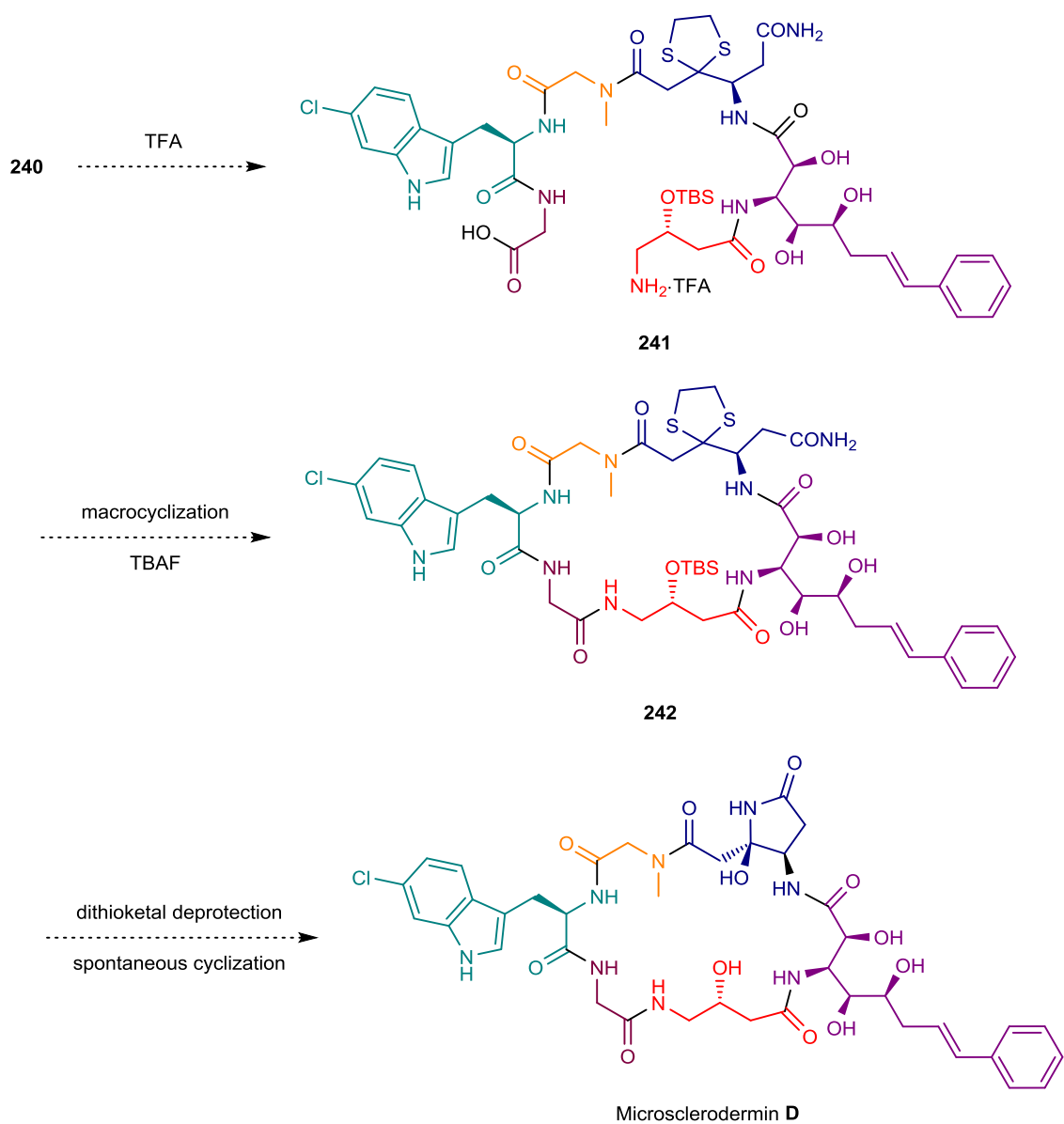
Scheme 83: Preparation of the hexapeptide **240**

3. Macrocyclization and total synthesis of microsclerodermin D

At the time of writing, linear hexapeptide **240** was the most advanced intermediate which has been obtained. The remaining steps of the synthesis consist of:

- a simultaneous deprotection of both the C- and N-terminal residues with TFA, most likely accompanied by acetonide, O-Boc removal from the APTO side chain, to give the macrocyclization precursor **241** (Scheme 84)
- macrocyclization followed by removal of and O-TBS will give the cyclic hexapeptide **242**
- finally deprotection of the dithioacetal was performed by treatment of the macrocyclic peptide with NBS will liberate the γ -ketoamide which will cyclize spontaneously to give microsclerodermin D.

Thus, it is expected that the first total synthesis of microsclerodermin D will be completed soon. The latest result was that we tried once treatment of hexapeptide **240** with TFA and we observed all removal of CO₂t-Bu and N-Boc, acetonide, O-Boc.



Scheme 84: Macrocyclization, dithioketal deprotection and spontaneous cyclization to access microsclerodermin D

GENERAL CONCLUSION

The objective of this PhD thesis was to accomplish the first total synthesis of microsclerodermin D (Figure 32), which features a 23-membered ring macrocyclic peptide comprised of six amino acids, of which three are common: glycine (Gly), sarcosine (Sar) and (*R*)- γ -amino- β -hydroxybutyric acid (GABOB). The other three amino acids possess some structural variations, but they can be classified as a modified tryptophan (Trp(6-Cl)), a polyhydroxylated β -amino acid (APTO) containing four contiguous stereogenic centers and a highly unusual 3-amino-4-hydroxypyrrolidone-4-acetic acid (PyrAA). We planned to develop a modular synthetic route to microsclerodermin D that could be applicable for the preparation of other microsclerodermin family members and their analogues thereof.

We proposed a convergent synthetic approach to microsclerodermin D in which the peptide backbone would be constructed from three dipeptide subunits, then macrolactamized between the glycine and GABOB residues, where there is little steric demand and the *C*-terminal residue is achiral and can be activated without racemization issue. The major difficulty to which we have to face is that the PyrAA unit which is highly sensitive and dehydrates easily in acidic or basic media. Our proposal is therefore to maintain this unit in a masked form all along the synthetic process and to liberate it in the very last step after formation of macrocyclic peptide and deprotection of the various hydroxyl groups.

On this premise, three dipeptides were required: Fmoc-mPyrAA-Sar-*O**t*-Bu (**R**)-**189** (Chapter 2), Fmoc-[D-Trp(6-Cl)]-Gly-*O**t*-Bu **216** (Chapter 3) and Boc-GABOB(TBS)-APTO-OH **235** (Chapter 4), which will be assembled first into a tetrapeptide, then a hexapeptide which would be cyclized before last-step unmasking of the PyrAA unit. This thesis includes 5 chapters.

In Chapter 1, an overview on bioactive natural products, peptides and marine cyclic peptides, as well as a detailed introduction on microsclerodermins was presented. The important thesis results we have achieved are summarized below from chapter 2 to chapter 5.

In Chapter 2, we focused on the synthesis of key dipeptide mPyrAA-Sar, including its synthesis and evaluation of the unmasking strategy. According to our synthetic strategy and route, a

N-Cbz protection synthetic route was first attempted, but *N*-Cbz protected β -ketoester **177** was sensitive to 1,2-ethanedithiol/BF₃·Et₂O, and underwent extensive degradation; the expected dithioketal product **178** was obtained only in low yield (Scheme 37). We decided to replace the Cbz group by a Fmoc group. However, this failed to give optically pure β -ketoester **180** using Masamune's procedure with *N*-Fmoc protected substrate **179** (Scheme 38). Many other methods were tried, such as direct condensation of a Weinreb amide with a lithium enolate (Scheme 51), coupling with Meldrum's acid followed by treatment with benzyl alcohol (Scheme 53), use of *N*-Phth protected substrate in the Masamune's procedure (Scheme 54), Mukaiyama aldol condensation followed by oxidation (Scheme 55) and homologation of an aldehyde through the Roskamp reaction (Scheme 57). The optically pure β -ketoester was finally obtained successfully *via* condensation of *N*-Fmoc protected UNCA with magnesium hemimalonate successfully. Optimization of the condensation of the magnesium hemimalonate to the Fmoc-UNCA derivative of L- and D-aspartic acid allowed the preparation of the key benzyl γ -amino- β -ketoester **180** with a good enantiomeric excess up to 90% (Table 8 and 9). Additionally, evaluation of the unmasking strategy was performed using racemic dipeptide **189**. Surprisingly, treatment of dipeptide **189** with NBS provided 33% yield of the hydroxypyrrolidone derivative **193**, as well as 5% yield of the dehydrated compound **194** (Table 6, entry 10). This encouraging result confirmed the potential of our strategy to install the sensitive hydroxypyrrolidinoacetic acid residue by the deprotection of dithioketal and cyclization sequence and it was therefore retained for the pursuit of our work the total synthesis of microsclerodermin D. Thus, (*S*)-mPyrAA–Sar dipeptide (*S*)-**189** was obtained in 20.1% over 8 steps through the synthesis developed above (Scheme 60). The same synthetic route was then applied to prepare the target (*R*)-mPyrAA–Sar dipeptide (*R*)-**189** from D-aspartic acid in 19.3% yield over 8 steps (Scheme 61). Similarly to the (*S*)-derivative, the key benzyl γ -amino- β -ketoester (*R*)-**180** was obtained with a good enantiomeric excess above 90%.

In Chapter 3, we concentrated on the synthesis of the dipeptide Trp(6-Cl)–Gly fragment. Based on Shiori's work, we have completed the synthesis of the Fmoc-[D-Trp(6-Cl)]–Gly–*O**t*-Bu dipeptide **216** in 32.2% yield over 7 steps with an enantiomeric excess of 94%, starting from 6-chloroindole (Scheme 71). The chiral center was constructed using a classic strategy for α -amino acids preparation based on the diastereoselective alkylation of the chiral Schiff base derived from 2-hydroxypinanone and glycine *t*-butyl ester with a gramine type ammonium salt. In order to

evaluate the enantiomeric excess, the racemic material was also prepared according to a similar strategy, but the chiral Schiff base was replaced by the benzophenone imine derivative **218** (Scheme 72). The racemic dipeptide (\pm)-**216** was obtained in good yield and used to establish chiral HPLC conditions to evaluate the enantiomeric excess.

In Chapter 4, firstly, the preparation of GABOB was completed over 4 steps in 45.2% yield from commercially available ethyl (*R*)-4-chloro-3-hydroxybutanoate according to Hayashi's procedures (Scheme 74). The protected ATPO derivative was then prepared from 2-deoxy-D-ribose according to an in-house the procedure. Starting from acetamide **63**, we were able to access the dipeptide GABOB–APTO **234** requires for the synthesis of microsclerodermin D in 20.2% yield over 7 steps and assumed to be enantiomerically pure. A key transformation was the completely diastereoselective addition of the lithium enolate of *O*-Boc methyl glycolate on a chiral sulfinimine derived from 2-deoxy-D-ribose which provided the fully protected APTO as a single diastereoisomer in 94% yield. Selective deprotection of the *tert*-butanesulfinyl group was ensured by the use of 4 M HCl in dioxane at low temperature. Finally, the ammonium salt **229** was directly engaged in the coupling with GABOB to give the dipeptide **234** in 72% yield in 2 steps and avoiding an unwanted Boc migration process (Scheme 80).

In Chapter 5, with the required three dipeptides: Fmoc–mPyrAA–Sar–*Ot*-Bu (*R*)-**189**, Fmoc–[D-Trp(6-Cl)]–Gly–*Ot*-Bu **216** and Boc–GABOB(TBS)–APTO–OH **235** (Chapter 4) in hand, the macrocyclic assembly was initiated with deprotection of Fmoc–mPyrAA–Sar–*Ot*-Bu (*R*)-**189** and Fmoc–[D-Trp(6-Cl)]–Gly–*Ot*-Bu **216**. Peptide coupling of **238** and **217** gave the corresponding tetrapeptide Fmoc–mPyrAA–Sar–[D-Trp(6-Cl)]–Gly–*Ot*-Bu **239** in 82% yield (Scheme 82). The *N*-terminal Fmoc removal of **239** and then direct coupling with the third dipeptide Boc–GABOB(TBS)–APTO–OH **235** provided the linear hexapeptide **240** in 33% yield over 2 steps (Scheme 83). The hexapeptide **240** is ready for deprotection and macrocyclization, and should give rise to the macrocyclic peptide **242**. The dithioketal group will be removed in the last step to liberate the γ -ketoamide which is expected to cyclize spontaneously to install the pyrrolidinoacetic acid residue to provide the target microsclerodermin D (Scheme 84).

In conclusion, it is expected that the first total synthesis of microsclerodermin D will be completed soon.

BIBLIOGRAPHY

-
- [1] "Biodiversity: A Continuing Source of Novel Drug Leads" G. M. Cragg, D. J. Newman, *Pure Appl. Chem.* **2005**, *77*, 7-24.
- [2] "Natural Products in Drug Discovery: Impacts and Opportunities – An Assessment" G. Brahmachari Dans *Bioactive Natural Products: Opportunities and Challenges in Medicinal Chemistry*; World Scientific Publishing Co. Pte. Ltd.: Singapore, 2012, p 1-199.
- [3] "Accessing Bioactive Natural Products from the Human Microbiome" A. Milshteyn, D. A. Colosimo, S. F. Brady, *Cell Host Microbe* **2018**, *23*, 725-736.
- [4] "Bioactive Natural Products" M. Christmann, *Bioorg. Med. Chem.* **2017**, *25*, 6087.
- [5] "*Bioactive Natural Products: Detection, Isolation, and Structural Determination*" 2nd ed.; S. M. Colegate, R. J. Molyneux, Eds.; CRC Press: Boca Raton, FL, 2007.
- [6] Y. Naya, K. Tachibana, K. Nakanishi Dans *Marine Biotechnology: Pharmaceutical and Bioactive Natural Product*; Attaway, D. H., Zaborsky, O. R., Eds.; Springer: Boston, MA, 1993; Vol. 1, p 45-76.
- [7] "Marine Natural Product Drug Discovery: Leads for Treatment of Inflammation, Cancer, Infections, and Neurological Disorders" F. A. Villa, L. Gerwick, *Immunopharmacol. Immunotoxicol.* **2010**, *32*, 228-237.
- [8] "Natural Products as a Resource for New Drugs" A. M. Clark, *Pharm. Res.* **1996**, *13*, 1133-1144.
- [9] "Natural Products as Sources of New drugs. A General Overview" M. d. C. Avendaño López, *An. R. Acad. Nac. Farm.* **2011**, *77*, 12-26.
- [10] "Natural Products in Modern Life Science" L. Bohlin, U. Göransson, C. Alsmark, C. Wedén, A. Backlund, *Phytochem. Rev.* **2010**, *9*, 279-301.
- [11] "Natural Products: Leads for Drug Discovery and Development" R. Sehgal, M. Nandave, S. K. Ojha, *Pharma Rev.* **2006**, *4*, 40-44.
- [12] "A Historical Overview of Natural Products in Drug Discovery" D. A. Dias, S. Urban, U. Roessner, *Metabolites* **2012**, *2*, 303-336.
- [13] "Natural Products" C. B. Spainhour Dans *Drug Discovery Handbook*; Wiley Online Library: 2005, p 11-72.
- [14] "Metabolites in Plants and its Classification" R. Irchhaiya, A. Kumar, A. Yadav, N. Gupta, S. Kumar, N. Gupta, S. Kumar, V. Yadav, A. Prakash, H. Gurjar, *World J. Pharm. Pharm. Sci.* **2015**, *4*, 287-305.

- [15] “Bioactive Microbial Metabolites: A Personal View” J. Bérdy, *J. Antibiot.* **2005**, *58*, 1-26.
- [16] “Studies in Natural Products Chemistry” R. Atta-ur Dans; Elsevier B.V.: 2019; Vol. 62, p 492.
- [17] “The Role of Natural Product Chemistry in Drug Discovery” M. S. Butler, *J. Nat. Prod.* **2004**, *67*, 2141-2153.
- [18] “Natural Products as Leads to Anticancer Drugs” M. Gordaliza, *Clin. Transl. Oncol.* **2007**, *9*, 767-776.
- [19] “Natural Products – The Future Scaffolds for Novel Antibiotics?” M. S. Butler, A. D. Buss, *Biochem. Pharmacol.* **2006**, *71*, 919-929.
- [20] “Phytochemistry and Medicinal Plants” J. D. Phillipson, *Phytochemistry* **2001**, *56*, 237-243.
- [21] “Medicinal Plants in Therapy” N. R. Farnsworth, O. Akerele, A. S. Bingel, D. D. Soejarto, Z. Guo, *Bull. World Health Organ.* **1985**, *63*, 965-981.
- [22] “Natural Products Chemistry in the Third Millennium” V. Bankova, *Chem. Cent. J.* **2007**, *1*, 1.
- [23] “Synthesis” R. B. Woodward Dans *Perspectives in Organic Chemistry*; Interscience Publishers, Inc.: New York, 1956, p 155-184.
- [24] “Modern Natural Products Drug Discovery and Its Relevance to Biodiversity Conservation” D. G. I. Kingston, *J. Nat. Prod.* **2011**, *74*, 496-511.
- [25] “Natural Products as Drug Leads: An Old Process or The New Hope for Drug Discovery?” D. G. I. Kingston, D. J. Newman, *IDrugs* **2005**, *8*, 990-992.
- [26] “A Review of the Microbial Production of Bioactive Natural Products and Biologics” J. V. Pham, M. A. Yilma, A. Feliz, M. T. Majid, N. Maffetone, J. R. Walker, E. Kim, H. J. Cho, J. M. Reynolds, M. C. Song, S. R. Park, Y. J. Yoon, *Front. Microbiol.* **2019**, *10*, 1404.
- [27] “Natural Products as Sources of New Drugs from 1981 to 2014” D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2016**, *79*, 629-661.
- [28] “Artemisinin: An Endoperoxidic Antimalarial from *Artemisia Annu L*” H. Ziffer, R. J. Hight, D. L. Klayman, *Fortschritte der Chemie Organischer Naturstoffe* **1997**, *72*, 121-214.
- [29] “Qinghaosu (Artemisinin) – Revelations from History and Reality” Y. Wu, *Huaxue Jinzhan* **2009**, *21*, 2365-2371.
- [30] “The Discovery of Artemisinin (Qinghaosu) and Gifts from Chinese Medicine” Y. Tu, *Nat.*

- Med.* **2011**, *17*, 1217-1220.
- [31] “Key Natural Products in Malaria Chemotherapy: From Quinine to Artemisinin and Beyond” J. Fotie Dans *Bioactive Natural Products: Opportunities and Challenges in Medicinal Chemistry*; World Scientific Publishing Co. Pte. Ltd.: Singapore, 2012, p 223-271.
- [32] “Artemisinin, A Novel Antimalarial Drug: Biochemical and Molecular Approaches for Enhanced Production” M. Z. Abdin, M. Israr, R. U. Rehman, S. K. Jain, *Planta Med.* **2003**, *69*, 289-299.
- [33] “A Brief History of Qinghaosu” N. J. White, T. T. Hien, F. H. Nosten, *Trends Parasitol.* **2015**, *31*, 607-610.
- [34] “Qinghaosu (Artemisinin): An Antimalarial Drug from China” D. L. Klayman, *Science (Washington, D. C., 1883-)* **1985**, *228*, 1049-1055.
- [35] “The History of Qing Hao in the Chinese Materia Medica” E. Hsu, *Trans. R. Soc. Trop. Med. Hyg.* **2006**, *100*, 505-508.
- [36] “Artemisinin: A Promise for the Development of Potent Anticancer Agents” D. L. da Silva, L. V. Modolo, I. M. O. Sousa, R. A. F. Rodrigues, Â. de Fátima Dans *Bioactive Natural Products: Opportunities and Challenges in Medicinal Chemistry*; World Scientific Publishing Co. Pte. Ltd.: 2012, p 311-334.
- [37] “Artemisinin and Its Derivatives: A Novel Class of Anti-Malarial and Anti-Cancer Agents” D. Chaturvedi, A. Goswami, P. Pratim Saikia, N. C. Barua, P. G. Rao, *Chem. Soc. Rev.* **2010**, *39*, 435-454.
- [38] “Recognition of the Role of Natural Products as Drugs to Treat Neglected Tropical Diseases by the 2015 Nobel Prize in Physiology or Medicine” J. H. McKerrow, *Nat. Prod. Rep.* **2015**, *32*, 1610-1611.
- [39] “Haem-Activated Promiscuous Targeting of Artemisinin in *Plasmodium Falciparum*” J. Wang, C.-J. Zhang, W. N. Chia, C. C. Y. Loh, Z. Li, Y. M. Lee, Y. He, L.-X. Yuan, T. K. Lim, M. Liu, C. X. Liew, Y. Q. Lee, J. Zhang, N. Lu, C. T. Lim, Z.-C. Hua, B. Liu, H.-M. Shen, K. S. W. Tan, Q. Lin, *Nat. Commun.* **2015**, *6*, 10111.
- [40] “Amphidinolide T, Novel 19-Membered Macrolide from Marine Dinoflagellate *Amphidinium* sp.” M. Tsuda, T. Endo, J. i. Kobayashi, *J. Org. Chem.* **2000**, *65*, 1349-1352.
- [41] “Amphidinolide T5, A New 19-Membered Macrolide from a Dinoflagellate and X-Ray Structure of Amphidinolide T1” T. Kubota, T. Endo, M. Tsuda, M. Shiro, J. i. Kobayashi,

- Tetrahedron* **2001**, *57*, 6175-6179.
- [42] “Amphidinolides T2, T3, and T4, New 19-Membered Macrolides from the Dinoflagellate *Amphidinium* sp. and the Biosynthesis of Amphidinolide T1” J. i. Kobayashi, T. Kubota, T. Endo, M. Tsuda, *J. Org. Chem.* **2001**, *66*, 134-142.
- [43] “Amphidinolides: Unique Macrolides from Marine Dinoflagellates” M. Ishibashi, J. i. Kobayashi, *Heterocycles* **1997**, *44*, 543-572.
- [44] “Chemistry of Potent Anti-Cancer Compounds, Amphidinolides” T. K. Chakraborty, S. Das, *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 131-149.
- [45] “Bioactive Macrolides and Polyketides from Marine Dinoflagellates” J. i. Kobayashi, K. Shimbo, T. Kubota, M. Tsuda, *Pure Appl. Chem.* **2003**, *75*, 337-342.
- [46] “Bioactive Macrolides and Polyketides from Marine Dinoflagellates of the Genus *Amphidinium*” J. i. Kobayashi, T. Kubota, *J. Nat. Prod.* **2007**, *70*, 451-460.
- [47] “Antitumor Marine Natural Products” I. Kitagawa, M. Kobayashi, *Yuki Gosei Kagaku Kyokaishi* **1991**, *49*, 1053-1061.
- [48] “Plant Antitumor Agents. VI. Isolation and Structure of Taxol, a Novel Antileukemic and Antitumor Agent from *Taxus Brevifolia*” M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327.
- [49] “Promotion of Microtubule Assembly *in vitro* by Taxol” P. B. Schiff, J. Fant, S. B. Horwitz, *Nature* **1979**, *277*, 665-667.
- [50] “Recent Advances in Medicinal Chemistry of Taxol” D. M. Vyas, *Pharmacochem. Libr.* **1993**, *20*, 261-270.
- [51] “*Taxol Science and Applications*; M. Suffness, Ed.; CRC Press: Boca Raton, FL, 1995.
- [52] “Taxol: From Discovery to Therapeutic Use” M. Suffness, *Annu. Rep. Med. Chem.* **1993**, *28*, 305-314.
- [53] “The Chemistry of Taxol, A Clinically Useful Anticancer Agent” D. G. I. Kingston, G. Samaranayake, C. A. Ivey, *J. Nat. Prod.* **1990**, *53*, 1-12.
- [54] “Recent Advances in the Chemistry of Taxol” D. G. I. Kingston, *J. Nat. Prod.* **2000**, *63*, 726-734.
- [55] “Paclitaxel (Taxol[®]): A Success Story with Valuable Lessons for Natural Product Drug Discovery and Development” G. M. Cragg, *Med. Res. Rev.* **1998**, *18*, 315-331.
- [56] “The Story of Taxol: Ecstasy and Torment” K. Kacprzak, *Wiad. Chem.* **1998**, *52*, 843-870.

- [57] "Tubulin-Interactive Natural Products as Anticancer Agents" D. G. I. Kingston, *J. Nat. Prod.* **2009**, *72*, 507-515.
- [58] "Chemical Studies of 10-Deacetyl Baccatin III. Hemisynthesis of Taxol Derivatives" F. Guéritte-Voegelein, V. Sénilh, B. David, D. Guénard, P. Potier, *Tetrahedron* **1986**, *42*, 4451-4460.
- [59] "Taxol and Derivatives: A Biogenetic Hypothesis" F. Guéritte-Voegelein, D. Guénard, P. Potier, *J. Nat. Prod.* **1987**, *50*, 9-18.
- [60] "Chemistry and Structure-Activity Relationships of Taxoids with Modified Skeletons" F. Guéritte-Voegelein, D. Guénard, J. Dubois, A. Wahl, R. Marder, R. Müller, M. Lund, L. Bricard, P. Potier, *ACS Symp. Ser.* **1995**, *583*, 189-202.
- [61] "Taxol and Taxotere: Discovery, Chemistry, and Structure-Activity Relationships" D. Guénard, F. Guéritte-Voegelein, P. Potier, *Acc. Chem. Res.* **1993**, *26*, 160-167.
- [62] "Highly Efficient, Practical Approach to Natural Taxol" J.-N. Denis, A. E. Greene, D. Guénard, F. Guéritte-Voegelein, L. Mangatal, P. Potier, *J. Am. Chem. Soc.* **1988**, *110*, 5917-5919.
- [63] "Structural Analysis and Biochemical Study of Isolated Products of the Yew: *Taxus Baccata* L. (Taxaceae)" G. Chauvière, D. Guénard, F. Picot, V. Sénilh, P. Potier, *C. R. Academie. Sci., Ser. II Univers* **1981**, *293*, 501-503.
- [64] "Taxol, Taxotere and Other New Taxanes" M. L. Rothenberg, *Curr. Opin. Invest. Drugs* **1993**, *2*, 1269-1277.
- [65] "Novel Chemistry of Taxol. Retrosynthetic and Synthetic Studies" K. C. Nicolaou, P. G. Nantermet, H. Ueno, R. K. Guy, *J. Chem. Soc., Chem. Commun.* **1994**, 295-296.
- [66] "Chemistry of Taxol and its Analogues" Z. Li, D. Chen, F. Wang, *Huaxi Yaoxue Zazhi* **2000**, *15*, 43-52.
- [67] "Studies on the chemistry of taxol" D. G. I. Kingston, *Pure Appl. Chem.* **1998**, *70*, 331-334.
- [68] "Investigations of the Chemistry of Taxol" J. M. Rimoldi, Virginia Polytechnic Institut and State University, **1993**.
- [69] "The Chemistry of Taxol and Related Taxoids" D. G. I. Kingston, P. G. Jagtap, H. Yuan, L. Samala, *Prog. Chem. Org. Nat. Prod.* **2002**, *84*, 53-225.
- [70] "Taxol: The Chemistry and Structure-Activity Relationships of a Novel Anticancer Agent" D. G. I. Kingston, *Trends Biotechnol.* **1994**, *12*, 222-227.

- [71] “Caminoside A, an Antimicrobial Glycolipid Isolated from the Marine Sponge *Caminus sphaeroconia*” R. G. Linington, M. Robertson, A. Gauthier, B. B. Finlay, R. van Soest, R. J. Andersen, *Org. Lett.* **2002**, *4*, 4089-4092.
- [72] “Caminosides B-D, Antimicrobial Glycolipids Isolated from the Marine Sponge *Caminus sphaeroconia*” R. G. Linington, M. Robertson, A. Gauthier, B. B. Finlay, J. B. MacMillan, T. F. Molinski, R. van Soest, R. J. Andersen, *J. Nat. Prod.* **2006**, *69*, 173-177.
- [73] “First Total Synthesis of Caminoside A, an Antimicrobial Glycolipid from Sponge” J. Sun, X. Han, B. Yu, *Synlett* **2005**, 437-440.
- [74] “Isolation and Structure Elucidation of Chaetocin” D. Hauser, H. P. Weber, H. P. Sigg, *Helv. Chim. Acta* **1970**, *53*, 1061-1073.
- [75] “The Anticancer Agent Chaetocin Is a Competitive Substrate and Inhibitor of Thioredoxin Reductase” J. D. Tibodeau, L. M. Benson, C. R. Isham, W. G. Owen, K. C. Bible, *Antioxid. Redox Signaling* **2009**, *11*, 1097-1106.
- [76] “Epidithiodiketopiperazines (ETPs) Exhibit *in vitro* Antiangiogenic and *in vivo* Antitumor Activity by Disrupting the HIF-1 α /p300 Complex in a Preclinical Model of Prostate Cancer” K. M. Reece, E. D. Richardson, K. M. Cook, T. J. Campbell, S. T. Pisle, A. J. Holly, D. J. Venzon, D. J. Liewehr, C. H. Chau, D. K. Price, W. D. Figg, *Mol. Cancer* **2014**, *13*, 91/91-91/12.
- [77] “Chaetocin: a promising new antimyeloma agent with *in vitro* and *in vivo* activity mediated via imposition of oxidative stress” C. R. Isham, J. D. Tibodeau, W. Jin, R. Xu, M. M. Timm, K. C. Bible, *Blood* **2007**, *109*, 2579-2588.
- [78] “The SUV39H1 Inhibitor Chaetocin Induces Differentiation and Shows Synergistic Cytotoxicity with Other Epigenetic Drugs in Acute Myeloid Leukemia Cells” Y. S. Lai, J. Y. Chen, H. J. Tsai, T. Y. Chen, W. C. Hung, *Blood Cancer J.* **2015**, *5*, e313.
- [79] “The SUV39H1 Methyltransferase Inhibitor Chaetocin Causes Induction of Integrated HIV-1 without Producing a T Cell Response” W. Bernhard, K. Barreto, A. Saunders, M. S. Dahabieh, P. Johnson, I. Sadowski, *FEBS Lett.* **2011**, *585*, 3549-3554.
- [80] “Chaetocin Antileukemia Activity Against Chronic Myelogenous Leukemia Cells is Potentiated by Bone Marrow Stromal Factors and Overcomes Innate Imatinib Resistance” L. Truitt, C. Hutchinson, J. F. De Coteau, C. R. Geyer, *Oncogenesis* **2014**, *3*, e122-121/e122-127.

- [81] “Chaetocin Induces Apoptosis in Human Melanoma Cells Through the Generation of Reactive Oxygen Species and the Intrinsic Mitochondrial Pathway, and Exerts its Anti-Tumor Activity *in vivo*” X. Han, Y. Han, Y. Zheng, Q. Sun, T. Ma, J. Zhang, L. Xu, *PLoS One* **2017**, *12*, e0175950/0175951-e0175950/0175918.
- [82] “Identification of Chaetocin as a Potent non-ROS-mediated Anticancer Drug Candidate for Gastric Cancer” X. Liao, Y. Fan, J. Hou, X. Chen, X. Xu, Y. Yang, J. Shen, P. Mi, W. Zhang, H. Cao, T. Hu, Y.-Y. Zhan, X. Huang, X. Hong, *J Cancer* **2019**, *10*, 3678-3690.
- [83] Y. Xu, L. Sun, J. Chen; CN103550222A, National Intellectual Property Administration, Nanjing Medical University: China, **2014**.
- [84] Y. Xu, X. Weng, Y. Zhao, Y. Li, Y. Hu, J. Song, “Application of Chaetocin in Manufacturing Drugs for Prevention and Treatment of Heart Disease” CN103356637A, **2013**; *Chem. Abstr.* 2013:1654499,
- [85] “Histone Methyltransferase Inhibitors Induce HIV-1 Recovery in Resting CD4+ T Cells from HIV-1-Infected HAART-Treated Patients” S. Bouchat, J.-S. Gatot, K. Kabeya, C. Cardona, L. Colin, G. Herbein, S. De Wit, N. Clumeck, O. Lambotte, C. Rouzioux, O. Rohr, C. Van Lint, *AIDS* **2012**, *26*, 1473-1482.
- [86] “Identification of a Specific Inhibitor of the Histone Methyltransferase SU(VAR)3-9” D. Greiner, T. Bonaldi, R. Eskeland, E. Roemer, A. Imhof, *Nat. Chem. Biol.* **2005**, *1*, 143-145.
- [87] “Effects of Hibarimicins and Hibarimicin-Related Compounds Produced by *Microbispora* on v-Src Kinase Activity and Growth and Differentiation of Human Myeloid Leukemia HL-60 Cells” S. I. Cho, H. Fukazawa, Y. Honma, T. Kajiura, H. Hori, Y. Igarashi, T. Furumai, T. Oki, Y. Uehara, *J. Antibiot.* **2002**, *55*, 270-278.
- [88] “The First Total Synthesis of Hibarimicinone, a Potent v-Src Tyrosine Kinase Inhibitor” K. Tatsuta, T. Fukuda, T. Ishimori, R. Yachi, S. Yoshida, H. Hashimoto, S. Hosokawa, *Tetrahedron Lett.* **2012**, *53*, 422-425.
- [89] “Total Syntheses of HMP-Y1, Hibarimicinone, and HMP-P1” B. B. Liao, B. C. Milgram, M. D. Shair, *J. Am. Chem. Soc.* **2012**, *134*, 16765-16772.
- [90] “Total Synthesis of Hibarimicinone, a v-Src Tyrosine Kinase Inhibitor Possessing the Pseudo-Dimer Structure of Tetracycline” K. Tatsuta, S. Hosokawa, *Chem. Rec.* **2014**, *14*, 28-40.
- [91] “Hyperforin, an Antibiotic from *Hypericum perforatum*” A. I. Gurevich, V. N. Dobrynin, M.

- N. Kolosov, S. A. Popravko, I. D. Ryabova, B. K. Chernov, N. A. Derbentseva, B. E. Aizenman, A. D. Garagulya, *Antibiotiki* **1971**, *16*, 510-513.
- [92] “The Absolute Configuration of Hyperforin, an Antibiotic from *Hypericum perforatum* L., Based on the Crystal Structure Determination of its *p*-Bromobenzoate Ester” I. Brondz, T. Greibrokk, P. Groth, A. J. Aasen, *Acta Chem. Scand., Ser. A* **1983**, *A37*, 263-265.
- [93] “The relative stereochemistry of hyperforin, an antibiotic from *Hypericum perforatum* L” I. Brondz, T. Greibrokk, P. A. Groth, A. J. Aasen, *Tetrahedron Lett.* **1982**, *23*, 1299-1300.
- [94] “Structure of Hyperforin” N. S. Bystrov, B. K. Chernov, V. N. Dobrynin, M. N. Kolosov, *Tetrahedron Lett.* **1975**, 2791-2794.
- [95] “Hyperforin – Antidepressant Activity by a Novel Mechanism of Action” W. E. Muller, A. Singer, M. Wonnemann, *Pharmacopsychiatry* **2001**, *34*, S98-S102.
- [96] “Hyperforin as a Possible Antidepressant Component of *Hypericum* Extracts” S. S. Chatterjee, S. K. Bhattacharya, M. Wonnemann, A. Singer, W. E. Muller, *Life Sci.* **1998**, *63*, 499-510.
- [97] “Hyperforin, a Major Antidepressant Constituent of St. John's Wort, Inhibits Serotonin Uptake by Elevating Free Intracellular Na⁺” A. Singer, M. Wonnemann, W. E. Muller, *J. Pharmacol. Exp. Ther.* **1999**, *290*, 1363-1368.
- [98] “*Hypericum perforatum*: a 'Modern' Herbal Antidepressant: Pharmacokinetics of Active Ingredients” M. Wurglics, M. Schubert-Zsilavecz, *Clin. Pharmacokinet.* **2006**, *45*, 449-468.
- [99] “Inhibition of Tumour Cell Growth by Hyperforin, a Novel Anticancer Drug from St. John's Wort that Acts by Induction of Apoptosis” C. M. Schempp, V. Kirkin, B. Simon-Haarhaus, A. Kersten, J. Kiss, C. C. Termeer, B. Gilb, T. Kaufmann, C. Borner, J. P. Sleeman, J. C. Simon, *Oncogene* **2002**, *21*, 1242-1250.
- [100] “Chemical Instability and Pharmacological Activity of Hyperforin” J. Bai, D. Yang, D. Wang, C. Liu, *Zhongcaoyao* **2004**, *35*, 338-340.
- [101] “Hyperforin” L. Beerhues, *Phytochemistry* **2006**, *67*, 2201-2207.
- [102] “Hyperforin Modifies Neuronal Membrane Properties *in vivo*” G. P. Eckert, J.-H. Keller, C. Jourdan, M. Karas, D. A. Volmer, M. Schubert-Zsilavecz, W. E. Müller, *Neurosci. Lett.* **2004**, *367*, 139-143.
- [103] “Hyperforin Use Against Neurodermatitis” K. Leuner, M. Kraus, W. H. Boehnke, C. M. Schempp, W. E. Müller, *Dtsch. Apoth. Ztg.* **2010**, *150*, 2155-2159.

- [104] “*In vivo* Photoprotective and Anti-Inflammatory Effect of Hyperforin is Associated with High Antioxidant Activity *in vitro* and *ex vivo*” M. C. Meinke, S. Schanzer, S. F. Haag, F. Casetti, M. L. Müller, U. Wölflle, A. Kleemann, J. Lademann, C. M. Schempp, *Eur. J. Pharm. Biopharm.* **2012**, *81*, 346-350.
- [105] “Recent Enhancement of the Immunity in AIDS and Other Immunocompromised Patients by Hyperforin an Antibiotic from *Hypericum perforatum* L. (*in vitro* Model) Part I” I. Brondz, A. Brondz, *J. Biophys. Chem.* **2012**, *3*, 304-310.
- [106] “Hyperforin Acts as an Angiogenesis Inhibitor *in vitro* and *in vivo*” C. M. Schempp, J. Kiss, V. Kirkin, M. Averbeck, B. Simon-Haarhaus, B. Kremer, C. C. Termeer, J. Sleeman, J. C. Simon, *Planta Med.* **2005**, *71*, 999-1004.
- [107] “Haliclolin A, a New Macrocyclic Diamide from the Sponge Haliclona sp” K. H. Jang, G. W. Kang, J.-e. Jeon, C. Lim, H.-S. Lee, C. J. Sim, K.-B. Oh, J. Shin, *Org. Lett.* **2009**, *11*, 1713-1716.
- [108] “Bioactive Nitrogenous Secondary Metabolites from the Marine Sponge Genus *Haliclona*” J. Zhu, Y. Liu, Z. Liu, H. Wang, H. Zhang, *Mar. Drugs* **2019**, *17*.
- [109] “Organocatalytic, Asymmetric Total Synthesis of (–)-Haliclolin A” L.-D. Guo, X.-Z. Huang, S.-P. Luo, W.-S. Cao, Y.-P. Ruan, J.-L. Ye, P.-Q. Huang, *Angew. Chem., Int. Ed.* **2016**, *55*, 4064-4068.
- [110] “Note sur un Nouvel Alkalai” P. J. Pelletier, J. B. Caventou, *Ann. Chim. Phys.* **1818**, *8*, 323.
- [111] “Chapter 17 - Skeletal Muscle Toxicity Biomarkers” R. C. Gupta, M. A. Lasher, R. B. Doss, D. Milatovic Dans *Biomarkers in Toxicology*; Academic Press: Boston, 2014, p 291-308.
- [112] “Strychnine. VII. The Toxicity of *Nux Vomica* Preparations” J. C. Munch, J. C. Ward, F. E. Garlough, *J. Am. Pharm. Assoc.* **1937**, *26*, 29-31.
- [113] “Toxicity of Central Nervous System Stimulants in Rats of Different Ages” I. Setnikar, M. J. Magistretti, *Proc. European Soc. Study Drug Toxicity* **1964**, *4*, 138-139.
- [114] “Toxicity of Strychnine for Male and Female Rats of Different Ages” C. F. Poe, J. F. Suchy, N. F. Witt, *J. Pharmacol. Exp. Ther.* **1936**, *58*, 239-242.
- [115] “The Toxicologic Study of Strychnine” J. M. B. Beguiristain, A. S.-C. Alderete, *Arch. Med. Exp.* **1954**, *17*, 169-176.
- [116] “Strychnine” R. M. Harris Dans *Molecules of Death*; 2nd ed.; Imperial College Press: London, 2007, p 367-385.

- [117] “Strychnine Poisoning” B. A. Smith, *J. Emerg. Med.* **1990**, 8, 321-325.
- [118] “Some Aspects of the Chemistry of Secologanin” L. F. Szabó, *Stud. Nat. Prod. Chem.* **2002**, 26, 95-148.
- [119] “4.16 - Human–Environment Interactions – Taste” K. Izawa, Y. Amino, M. Kohmura, Y. Ueda, M. Kuroda Dans *Comprehensive Natural Products II*; Elsevier: Oxford, 2010, p 631-671.
- [120] “Botany, Phytochemistry, Pharmacology and Toxicity of *Strychnos Nux-vomica* L.: A Review” R. Guo, T. Wang, G. Zhou, M. Xu, X. Yu, X. Zhang, F. Sui, C. Li, L. Tang, Z. Wang, *Am. J. Chin. Med.* **2018**, 46, 1-23.
- [121] “Research on Pharmacology, Toxicology and Safety of Semen *Strychni*: Review and Prospect” Z.-h. Guo, H.-m. Ma, B.-l. Zhang, *J. Chin. Integr. Med.* **2008**, 6, 645-649.
- [122] “Antitumor Activities of Alkaloids from *Strychnos Nux-vomica in vitro*” X. Yang, F. Ran, J. Wu, R. Wang, B. Xu, J. Cui, *Zhongguo Xiandai Zhongyao* **2006**, 8, 11-13.
- [123] “The Anti-Tumor Effects of Alkaloids from the Seeds of *Strychnos Nux-vomica* on HepG2 Cells and its Possible Mechanism” X.-K. Deng, W. Yin, W.-D. Li, F.-Z. Yin, X.-Y. Lu, X.-C. Zhang, Z.-C. Hua, B.-C. Cai, *J. Ethnopharmacol.* **2006**, 106, 179-186.
- [124] “Based on Anti-Tumor Activity Study of *Strychnos Nux-vomica* with Strychnine and Brucine as the Main Active Components” F. Zhang, C.-l. Xu, X.-m. Wang, Z. Qiu, *Zhonghua Zhongyiyao Zazhi* **2014**, 29, 3491-3493.
- [125] “Extraction and Purification of *Strychnos Nux-vomica* Total Alkaloids and their Antitumor Effect” Y. Qi, J. Chen, B. Cai, W. Wang, Y. Gao, *Zhongchengyao* **2010**, 32, 405-408.
- [126] “A Short Review on Anticancer Investigations of *Strychnos Nux-vomica*” A. Sah, G. L. Khatik, M. Vyas, P. Yadav, *Int. J. Green Pharm.* **2016**, 10, S87-S90.
- [127] “Analgesic and Anti-Inflammatory Activity and Pharmacokinetics of Alkaloids from Seeds of *Strychnos Nux-vomica* after Transdermal Administration: Effect of Changes in Alkaloid Composition” J. Chen, X. Wang, Y.-G. Qu, Z.-P. Chen, H. Cai, X. Liu, F. Xu, T.-L. Lu, B.-C. Cai, *J. Ethnopharmacol.* **2012**, 139, 181-188.
- [128] “The Antibacterial and Antitoxic Activity of Bile. III. The Variation of the Toxicity of Alkaloid Solutions by Acidification in Presence of Bile” A. Clementi, R. Pistorio, *Archivio di Scienze Biologiche Arch. Sci. Biol. (Bologna)* **1929**, 13, 320-330.
- [129] “Toxicity of Alkaloids for Certain Bacteria. I. Coniine, Nicotine, and Strychnine” C. C.

- Johnson, G. Johnson, C. F. Poe, *Acta Pharmacol. Toxicol.* **1949**, 5, 222-230.
- [130] "Constitution of Strychnine" R. Robinson, *Experientia* **1946**, 2, 28-29.
- [131] "Constitution of Strychnine and its Relation to Cinchonine" R. Robinson, *Nature* **1947**, 159, 263.
- [132] "Constitution of Strychnine and the Biogenetic Relationship of Strychnine and Quinine" H. T. Openshaw, R. Robinson, *Nature* **1946**, 157, 438.
- [133] "Total Synthesis of Strychnine" R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, I. U. Daeniker, K. Schenker, *J. Am. Chem. Soc.* **1954**, 76, 4749-4751.
- [134] "Joseph Pelletier and Joseph Caventou" M. Delépine, *J. Chem. Educ.* **1951**, 28, 454-461.
- [135] "Notice sur la Matière Verte des Feuilles" P. J. Pelletier, J. B. Caventou, *J. Pharm. Sci. Acc.* **1817**, 3, 486-491.
- [136] "Natural Pigments. IV. Chlorophyll" H. Fischer, M. Strell, *Fiat Rev. German Sci., Biochemistry* **1947**, 141-186.
- [137] "Investigations on Chlorophyll. Methods and Results"; R. Willstätter, A. Stoll; Science Press Printing Company, 1928.
- [138] "Chapter 4 - Nutraceuticals From Algae and Cyanobacteria" A. Udayan, M. Arumugam, A. Pandey Dans *Algal Green Chemistry*; Elsevier: Amsterdam, 2017, p 65-89.
- [139] "11 - Natural Dyes" B. H. Patel Dans *Handbook of Textile and Industrial Dyeing*; Woodhead Publishing: Oxford, 2011; Vol. 1, p 395-424.
- [140] "The Total Synthesis of Chlorophyll" R. B. Woodward, W. A. Ayer, J. M. Beaton, F. Bickelhaupt, R. Bonnett, P. Buchschacher, G. L. Closs, H. Dutler, J. Hannah, F. P. Hauck, S. Ito, A. Langemann, E. LeGoff, W. Leimgruber, W. Lwowski, J. Sauer, Z. Valenta, H. Voltz, *J. Am. Chem. Soc.* **1960**, 82, 3800-3802.
- [141] "The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century" K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem., Int. Ed.* **2000**, 39, 44-122.
- [142] "The Total Synthesis of Chlorophyll *a*" R. B. Woodward, W. A. Ayer, J. M. Beaton, F. Bickelhaupt, R. Bonnett, P. Buchschacher, G. L. Closs, H. Dutler, J. Hannah, F. P. Hauck, S. Itō, A. Langemann, E. Le Goff, W. Leimgruber, W. Lwowski, J. Sauer, Z. Valenta, H. Volz, *Tetrahedron* **1990**, 46, 7599-7659.
- [143] "Extraction, Separation, Estimation, and Isolation of the Chlorophylls" H. H. Strain, W. A.

- Svec Dans *The Chlorophylls*; Academic Press: New York, 1966, p 21-66.
- [144] “An Overview of Chlorophylls and Bacteriochlorophylls: Biochemistry, Biophysics, Functions and Applications” H. Scheer, *Adv. Photosynth. Respir.* **2006**, *25*, 1-26.
- [145] “Chlorophylls and their Derivatives Used in Food Industry and Medicine” K. Solymosi, B. Mysliwa-Kurdziel, *Mini-Rev. Med. Chem.* **2017**, *17*, 1194-1222.
- [146] “The Present Status of Topical Chlorophyll Therapy” L. W. Smith, *N. Y. State J. Med.* **1955**, *55*, 2041-2050.
- [147] “Clinical Experiences with Chlorophyll Preparations with Particular Reference to Chronic Osteomyelitis and Chronic Ulcers” E. B. Carpenter, *Am. J. Surg.* **1949**, *77*, 167-171.
- [148] “Ptilomycalin A: a Novel Polycyclic Guanidine Alkaloid of Marine Origin” Y. Kashman, S. Hirsh, O. J. McConnell, I. Ohtani, T. Kusumi, H. Kakisawa, *J. Am. Chem. Soc.* **1989**, *111*, 8925-8956.
- [149] “Structure and Chemical Properties of Ptilomycalin A” I. Ohtani, T. Kusumi, H. Kakisawa, Y. Kashman, S. Hirsh, *J. Am. Chem. Soc.* **1992**, *114*, 8472-8479.
- [150] “Synthesis and Biological Activity of Analogues of Ptilomycalin A” G. P. Black, S. J. Coles, A. Hizi, A. G. Howard-Jones, M. B. Hursthouse, A. T. McGown, S. Loya, C. G. Moore, P. J. Murphy, N. K. Smith, N. D. A. Walshe, *Tetrahedron Lett.* **2001**, *42*, 3377-3381.
- [151] “Ptilomycalin A Inhibits Laccase and Melanization in *Cryptococcus neoformans*” D. S. Dalisay, J. P. Saludes, T. F. Molinski, *Bioorg. Med. Chem.* **2011**, *19*, 6654-6657.
- [152] “CP-225,917 and CP-263,114, Novel Ras Farnesylation Inhibitors from an Unidentified Fungus. I. Taxonomy, Fermentation, Isolation, and Biochemical Properties” T. T. Dabrah, H. J. Harwood, Jr., L. H. Huang, N. D. Jankovich, T. Kaneko, J.-C. Li, S. Lindsey, P. M. Moshier, T. A. Subashi, M. Therrien, P. C. Watts, *J. Antibiot.* **1997**, *50*, 1-7.
- [153] “Investigations into the Production and Interconversion of Phomoidrides A-D” P. Spencer, F. Agnelli, G. A. Sulikowski, *Org. Lett.* **2001**, *3*, 1443-1445.
- [154] “36 - Antineoplastic Drugs” K. K. Kwok, E. C. Vincent, J. N. Gibson Dans *Pharmacology and Therapeutics for Dentistry*; 7th ed.; Mosby: Saint-Louis, MO, 2017, p 530-562.
- [155] “Role of Chance Observations in Chemotherapy: *Vinca rosea*” R. L. Noble, C. T. Beer, J. H. Cutts, *Ann. N. Y. Acad. Sci.* **1958**, *76*, 882-894.
- [156] “Biological Properties of Vincalukoblastine, an Alkaloid in *Vinca rosea* Linn, with Reference to its Antitumor Action” J. H. Cutts, C. T. Beer, R. L. Noble, *Cancer Res.* **1960**,

- 20, 1023-1031.
- [157] "Current Status of Research on the Alkaloids of *Vinca rosea* Linn. (*Catharanthus roseus* G. Don)" G. H. Svoboda, I. S. Johnson, M. Gorman, N. Neuss, *J. Pharm. Sci.* **1962**, *51*, 707-720.
- [158] "A note on the Alkaloids of *Vinca rosea* Linn. (*Catharanthus roseus* G. Don.). II. Catharanthine, Lochnericine, Vindolinine, and Vindoline" M. Gorman, N. Neuss, G. H. Svoboda, A. J. Barnes, Jr., N. J. Cone, *J. Am. Pharm. Assoc. Am. Pharm. Assoc.* **1959**, *48*, 256-257.
- [159] "Cancer: Principles and Practice of Oncology" R. Hughes, *J. Am. Med. Assoc.* **2005**, *294*, 747-748.
- [160] "Alkaloids of *Vinca rosea* and Their Role in Cancer Chemotherapy" G. H. Svoboda, *Abh. Dtsch. Akad. Wiss. Berlin, Kl. Chem., Geol. Biol.* **1966**, 465-478.
- [161] "Anticancer Agents From Natural Products" 2nd ed.; G. M. Cragg, D. G. I. Kingston, D. J. Newman, Eds.; CRC Press: Boca Raton, FL, 2012.
- [162] "Chapter 7 - Cytotoxic Chemotherapy in Clinical Treatment of Cancer" R. Thirumaran, G. C. Prendergast, P. B. Gilman Dans *Cancer Immunotherapy*; Academic Press: Burlington, 2007, p 101-116.
- [163] "Isolation and Detection of Vinca Alkaloids from Endophytes Isolated from *Catharanthus roseus*" H. Ashoka, P. Hegde, K. H. Manasa, C. Madihalli, S. Pradeep, A. K. Shettihalli, *Eur. J. Biomed. Pharm. Sci.* **2017**, *4*, 675-683.
- [164] "Search for Natural Substances with Therapeutic Activity: Pierre Potier (1934-2006)" P. P. J. Da Silva, L. Meijer, *Med. Sci. (Paris)* **2012**, *28*, 534-542.
- [165] "Pierre Potier (1934-2006)" F. Chast, *Nature* **2006**, *440*, 291-291.
- [166] "Pierre Potier (1934-2006)" S. Z. Zard, *Angew. Chem., Int. Ed.* **2006**, *45*, 2496-2497.
- [167] "The Role of Vindesine in Oncology - Recommendations after 10 Years' Experience" J. Dancey, W. P. Steward, *Anti-Cancer Drugs* **1995**, *6*, 625-636.
- [168] "Superior *in vivo* Experimental Antitumour Activity of Vinflunine, Relative to Vinorelbine, in a Panel of Human Tumour Xenografts" B. T. Hill, H. H. Fiebig, W. R. Waud, M. F. Poupon, F. Colpaert, A. Kruczynski, *Eur. J. Cancer* **1999**, *35*, 512-520.
- [169] "Reactivity of Vinca Alkaloids in Superacid" J.-C. Jacquesy, *J. Fluorine Chem.* **2006**, *127*, 1484-1487.

- [170] “Additional Antitumor Ecteinasidins from a Caribbean Tunicate: Crystal Structures and Activities *in vivo*” R. Sakai, K. L. Rinehart, Y. Guan, A. H. J. Wang, *Proc. Natl. Acad. Sci. U. S. A.* **1992**, *89*, 11456-11460.
- [171] “Ecteinasidins: Putative Biosynthetic Precursors and Absolute Stereochemistry” R. Sakai, E. A. Jares-Erijman, I. Manzanares, M. V. S. Elipe, K. L. Rinehart, *J. Am. Chem. Soc.* **1996**, *118*, 9017-9023.
- [172] “A Review of Trabectedin (ET-743): A Unique Mechanism of Action” M. D’Incalci, C. M. Galmarini, *Mol. Cancer Ther.* **2010**, *9*, 2157-2163.
- [173] “Development of Yondelis (Trabectedin, ET-743). A Semisynthetic Process Solves the Supply Problem” C. Cuevas, A. Francesch, *Nat. Prod. Rep.* **2009**, *26*, 322-337.
- [174] “Trabectedin: The Evidence for its Place in Therapy in the Treatment of Soft Tissue Sarcoma” K. A. Thornton, *Core Evid.* **2009**, *4*, 191-198.
- [175] “Trabectedin: Safety and Efficacy in the Treatment of Advanced Sarcoma” C. Gajdos, A. Elias, *Clin. Med. Insights: Oncol.* **2011**, *5*, 35-43.
- [176] “Trabectedin: A Review of its Use in the Management of Soft Tissue Sarcoma and Ovarian Cancer” N. J. Carter, S. J. Keam, *Drugs* **2007**, *67*, 2257-2276.
- [177] “Trabectedin for Soft Tissue Sarcoma: Current Status and Future Perspectives” E. M. Gordon, K. K. Sankhala, N. Chawla, S. P. Chawla, *Adv. Ther.* **2016**, *33*, 1055-1071.
- [178] “Nature’s Lessons to Design an Effective, Rational and Selective Drug for Soft Tissue Sarcoma Treatment: The Ecteinasidins” J. A. P. Henriques, D. G. Soares, D. Bonatto, M. Salvador, G. Schwartzmann, A. K. Larsen, *Drug Des. Rev.-Online* **2005**, *2*, 501-525.
- [179] “Clinical Impact of Trabectedin (Ecteinasidin-743) in Advanced/Metastatic Soft Tissue Sarcoma” P. Schöffski, H. Dumez, P. Wolter, C. Stefan, A. Wozniak, J. Jimeno, A. T. Van Oosterom, *Expert Opin. Pharmacother.* **2008**, *9*, 1609-1618.
- [180] “Antitumor Compounds from Tunicates” K. L. Rinehart, *Med. Res. Rev.* **2000**, *20*, 1-27.
- [181] “Yondelis (Trabectedin, ET-743): The Development of an Anticancer Agent of Marine Origin” C. van Kesteren, M. M. M. de Vooght, L. López-Lázaro, R. A. A. Mathôt, J. H. M. Schellens, J. M. Jimeno, J. H. Beijnen, *Anti-Cancer Drugs* **2003**, *14*, 487-502.
- [182] “Trabectedin: An Anticancer Drug from the Sea” K. N. Ganjoo, S. R. Patel, *Expert Opin. Pharmacother.* **2009**, *10*, 2735-2743.
- [183] “Trabectedin (Yondelis, Formerly ET-743), a Mass Balance Study in Patients with Advanced

- Cancer” J. H. Beumer, J. M. Rademaker-Lakhai, H. Rosing, L. López-Lázaro, J. H. Beijnen, J. H. M. Schellens, *Invest. New Drugs* **2005**, *23*, 429-436.
- [184] “Replication and Homologous Recombination Repair Regulate DNA Double-Strand Break Formation by the Antitumor Alkylator Ecteinascidin 743” D. Grazziotin Soares, A. E. Escargueil, V. Poindessous, A. Sarasin, A. de Gramont, D. Bonatto, J. A. Pêgas Henriques, A. K. Larsen, *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 13062-13067.
- [185] “The Impairment of the High Mobility Group A (HMGA) Protein Function Contributes to the Anticancer Activity of Trabectedin” D. D'Angelo, E. Borbone, D. Palmieri, S. Ubaldi, F. Esposito, R. Frapolli, R. Pacelli, M. D'Incalci, A. Fusco, *Eur. J. Cancer* **2013**, *49*, 1142-1151.
- [186] “Anticancer Drug Discovery from the Marine Environment” C. Nastrucci, A. Cesario, P. Russo, *Recent Pat. Anti-Cancer Drug Discovery* **2012**, *7*, 218-232.
- [187] “Origins and Bioactivities of Natural Compounds Derived from Marine Ascidians and Their Symbionts” X. Dou, B. Dong, *Mar. Drugs* **2019**, *17*.
- [188] “Marine Pharmacology in 2005-2006: Antitumour and Cytotoxic Compounds” A. M. S. Mayer, K. R. Gustafson, *Eur. J. Cancer* **2008**, *44*, 2357-2387.
- [189] “Drugs from the Deep: Marine Natural Products as Drug Candidates” B. Haefner, *Drug Discov. Today* **2003**, *8*, 536-544.
- [190] “Drug Development from Marine Natural Products” T. F. Molinski, D. S. Dalisay, S. L. Lievens, J. P. Saludes, *Nat. Rev. Drug Discovery* **2009**, *8*, 69-85.
- [191] “Marine natural product libraries for high-throughput screening and rapid drug discovery” T. S. Bugni, B. Richards, L. Bhoite, D. Cimborá, M. K. Harper, C. M. Ireland, *J. Nat. Prod.* **2008**, *71*, 1095-1098.
- [192] “Calicheimicins, a Novel Family of Antitumor Antibiotics. 1. Chemistry and Partial Structure of Calicheimicin γ 1I” M. D. Lee, T. S. Dunne, M. M. Siegel, C. C. Chang, G. O. Morton, D. B. Borders, *J. Am. Chem. Soc.* **1987**, *109*, 3464-3456.
- [193] “Calicheimicins, a Novel Family of Antitumor Antibiotics. 2. Chemistry and Structure of Calicheimicin γ 1I” M. D. Lee, T. S. Dunne, C. C. Chang, G. A. Ellestad, M. M. Siegel, G. O. Morton, W. J. McGahren, D. B. Borders, *J. Am. Chem. Soc.* **1987**, *109*, 3466-3468.
- [194] “Calicheimicins, a Novel Family of Antitumor Antibiotics. 3. Isolation, Purification and Characterization of Calicheimicins β 1Br, γ 1Br, α 2I, α 3I, β 1I, γ 1I, and δ 1I” M. D. Lee, J. K.

- Manning, D. R. Williams, N. A. Kuck, R. T. Testa, D. B. Borders, *J. Antibiot.* **1989**, *42*, 1070-1087.
- [195] "Calicheamicins, a Novel Family of Antitumor Antibiotics. 4. Structure Elucidation of Calicheamicins β 1Br, γ 1Br, α 2I, α 3I, β 1I, γ 1I, and δ 1I" M. D. Lee, T. S. Dunne, C. C. Chang, M. M. Siegel, G. O. Morton, G. A. Ellestad, W. J. McGahren, D. B. Borders, *J. Am. Chem. Soc.* **1992**, *114*, 985-997.
- [196] "Calicheamicins, a Novel Family of Antitumor Antibiotics: Taxonomy, Fermentation and Biological Properties" W. M. Maiese, M. P. Lechevalier, H. A. Lechevalier, J. Korshalla, N. Kuck, A. Fantini, M. J. Wildey, J. Thomas, M. Greenstein, *J. Antibiot.* **1989**, *42*, 558-563.
- [197] "LL-D49194 Antibiotics, a Novel Family of Antitumor Agents: Taxonomy, Fermentation and Biological Properties" W. M. Maiese, D. P. Labeda, J. Korshalla, N. Kuck, A. A. Fantini, M. J. Wildey, J. Thomas, M. Greenstein, *J. Antibiot.* **1990**, *43*, 253-258.
- [198] "Calicheamicins: Discovery, Structure, Chemistry, and Interaction with DNA" M. D. Lee, G. A. Ellestad, D. B. Borders, *Acc. Chem. Res.* **1991**, *24*, 235-243.
- [199] "Gemtuzumab Ozogamicin, A Potent and Selective Anti-CD33 Antibody-Calicheamicin Conjugate for Treatment of Acute Myeloid Leukemia" P. R. Hamann, L. M. Hinman, I. Hollander, C. F. Beyer, D. Lindh, R. Holcomb, W. Hallett, H.-R. Tsou, J. Upešlaciš, D. Shochat, A. Mountain, D. A. Flowers, I. Bernstein, *Bioconjugate Chem.* **2002**, *13*, 47-58.
- [200] "An Anti-CD33 Antibody-Calicheamicin Conjugate for Treatment of Acute Myeloid Leukemia. Choice of Linker" P. R. Hamann, L. M. Hinman, C. F. Beyer, D. Lindh, J. Upešlaciš, D. A. Flowers, I. Bernstein, *Bioconjugate Chem.* **2002**, *13*, 40-46.
- [201] "A Calicheamicin Conjugate with a Fully Humanized Anti-MUC1 Antibody Shows Potent Antitumor Effects in Breast and Ovarian Tumor Xenografts" P. R. Hamann, L. M. Hinman, C. F. Beyer, D. Lindh, J. Upešlaciš, D. Shochat, A. Mountain, *Bioconjugate Chem.* **2005**, *16*, 354-360.
- [202] R. Y. Zhao, Q. Yang, Y. Huang, S. Gai, L. Zhao, H. Ye, H. Guo, Q. Tong, M. Cao, J. Jia, C. Yang, W. Li, X. Zhou, H. Xie, C. Lin, Z. Guo, Z. Ye, "Preparation of Specific Conjugation Bridge Linkers and Immunoconjugates and Methods of Using Them" *WO2016059622*, **2016**; *Chem. Abstr.* 2016:640334,
- [203] R. Y. Zhao, "Preparation of Novel Bridge Linkers Containing an Acetylenedicarbonyl Group for Specific Conjugation of a Cytotoxic Agent to a Cell-Binding Molecule" *WO2015151080*,

- 2015**; *Chem. Abstr.* 2015:1623828,
- [204] "Selection of Reaction Additives Used in the Preparation of Monomeric Antibody-Calicheamicin Conjugates" I. Hollander, A. Kunz, P. R. Hamann, *Bioconjugate Chem.* **2008**, *19*, 358-361.
- [205] "Antibody-Targeted Chemotherapy with the Calicheamicin Conjugate hu3S193-N-acetyl γ Calicheamicin Dimethyl Hydrazide Targets Lewis and Eliminates Lewis-Positive Human Carcinoma Cells and Xenografts" E. R. Boghaert, L. Sridharan, D. C. Armellino, K. M. Khandke, J. F. DiJoseph, A. Kunz, M. M. Dougher, F. Jiang, L. B. Kalyandrug, P. R. Hamann, P. Frost, N. K. Damle, *Clin. Cancer Res.* **2004**, *10*, 4538-4549.
- [206] R. Y. Zhao, "Preparation of Bridge Linkers used for Specific Conjugation of Two or More Cytotoxic Agents to a Cell-Binding Molecule" WO2015155753, **2015**; *Chem. Abstr.* 2015:1650548,
- [207] "Targeted Cancer Therapy: Conferring Specificity to Cytotoxic Drugs" R. V. J. Chari, *Acc. Chem. Res.* **2008**, *41*, 98-107.
- [208] "CHAPTER 5 - Natural Product Chemistry and Anticancer Drug Discovery" D. M. Huryn, P. Wipf Dans *Cancer Drug Design and Discovery*; Academic Press: New York, 2008, p 107-130.
- [209] "Halichondrins-Antitumor Polyether Macrolides from a Marine Sponge" Y. Hirata, D. Uemura, *Pure Appl. Chem.* **1986**, *58*, 701-710.
- [210] "Antineoplastic Agents. 219. Isolation and Structure of the Cell Growth Inhibitory Constituents from the Western Pacific Marine Sponge *Axinella* sp" G. R. Pettit, C. L. Herald, M. R. Boyd, J. E. Leet, C. Dufresne, D. L. Doubek, J. M. Schmidt, R. L. Cerny, J. N. A. Hooper, K. C. Rutzler, *J. Med. Chem.* **1991**, *34*, 3339-3340.
- [211] "Antitumour Polyether Macrolides: Four New Halichondrins from the New Zealand Deep-water Marine sponge *Lissodendoryx* sp" S. J. H. Hickford, J. W. Blunt, M. H. G. Munro, *Bioorg. Med. Chem.* **2009**, *17*, 2199-2203.
- [212] "Microtubulin Binding Sites as Target for Developing Anticancer Agents" M. N. Islam, M. N. Iskander, *Mini-Rev. Med. Chem.* **2004**, *4*, 1077-1104.
- [213] "Induction of Morphological and Biochemical Apoptosis following Prolonged Mitotic Blockage by Halichondrin B Macrocyclic Ketone Analog E7389" G. Kuznetsov, M. J. Towle, H. Cheng, T. Kawamura, K. TenDyke, D. Liu, Y. Kishi, M. J. Yu, B. A. Littlefield,

- Cancer Res.* **2004**, *64*, 5760-5766.
- [214] “Potential Clinical Applications of Halichondrins in Breast Cancer and Other Neoplasms” V. Ortega, J. Cortés, *Breast Cancer: Targets Ther.* **2012**, *4*, 9-19.
- [215] “Advances in Therapy: Eribulin Improves Survival for Metastatic Breast Cancer” P. G. Morris, *Anti-Cancer Drugs* **2010**, *21*, 885-889.
- [216] “Interaction of Halichondrin B and Homohalichondrin B with Bovine Brain Tubulin” R. F. Luduena, M. C. Roach, V. Prasad, G. R. Pettit, *Biochem. Pharmacol.* **1993**, *45*, 421-427.
- [217] “Halichondrin B and Homohalichondrin B, Marine Natural Products Binding in the Vinca Domain of Tubulin. Discovery of Tubulin-Based Mechanism of Action by Analysis of Differential Cytotoxicity Data” R. Bai, K. D. Paull, C. L. Herald, L. Malspeis, G. R. Pettit, E. Hamel, *J. Biol. Chem.* **1991**, *266*, 15882-15889.
- [218] “Comparative Antitumor Activities of Halichondrins and Vinblastine Against Human Tumor Xenografts” O. Fodstad, K. Breistøl, G. R. Pettit, R. H. Shoemaker, M. R. Boyd, *J. Exp. Ther. Oncol.* **1996**, *1*, 119-125.
- [219] “A Landmark in Drug Discovery Based on Complex Natural Product Synthesis” S. Kawano, K. Ito, K. Yahata, K. Kira, T. Abe, T. Akagi, M. Asano, K. Iso, Y. Sato, F. Matsuura, I. Ohashi, Y. Matsumoto, M. Isomura, T. Sasaki, T. Fukuyama, Y. Miyashita, Y. Kaburagi, A. Yokoi, O. Asano, T. Owa, Y. Kishi, *Sci. Rep.* **2019**, *9*, 1-9.
- [220] “Marine Natural Products as Anticancer Drugs” T. L. Simmons, E. Andrianasolo, K. McPhail, P. Flatt, W. H. Gerwick, *Mol. Cancer Ther.* **2005**, *4*, 333-342.
- [221] D. Uemura Dans *Pacifichem 2010, International Chemical Congress of Pacific Basin Societies*; American Chemical Society: Honolulu, HI, United States, 2010, p ORGN-461.
- [222] “The Halichondrins and E7389” K. L. Jackson, J. A. Henderson, A. J. Phillips, *Chem. Rev.* **2009**, *109*, 3044-3079.
- [223] “Biologically Active Marine Natural Products” K. Nakamura, M. Kitamura, D. Uemura, *Heterocycles* **2009**, *78*, 1-17.
- [224] “Bioactive Substances of Marine Animals: Polyoxygenated Substances” Y. Hirata, *Pure Appl. Chem.* **1989**, *61*, 293-302.
- [225] “Bioactive Polyethers” D. Uemura Dans *Bioorganic Marine Chemistry*; Springer-Verlag: Berlin, 1991; Vol. 4, p 1-31.
- [226] “Antitumor Polyethermacrolides Produced by Sponges” D. Uemura, *Kagaku, Zokan (Kyoto)*

- 1987**, 145-153.
- [227] “The Halichondrins: Chemistry, Biology, Supply and Delivery” J. B. Hart, R. E. Lill, S. J. H. Hickford, J. W. Blunt, M. H. G. Munro Dans *Drugs from the Sea*; Karger: Basel, 2000, p 134-153.
- [228] “Total Synthesis of Halichondrin B and Norhalichondrin B” T. D. Aicher, K. R. Buszek, F. G. Fang, C. J. Forsyth, S. H. Jung, Y. Kishi, M. C. Matelich, P. M. Scola, D. M. Spero, S. K. Yoon, *J. Am. Chem. Soc.* **1992**, *114*, 3162-3164.
- [229] “Chapter 26 - To Market, To Market—2010” J. Bronson, M. Dhar, W. Ewing, N. Lonberg Dans *Annu. Rep. Med. Chem.*; Academic Press: 2011; Vol. 46, p 433-502.
- [230] “Eribulin: Rediscovering Tubulin as an Anticancer Target” A. Jimeno, *Clin. Cancer Res.* **2009**, *15*, 3903-3905.
- [231] “Eribulin (halaven): Development of Anticancer Drug from Marine Natural Products” Y. Kawazoe, D. Uemura, *Saibo Kogaku* **2013**, *32*, 675-681.
- [232] “Bioactive Natural Peptides” S. Daffre, P. Bulet, A. Spisni, L. Ehret-Sabatier, E. G. Rodrigues, L. R. Travassos, *Stud. Nat. Prod. Chem.* **2008**, *35*, 597-691.
- [233] “Bioactive Peptides from Marine Sources: Pharmacological Properties and Isolation Procedures” A. Aneiros, A. Garateix, *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2004**, *803*, 41-53.
- [234] “Marine Natural Product Peptides with Therapeutic Potential: Chemistry, Biosynthesis, and Pharmacology” V. Gogineni, M. T. Hamann, *Biochim. Biophys. Acta, Gen. Subj.* **2018**, *1862*, 81-196.
- [235] “Recent Updates of Marine Antimicrobial Peptides” M. H. Semreen, M. I. El-Gamal, S. Abdin, H. Alkhazraji, L. Kamal, S. Hammad, F. El-Awady, D. Waleed, L. Kourbaj, M. I. El-Gamal, *Saudi Pharm J* **2018**, *26*, 396-409.
- [236] “Bioactive Peptides” E. B.-M. Daliri, D. H. Oh, B. H. Lee, *Foods* **2017**, *6*, 32/31-21.
- [237] “The Emergence of Peptides in the Pharmaceutical Business: From Exploration to Exploitation” T. Uhlig, T. Kyprianou, F. G. Martinelli, C. A. Oppici, D. Heiligers, D. Hills, X. R. Calvo, P. Verhaert, *EuPa Open Proteom.* **2014**, *4*, 58-69.
- [238] “Bioactive Peptide Natural Products as Lead Structures for Medicinal Use” T. Dang, R. D. Suessmuth, *Acc. Chem. Res.* **2017**, *50*, 1566-1576.
- [239] “Functional Significance of Bioactive Peptides Derived from Soybean” B. P. Singh, S. Vij, S.

- Hati, *Peptides* **2014**, *54*, 171-179.
- [240] “Bioactive Peptides” F. Shahidi, Y. Zhong, *J. AOAC Int.* **2008**, *91*, 914-931.
- [241] “Bioactive Peptides: A Review” A. Sánchez, A. Vázquez, *Food Qual. Saf.* **2017**, *1*, 29-46.
- [242] “Insulin: understanding its action in health and disease” P. Sonksen, J. Sonksen, *Br. J. Anaesth.* **2000**, *85*, 69-79.
- [243] “Natural Peptides in Drug Discovery Targeting Acetylcholinesterase” V. Prasasty, M. Radifar, E. Istyastono, *Molecules* **2018**, *23*, 2344/2341-2321.
- [244] “Computer-Aided Characteristics of Proteins as Potential Precursors of Bioactive Peptides” J. Dziuba, A. Iwaniak, P. Minkiewicz, *Polimery (Warsaw, Pol.)* **2003**, *48*, 50-53.
- [245] “Ultrasound Applications for the Extraction, Identification and Delivery of Food Proteins and Bioactive Peptides” S. U. Kadam, B. K. Tiwari, C. Álvarez, C. P. O'Donnell, *Trends Food Sci. Technol.* **2015**, *46*, 60-67.
- [246] “Recent Advances in Antibacterial and Antiendotoxic Peptides or Proteins from Marine Resources” Z. Wang, X. Wang, J. Wang, *Mar. Drugs* **2018**, *16*, 57/51-57/18.
- [247] “Peptides and Peptidomimetics as Potential Antiobesity Agents: Overview of Current Status” M. S. Kumar, *Front. Nutr.* **2019**, *11*.
- [248] “New Peptides Isolated from Marine Cyanobacteria, an Overview Over the Past Decade” Y. Mi, J. Zhang, S. He, X. Yan, *Mar. Drugs* **2017**, *15*, 132/131-132/127.
- [249] “Marine Peptides: Bioactivities and Applications” R. C. F. Cheung, T. B. Ng, J. H. Wong, *Mar. Drugs* **2015**, *13*, 4006-4043.
- [250] “Marine Peptides as Potential Agents for the Management of Type 2 Diabetes Mellitus-A Prospect” E.-Q. Xia, S.-S. Zhu, M.-J. He, F. Luo, C.-Z. Fu, T.-B. Zou, *Mar. Drugs* **2017**, *15*.
- [251] “Marine Peptides as Anticancer Agents: A Remedy to Mankind by Nature” B. Negi, D. Kumar, D. S. Rawat, *Curr. Protein Pept. Sci.* **2017**, *18*, 885-904.
- [252] “Marine Peptides and their Anti-Infective Activities” H. K. Kang, C. H. Seo, Y. Park, *Mar. Drugs* **2015**, *13*, 618-654.
- [253] “Marine Bioactive Peptides: Types, Structures, and Physiological Functions” C. Jo, F. F. Khan, M. I. Khan, J. Iqbal, *Food Rev. Int.* **2017**, *33*, 44-61.
- [254] “Bioactive Peptides from Marine Organisms: A Short Overview” F. Lazcano-Peréz, S. A. Román-González, N. Sánchez-Puig, R. Arreguin-Espinosa, *Protein Pept. Lett.* **2012**, *19*, 700-707.

- [255] "Bioactive Peptides from Marine Ascidians and Future Drug Development – A Review" V. Arumugam, M. Venkatesan, S. Ramachandran, U. Sundaresan, *Int. J. Pept. Res. Ther.* **2018**, *24*, 13-18.
- [256] "Bioactive Nitrogenous Metabolites from Ascidians" W. Wang, M. Namikoshi, *Heterocycles* **2007**, *74*, 53-88.
- [257] "Bioactive Marine Metabolites. Part 67. Discodermins F-H, Cytotoxic and Antimicrobial Tetradecapeptides from the Marine Sponge *Discodermia kiiensis*: Structure Revision of Discodermins A-D" G. Ryu, S. Matsunaga, N. Fusetani, *Tetrahedron* **1994**, *50*, 13409-13416.
- [258] "Bioactive Compounds from Aquatic and Terrestrial Sources" K. L. Rinehart, T. G. Holt, N. L. Fregeau, P. A. Keifer, G. R. Wilson, T. J. Perun, Jr., R. Sakai, A. G. Thompson, J. G. Stroh, L. S. Shield, D. S. Seigler, H. L. Li, D. G. Martin, C. J. P. Grimmelikhuijzen, G. Gäde, *J. Nat. Prod.* **1990**, *53*, 771-792.
- [259] "Recent Progress of the Synthetic Studies of Biologically Active Marine Cyclic Peptides and Depsipeptides" Y. Hamada, T. Shioiri, *Chem. Rev.* **2005**, *105*, 4441-4482.
- [260] "Recent Progress of Marine Polypeptides as Anticancer Agents" L. Zheng, Y. Xu, X. Lin, M. Liu, S. Cao, Z. Yuan, F. Zhang, R. J. Linhardt, *Recent Pat. Anti-Cancer Drug Discovery* **2018**, *13*, 445-454.
- [261] "Peptides, Peptidomimetics, and Polypeptides from Marine Sources: A Wealth of Natural Sources for Pharmaceutical Applications" R. Sable, P. Parajuli, S. Jois, *Mar. Drugs* **2017**, *15*, 124/121-124/137.
- [262] "Natural Product Peptides from Marine Organisms" C. M. Ireland, T. F. Molinski, D. M. Roll, T. M. Zabriskie, T. C. McKee, J. C. Swersey, M. P. Foster Dans *Bioorganic Marine Chemistry*; Springer-Verlag: Berlin, 1989; Vol. 3, p 1-46.
- [263] "Microsclerodermins from Terrestrial Myxobacteria: An Intriguing Biosynthesis Likely Connected to a Sponge Symbiont" T. Hoffmann, S. Müller, S. Nadmid, R. Garcia, R. Müller, *J. Am. Chem. Soc.* **2013**, *135*, 16904-16911.
- [264] "Marine Peptides: Emerging Perspectives for Pharmaceuticals" S.-K. Kim, *Curr. Protein Pept. Sci.* **2013**, *14*, 161.
- [265] "Marine Peptides and Related Compounds in Clinical Trial" D. S. Rawat, M. C. Joshi, P. Joshi, H. Atheaya, *Anti-Cancer Agents Med. Chem.* **2006**, *6*, 33-40.

- [266] “Marine Peptides and Proteins with Cytotoxic and Antitumoral Properties” J. Varela, C. Vizetto-Duarte, L. Custódio, L. Barreira, F. Albericio Dans *Marine Proteins and Peptides: Biological Activities and Applications*; 1st ed.; Wiley-Blackwell: Chichester, 2013, p 407-430.
- [267] “Marine Peptide Secondary Metabolites” B. Banaigs, I. Bonnard, A. Witczak, N. Inguibert Dans *Outstanding Marine Molecules*; Wiley-Blackwell: Chichester, 2014, p 285-318.
- [268] “Antimicrobial Peptides Derived from Marine Sponges” A. Vitali, *Am. J. Clin. Microbiol. Antimicrob.* **2018**, *1*, 1006.
- [269] “Marine Natural Products” W. Zhang, Y.-W. Guo Dans *Introduction to Natural Products Chemistry*; CRC Press: Boca Raton, FL, 2011, p 269-292.
- [270] “FR901228, A Novel Antitumor Bicyclic Depsipeptide Produced by *Chromobacterium violaceum* No. 968. III. Antitumor Activities on Experimental Tumors in Mice” H. Ueda, T. Manda, S. Matsumoto, S. Mukumoto, F. Nishigaki, I. Kawamura, K. Shimomura, *J. Antibiot.* **1994**, *47*, 315-323.
- [271] “FR901228, A Novel Antitumor Bicyclic Depsipeptide Produced by *Chromobacterium violaceum* No. 968. II. Structure Determination” N. Shigematsu, H. Ueda, S. Takase, H. Tanaka, K. Yamamoto, T. Tada, *J. Antibiot.* **1994**, *47*, 311-314.
- [272] “FR901228, A Novel Antitumor Bicyclic Depsipeptide Produced by *Chromobacterium violaceum* No. 968. I. Taxonomy, Fermentation, Isolation, Physico-Chemical and Biological Properties, and Antitumor Activity” H. Ueda, H. Nakajima, Y. Hori, T. Fujita, M. Nishimura, T. Goto, M. Okuhara, *J. Antibiot.* **1994**, *47*, 301-310.
- [273] “Romidepsin (Istodax, NSC 630176, FR901228, FK228, depsipeptide): A Natural Product Recently Approved for Cutaneous T-Cell Lymphoma” K. M. Van der Molen, W. McCulloch, C. J. Pearce, N. H. Oberlies, *J. Antibiot.* **2011**, *64*, 525-531.
- [274] “Inhibitor of Histone Deacetylation, Depsipeptide (FR901228), in the Treatment of Peripheral and Cutaneous T-Cell Lymphoma: A Case Report” R. L. Piekarz, R. Robey, V. Sandor, S. Bakke, W. H. Wilson, L. Dahmouh, D. M. Kingma, M. L. Turner, R. Altemus, S. E. Bates, *Blood* **2001**, *98*, 2865-2868.
- [275] “The Histone Deacetylase Inhibitor FK228 Given Prior to Adenovirus Infection Can Boost Infection in Melanoma Xenograft Model Systems” M. E. Goldsmith, A. Aguila, K. Steadman, A. Martinez, S. M. Steinberg, M. C. Alley, W. R. Waud, S. E. Bates, T. Fojo, *Mol.*

Cancer Ther. **2007**, *6*, 496-505.

- [276] “FR901228, A Potent Antitumor Antibiotic, is A Novel Histone Deacetylase Inhibitor” H. Nakajima, Y. B. Kim, H. Terano, M. Yoshida, S. Horinouchi, *Exp. Cell Res.* **1998**, *241*, 126-133.
- [277] “Depsipeptide Induces Cell Death in Hodgkin Lymphoma-Derived Cell Lines” I. Hartlapp, C. Pallasch, G. Weibert, A. Kemkers, M. Hummel, D. Re, *Leuk. Res.* **2009**, *33*, 929-936.
- [278] “Apoptosis Induced by the Histone Deacetylase Inhibitor FR901228 in Human T-Cell Leukemia Virus Type 1-Infected T-Cell Lines and Primary Adult T-Cell Leukemia Cells” N. Mori, T. Matsuda, M. Tadano, T. Kinjo, Y. Yamada, K. Tsukasaki, S. Ikeda, Y. Yamasaki, Y. Tanaka, T. Ohta, T. Iwamasa, M. Tomonaga, N. Yamamoto, *J. Virol.* **2004**, *78*, 4582-4590.
- [279] “Vancomycin, A New Antibiotic. I. Chemical and Biologic Properties” M. H. McCormick, W. M. Stark, G. E. Pittenger, R. C. Pittenger, J. M. McGuire, *Antibiot. Annu.* **1956**, 606-611.
- [280] “Structure of Vancomycin and its Complex with Acetyl-D-alanyl-D-alanine” G. M. Sheldrick, P. G. Jones, O. Kennard, D. H. Williams, G. A. Smith, *Nature* **1978**, *271*, 223-225.
- [281] “Introduction to Vancomycin” R. S. Griffith, *Rev. Infect. Dis.* **1981**, *3*, 200-204.
- [282] “Vancomycin, A New Antibiotic. IV. Pharmacologic and Toxicologic Studies” R. C. Anderson, H. M. Worth, P. N. Harris, K. K. Chen, *Antibiot. Annu.* **1957**, 75-81.
- [283] “Vancomycin, A New Antibiotic. II. *In vitro* Antibacterial Studies” D. W. Ziegler, R. N. Wolfe, J. M. McGuire, *Antibiot. Annu.* **1956**, 612-618.
- [284] “Vancomycin in Serious Staphylococcal Infections” J. E. Geraci, D. R. Nichols, W. E. Wellman, *Arch. Intern. Med.* **1962**, *109*, 507-515.
- [285] “Retrospective Study of the Toxicity of Preparations of Vancomycin from 1974 to 1981” B. F. Farber, R. C. Moellering, Jr., *Antimicrob. Agents Chemother.* **1983**, *23*, 138-141.
- [286] “Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children: Executive Summary” C. Liu, A. Bayer, S. E. Cosgrove, R. S. Daum, S. K. Fridkin, R. J. Gorwitz, S. L. Kaplan, A. W. Karchmer, D. P. Levine, B. E. Murray, J. R. Michael, D. A. Talan, H. F. Chambers, *Clin. Infect. Dis.* **2011**, *52*, 285-292.
- [287] “Vancomycin: A History” D. P. Levine, *Clin. Infect. Dis.* **2006**, *42*, S5-S12.
- [288] “Vancomycin: A 50-Year Reassessment” R. C. Moellering, Jr., *Clin. Infect. Dis.* **2006**, *42*,

S3-S4.

- [289] "A Polypeptide Antibacterial Agent Isolated from *Trichoderma viride*" C. E. Meyer, F. Reusser, *Experientia* **1967**, *23*, 85-86.
- [290] "Separation, purification, and characterisation of alamethicins produced from *Trichoderma viride*" M. J., M. A. I., *Proc. Intersect Congr. Int. Assoc. Microbiol. Soc.* **1975**, *5*, 446-451.
- [291] "Sequences of alamethicins F30 and F50 reconsidered and reconciled" J. Kirschbaum, C. Krause, R. K. Winzheimer, H. Brueckner, *J. Pept. Sci.* **2003**, *9*, 799-809.
- [292] "Synthesis and Characterization of the Major Component of Alamethicin" T. M. Balasubramanian, N. C. E. Kendrick, M. Taylor, G. R. Marshall, J. E. Hall, I. Vodyanoy, F. Reusser, *J. Am. Chem. Soc.* **1981**, *103*, 6127-6132.
- [293] "Total Synthesis in Solution of Alamethicin F50/5 by an Easily Tunable Segment Condensation Approach" C. Peggion, I. Coin, C. Toniolo, *Biopolymers* **2004**, *76*, 485-493.
- [294] "*In vitro* and *in vivo* Antitrypanosomal Activities of Three Peptide Antibiotics: Leucinostatin A and B, Alamethicin I and Tsushimycin" A. Ishiyama, K. Otaguro, M. Iwatsuki, M. Namatame, A. Nishihara, K. Nonaka, Y. Kinoshita, Y. Takahashi, R. Masuma, K. Shiomi, H. Yamada, S. Omura, *J. Antibiot.* **2009**, *62*, 303-308.
- [295] "Enhancing the Antimicrobial Activity of Alamethicin F50/5 by Incorporating *N*-terminal Hydrophobic Triazole Substituents" S. Das, K. Ben Haj Salah, E. Wenger, J. Martinez, J. Kotarba, V. Andreu, N. Ruiz, F. Savini, L. Stella, C. Didierjean, B. Legrand, N. Inguibert, *Chem. - Eur. J.* **2017**, *23*, 17964-17972.
- [296] "Structure and Orientation of Antibiotic Peptide Alamethicin in Phospholipid Bilayers as Revealed by Chemical Shift Oscillation Analysis of Solid State Nuclear Magnetic Resonance and Molecular Dynamics Simulation" T. Nagao, D. Mishima, N. Javkhlantugs, J. Wang, D. Ishioka, K. Yokota, K. Norisada, I. Kawamura, K. Ueda, A. Naito, *Biochim. Biophys. Acta, Biomembr.* **2015**, *1848*, 2789-2798.
- [297] "Non-Ribosomal Biosynthesis of the Cyclic Octadecapeptide Alamethicin" H. Kleinkauf, H. Rindfleisch, *Acta Microbiol. Acad. Sci. Hung.* **1975**, *22*, 411-418.
- [298] "Action Potentials Induced in Biomolecular Lipid Membranes" P. Mueller, D. O. Rudin, *Nature* **1968**, *217*, 713-719.
- [299] "Marine Natural Products and their Potential Applications as Anti-Infective Agents" G. M. Abou-Elela, H. Abd-Elnaby, H. A. H. Ibrahim, M. A. Okbah, *World Appl. Sci. J.* **2009**, *7*,

- 872-880.
- [300] "Marine Natural Products and their Potential Applications as Anti-Infective Agents" M. Donia, M. T. Hamann, *Lancet Infect. Dis.* **2003**, *3*, 338-348.
- [301] "Marine natural products" R. H. Thomson, *Chem. Br.* **1978**, *14*, 133-139, 154.
- [302] "Natural Products of Marine Algae" V. L. Teixeira, A. Kelecom, O. R. Gottlieb, *Quim. Nova* **1991**, *14*, 83-90.
- [303] "Bioactive Marine Natural Products" B. W. Son, *Saengyak Hakhoechi* **1990**, *21*, 1-48.
- [304] "Marine Natural Products" A. Sato, S. Takahashi, T. Ogita, M. Sugano, K. Kodama, *Annu. Rep. Sankyo Res. Lab.* **1995**, *47*, 1-58.
- [305] "Marine Natural Products: A Lead for Anti-Cancer" H. M. Sarfaraj, F. Sheeba, A. Saba, S. k. Mohd, *Indian J. Geo-Mar. Sci.* **2012**, *41*, 27-39.
- [306] "Biologically Active Natural Products" K. L. Rinehart, R. Sakai, T. G. Holt, N. L. Fregeau, T. J. Perun, Jr., D. S. Seigler, G. R. Wilson, L. S. Shield, *Pure Appl. Chem.* **1990**, *62*, 1277-1280.
- [307] "Marine Natural Products: A New Wave of Drugs?" R. Montaser, H. Luesch, *Future Med. Chem.* **2011**, *3*, 1475-1489.
- [308] "Bioactive Marine Natural Products"; D. S. Bhakuni, R. Verma; Springer-Verlag: New-York, 2005.
- [309] "Bioactive Natural Products from Marine Sources" M. J. Abad, P. Bermejo, *Stud. Nat. Prod. Chem.* **2001**, *25*, 683-755.
- [310] "Marine Natural Products: Biodiscovery, Biodiversity, and Bioproduction" M. C. Leal, R. Calado Dans *Bioactive Natural Products: Chemistry and Biology*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2015, p 473-490.
- [311] "Natural Products from Marine Organisms and their Associated Microbes" G. M. König, S. Kehraus, S. F. Seibert, A. Abdel-Lateff, D. Müller, *ChemBioChem* **2006**, *7*, 229-238.
- [312] "Chemistry of Marine Natural Products" I. Kitagawa, M. Kobayashi, *Farumashia* **1988**, *24*, 372-378.
- [313] "Bioactive Marine Natural Products" I. Kitagawa, *Yakugaku Zasshi* **1988**, *108*, 398-416.
- [314] "Marine Natural Products" R. A. Hill, *Annu. Rep. Prog. Chem., Sect. B, Org. Chem.* **2013**, *109*, 146-166.
- [315] "Marine Natural Products: Chemical Diversity" N. Fusetani Dans *Wiley Encyclopedia of*

- Chemical Biology*; John Wiley & Sons, Inc.: 2009; Vol. 2, p 633-654.
- [316] "Marine natural products" N. Fusetani 2012; John Wiley & Sons, Inc., p 31-64.
- [317] "Natural products chemistry in the marine environment" W. Fenical, *Science (Washington, D. C., 1883-)* **1982**, *215*, 923-928.
- [318] "Marine natural products" D. J. Faulkner, *Nat. Prod. Rep.* **2000**, *17*, 7-55.
- [319] "Academic chemistry and the discovery of bioactive marine natural products" D. J. Faulkner 1993; Plenum: Vol. 1, p 459-474.
- [320] "Highlights of marine natural products chemistry (1972-1999)" D. J. Faulkner, *Nat. Prod. Rep.* **2000**, *17*, 1-6.
- [321] "Interesting aspects of marine natural products chemistry" D. J. Faulkner, *Tetrahedron* **1977**, *33*, 1421-1443.
- [322] "Bioactive marine natural products" K. L. Desjardine, **2007**.
- [323] "Marine natural products" A. R. Carroll, B. R. Copp, R. A. Davis, R. A. Keyzers, M. R. Prinsep, *Nat. Prod. Rep.* **2019**, *36*, 122-173.
- [324] "Marine Natural Products Chemistry: Past, Present, and Future" R. J. Capon, *Aust. J. Chem.* **2010**, *63*, 851-854.
- [325] "Marine natural products" J. W. Blunt, A. R. Carroll, B. R. Copp, R. A. Davis, R. A. Keyzers, M. R. Prinsep, *Nat. Prod. Rep.* **2018**, *35*, 8-53.
- [326] "Drugs from the sea. The search continues" W. H. Gerwick, *J. Pharm. Technol.* **1987**, *3*, 136-141.
- [327] "Nonribosomal Peptides from Marine Microbes and Their Antimicrobial and Anticancer Potential" S. Agrawal, D. Acharya, A. Adholeya, S. K. Deshmukh, S. Agrawal, C. J. Barrow, *Front Pharmacol* **2017**, *8*, 828.
- [328] "Structural diversity of marine cyclic peptides and their molecular mechanisms for anticancer, antibacterial, antifungal, and other clinical applications" Y. Lee, C. Phat, S.-C. Hong, *Peptides (N. Y., NY, U. S.)* **2017**, *95*, 94-105.
- [329] "Therapeutic properties and biological benefits of marine-derived anticancer peptides" H. K. Kang, M.-C. Choi, C. H. Seo, Y. Park, *Int. J. Mol. Sci.* **2018**, *19*, 919/911-919/940.
- [330] "Bioactive marine metabolites. VI. Structure elucidation of discodermin A, an antimicrobial peptide from the marine sponge *Discodermia kiiensis*" S. Matsunaga, N. Fusetani, S. Konosu, *Tetrahedron Lett.* **1984**, *25*, 5165-5168.

- [331] "Bioactive marine metabolites, IV. Isolation and the amino acid composition of discodermin A, an antimicrobial peptide, from the marine sponge *Discodermia kiiensis*" S. Matsunaga, N. Fusetani, S. Konosu, *J. Nat. Prod.* **1985**, *48*, 236-241.
- [332] "Theonellamides A-E, cytotoxic bicyclic peptides, from a marine sponge *Theonella* sp" S. Matsunaga, N. Fusetani, *J. Org. Chem.* **1995**, *60*, 1177-1181.
- [333] "Theonellamide F, a bicyclic peptide marine toxin, induces formation of vacuoles in 3Y1 rat embryonic fibroblast" S.-I. Wada, S. Matsunaga, N. Fusetani, S. Watabe, *Mar. Biotechnol.* **1999**, *1*, 337-341.
- [334] "Theonellamide G, a potent antifungal and cytotoxic bicyclic glycopeptide from the Red Sea marine sponge *Theonella swinhoei*" D. T. A. Youssef, G. A. Mohamed, J. M. Badr, L. A. Shaala, F. H. Bamanie, S. R. M. Ibrahim, *Mar Drugs* **2014**, *12*, 1911-1923.
- [335] "Aciculitins A-C: cytotoxic and antifungal cyclic peptides from the lithistid sponge *Aciculites orientalis*" C. A. Bewley, H. He, D. H. Williams, D. J. Faulkner, *J. Am. Chem. Soc.* **1996**, *118*, 4314-4321.
- [336] "Thiocoraline, a new depsipeptide with antitumor activity produced by a marine *Micromonospora*. I. Taxonomy, fermentation, isolation, and biological activities" F. Romero, F. Espliego, J. Perez Baz, T. Garcia de Quesada, D. Gravalos, F. De la Calle, J. L. Fernandez-Puentes, *J. Antibiot.* **1997**, *50*, sssca734-737.
- [337] "Thiocoraline, a novel depsipeptide with antitumor activity produced by a marine *Micromonospora*. II. Physico-chemical properties and structure determination" J. Perez Baz, L. M. Canedo, J. L. Fernandez Puentes, M. V. Silva Elipe, *J. Antibiot.* **1997**, *50*, 738-741.
- [338] "Mode of action of thiocoraline, a natural marine compound with anti-tumor activity" E. Erba, D. Bergamaschi, S. Ronzoni, M. Faretta, S. Taverna, M. Bonfanti, C. V. Catapano, G. Faircloth, J. Jimeno, M. D'Incalci, *Br. J. Cancer* **1999**, *80*, 971-980.
- [339] "Antitumor activity, X-ray crystal structure, and DNA binding properties of thiocoraline A, a natural bisintercalating thiodepsipeptide" A. Negri, E. Marco, V. Garcia-Hernandez, A. Domingo, A. L. Llamas-Saiz, S. Porto-Sanda, R. Riguera, W. Laine, M.-H. David-Cordonnier, C. Bailly, L. F. Garcia-Fernandez, J. J. Vaquero, F. Gago, *J. Med. Chem.* **2007**, *50*, 3322-3333.
- [340] "Deciphering the biosynthesis pathway of the antitumor thiocoraline from a marine actinomycete and its expression in two streptomyces species" F. Lombo, A. Velasco, A.

- Castro, I. C. F. de, A. F. Brana, J. M. Sanchez-Puelles, C. Mendez, J. A. Salas, *ChemBioChem* **2006**, *7*, 366-376.
- [341] “In vitro characterization of the biotransformation of thiocoraline, a novel marine anti-cancer drug” E. F. A. Brandon, R. W. Sparidans, I. Meijerman, I. Manzanares, J. H. Beijnen, J. H. M. Schellens, *Invest. New Drugs* **2004**, *22*, 241-251.
- [342] “Total Syntheses of Thiocoraline and BE-22179: Establishment of Relative and Absolute Stereochemistry” D. L. Boger, S. Ichikawa, *J. Am. Chem. Soc.* **2000**, *122*, 2956-2957.
- [343] “Microsclerodermins A and B. Antifungal Cyclic Peptides from the Lithistid Sponge *Microscleroderma* sp” C. A. Bewley, C. Debitus, D. J. Faulkner, *J. Am. Chem. Soc.* **1994**, *116*, 7631-7636.
- [344] “Microsclerodermins C - E, antifungal cyclic peptides from the lithistid marine sponges *Theonella* sp. and *Microscleroderma* sp” E. W. Schmidt, D. J. Faulkner, *Tetrahedron* **1998**, *54*, 3043-3056.
- [345] “Microsclerodermins F-I, antitumor and antifungal cyclic peptides from the lithistid sponge *Microscleroderma* sp” A. Qureshi, P. L. Colin, D. J. Faulkner, *Tetrahedron* **2000**, *56*, 3679-3685.
- [346] “Antifungal cyclic peptides from the marine sponge *Microscleroderma herdmani*” X. Zhang, M. R. Jacob, R. R. Rao, Y.-H. Wang, A. K. Agarwal, D. J. Newman, I. A. Khan, A. M. Clark, X.-C. Li, *Research and Reports in Medicinal Chemistry* **2012**, *2*, 7-14.
- [347] “Antifungal cyclic peptides from the marine sponge *Microscleroderma herdmani* [Erratum to document cited in CA161:356500]” X. Zhang, M. R. Jacob, R. R. Rao, Y.-H. Wang, A. K. Agarwal, D. J. Newman, I. A. Khan, A. M. Clark, X.-C. Li, *Research and Reports in Medicinal Chemistry* **2013**, *3*, 9.
- [348] “Microsclerodermins N and O, cytotoxic cyclic peptides containing a p-ethoxyphenyl moiety from a deep-sea marine sponge *Pachastrella* sp” T. Tian, K. Takada, Y. Ise, S. Ohtsuka, S. Okada, S. Matsunaga, *Tetrahedron* **2020**, *76*, 130997.
- [349] “Pedin A and B: production, isolation, structure elucidation and biological properties of new antifungal cyclopeptides from *Chondromyces pediculatus* (Myxobacteria)” B. Kunze, B. Böhlendorf, H. Reichenbach, G. Höfle, *J. Antibiot.* **2008**, *61*, 18-26.
- [350] “The marine natural product microsclerodermin A is a novel inhibitor of the nuclear factor kappa B and induces apoptosis in pancreatic cancer cells” E. A. Guzmán, K. Maers, J.

- Roberts, H. V. Kemami-Wangun, D. Harmody, A. E. Wright, *Invest. New Drugs* **2015**, *33*, 86-94.
- [351] “Synthetic studies of microsclerodermins. A stereoselective synthesis of a core building block for (2S, 3R, 4S, 5S, 6S, 11E)-3-amino-6-methyl-12-(4-methoxyphenyl)-2,4,5-trihydroxydodec-11-enoic acid (AMMTD)” S. Sasaki, Y. Hamada, T. Shioiri, *Tetrahedron Lett.* **1997**, *38*, 3013-3016.
- [352] “The osmium-catalyzed asymmetric dihydroxylation: a new ligand class and a process improvement” K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, a. et, *J. Org. Chem.* **1992**, *57*, 2768-2771.
- [353] “Selective asymmetric dihydroxylation (AD) of dienes” D. Xu, G. A. Crispino, K. B. Sharpless, *J. Am. Chem. Soc.* **1992**, *114*, 7570-7571.
- [354] “Addition of 2-lithiofuran to chiral α -alkoxy nitrones; a stereoselective approach to α -epimeric β -alkoxy- α -amino acids” A. Dondoni, F. Junquera, F. L. Merchan, P. Merino, T. Tejero, *Synthesis* **1994**, 1450-1456.
- [355] “The efficient stereoselective synthesis of (2S,3R,4S,5S,6S,11E)-3-amino-6-methyl-12-(4-methoxyphenyl)-2,4,5-trihydroxydodec-11-enoic acid (AMMTD), a component of microsclerodermins of marine sponge origin, as its protected form” S. Sasaki, Y. Hamada, T. Shioiri, *Tetrahedron Lett.* **1999**, *40*, 3187-3190.
- [356] S. Sasaki, Y. Hamada, T. Shioiri Dans *Peptide Science – Present and Future (Proceedings of the 1st International Peptide Symposium)*; Shimonishi, Y., Ed.; Springer: Dordrecht, 1999; Vol. 35, p 519-520.
- [357] “Nickel- or palladium-catalyzed cross coupling. 31. Palladium- or nickel-catalyzed reactions of alkenylmetals with unsaturated organic halides as a selective route to arylated alkenes and conjugated dienes: scope, limitations, and mechanism” E. Negishi, T. Takahashi, S. Baba, D. E. Van Horn, N. Okukado, *J. Am. Chem. Soc.* **1987**, *109*, 2393-2401.
- [358] “Studies in polypropionate synthesis: high π -face selectivity in syn and anti aldol reactions of chiral boron enolates of lactate-derived ketones” I. Paterson, D. J. Wallace, S. M. Velazquez, *Tetrahedron Lett.* **1994**, *35*, 9083-9086.
- [359] “Construction of Three Building Blocks for the Total Synthesis of Microsclerodermins” S. Sasaki, Y. Hamada, T. Shioiri, *Synlett* **1999**, 453-455.
- [360] “Synthetic approach to microsclerodermins: construction of three building blocks” T. Shioiri,

- S. Sasaki, Y. Hamada, *ARKIVOC (Gainesville, FL, U. S.)* **2003**, 103-122.
- [361] "Amino acids and peptides. XXIX. A new efficient asymmetric synthesis of α -amino acid derivatives with recycling of a chiral reagent - asymmetric alkylation of a chiral Schiff base from glycine" T. Oguri, N. Kawai, T. Shioiri, S. Yamada, *Chem. Pharm. Bull.* **1978**, *26*, 803-808.
- [362] "A new asymmetric synthesis of (S)-dolaphenine and its heteroaromatic congeners utilizing (+)-2-hydroxy-3-pinanone and (-)-3-hydroxy-2-caranone as chiral auxiliaries" N. Irako, Y. Hamada, T. Shioiri, *Tetrahedron* **1995**, *51*, 12731-12744.
- [363] "A revised mechanism for chemoselective reduction of esters with borane-dimethyl sulfide complex and catalytic sodium tetrahydroborate directed by adjacent hydroxyl group" S. Saito, T. Ishikawa, A. Kuroda, K. Koga, T. Moriwake, *Tetrahedron* **1992**, *48*, 4067-4086.
- [364] "Combination of borane-dimethyl sulfide complex with catalytic sodium tetrahydroborate as a selective reducing agent for α -hydroxy esters. Versatile chiral building block from (S)-(-)-malic acid" S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu, T. Moriwake, *Chem. Lett.* **1984**, 1389-1392.
- [365] "A new, short and efficient synthesis of both enantiomers of carnitine" F. D. Bellamy, M. Bondoux, P. Dodey, *Tetrahedron Lett.* **1990**, *31*, 7323-7326.
- [366] "C-Acylation under Virtually Neutral Conditions" D. W. Brooks, L. D.-L. Lu, S. Masamune, *Angewandte Chemie International Edition in English* **1979**, *18*, 72-74.
- [367] "Stereoselective synthesis of the C1-C20 segment of the Microsclerodermins A and B" S. Chandrasekhar, S. S. Sultana, *Tetrahedron Lett.* **2006**, *47*, 7255-7258.
- [368] "An expedient total synthesis of cis-(+)-sertraline from D-phenylglycine" S. Chandrasekhar, M. V. Reddy, *Tetrahedron* **2000**, *56*, 1111-1114.
- [369] "A mild oxidizing reagent for alcohols and 1,2-diols: o-iodoxybenzoic acid (IBX) in DMSO" M. Frigerio, M. Santagostino, *Tetrahedron Lett.* **1994**, *35*, 8019-8022.
- [370] "A novel deoxygenation-isomerization reaction of 4-hydroxy-2-ynoic esters and γ -hydroxy- α,β -ynones" C. Guo, X. Lu, *J. Chem. Soc., Chem. Commun.* **1993**, 394-395.
- [371] "Reactions of Electron-Deficient Alkynes and Allenes under Phosphine Catalysis" X. Lu, C. Zhang, Z. Xu, *Account of Chemical Research* **2001**, *34*, 535-544.
- [372] "Catalytic asymmetric aminohydroxylation (AA) of olefins" G. Li, H.-T. Chang, K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451-454.

- [373] "The Sharpless asymmetric aminohydroxylation" J. A. Bodkin, M. D. McLeod, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733-2746.
- [374] "Diastereoselective synthesis of α -bromo amides leading to diastereomerically enriched α -amino-, α -hydroxy-, and α -thiocarboxylic acid derivatives" R. S. Ward, A. Pelter, D. Goubet, M. C. Pritchard, *Tetrahedron: Asymmetry* **1995**, 6, 469-498.
- [375] "Amino analogs of actic acids-synthesis and lactamization" H. Bernsmann, Y. Wang, R. Frohlich, P. Metz, *Tetrahedron* **2002**, 58, 4451-4457.
- [376] "Sulfinyl moiety as an internal nucleophile. Part 6: Stereospecific synthesis of 3-amino-2-hydroxy-4-phenylbutanoate" S. Raghavan, M. A. Rasheed, *Tetrahedron: Asymmetry* **2003**, 14, 1371-1374.
- [377] "Azides: their preparation and synthetic uses" E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, 88, 297-368.
- [378] "Convenient Preparation of trans-Arylalkenes via Palladium(II)-Catalyzed Isomerization of cis-Arylalkenes" J. Yu, M. J. Gaunt, J. B. Spencer, *J. Org. Chem.* **2002**, 67, 4627-4629.
- [379] "Selective removal of the isopropylidene group in 4-O-protected 1,6-anhydro-2,3-O-isopropylidene- β -D-mannopyranose and the conformational impact of it" R. Van Rijsbergen, M. J. O. Anteunis, A. De Bruyn, *J. Carbohydr. Chem.* **1983**, 2, 395-404.
- [380] "The enantioselective synthesis of APTO and AETD: Polyhydroxylated β -amino acid constituents of the microsclerodermin cyclic peptides" E. C. Shuter, H. Duong, C. A. Hutton, M. D. McLeod, *Org. Biomol. Chem.* **2007**, 5, 3183-3189.
- [381] "Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands" M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, 1, 953-956.
- [382] "Electronic effects on the regio- and enantioselectivity of the asymmetric aminohydroxylation of O-substituted 4-hydroxy-2-butenates" C.-Y. Chuang, V. C. Vassar, Z. Ma, R. Geney, I. Ojima, *Chirality* **2002**, 14, 151-162.
- [383] "A useful 12-I-5 triacetoxyperiodinane (the Dess-Martin periodinane) for the selective oxidation of primary or secondary alcohols and a variety of related 12-I-5 species" D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, 113, 7277-7287.
- [384] "A stereoselective synthesis of trans-1,2-disubstituted alkenes based on the condensation of aldehydes with metalated 1-phenyl-1H-tetrazol-5-yl sulfones" P. R. Blakemore, W. J. Cole, P.

- J. Kocienski, A. Morley, *Synlett* **1998**, 26-28.
- [385] "Insect sex pheromones. Stereospecific synthesis of (E)-13,13-dimethyl-11-tetradecen-1-ol acetate via a thiophenol-mediated olefin inversion" M. Schwarz, G. F. Graminski, R. M. Waters, *J. Org. Chem.* **1986**, *51*, 260-263.
- [386] "Catalytic Asymmetric Dihydroxylation" H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev. (Washington, D. C.)* **1994**, *94*, 2483-2547.
- [387] "Rapid Assembly of the Polyhydroxylated β -Amino Acid Constituents of Microsclerodermins C, D, and E" T. Hjelmgaard, S. Faure, P. Lemoine, B. Viossat, D. J. Aitken, *Org. Lett.* **2008**, *10*, 841-844.
- [388] "Acetonation of L-fucose, L-rhamnose, and 2-deoxy-D-erythro-pentose under kinetically controlled conditions" J. Barbat, J. Gelas, D. Horton, *Carbohydr. Res.* **1983**, *116*, 312-316.
- [389] "Asymmetric synthesis of amino acids using sulfinimines (thiooxime S-oxides)" F. A. Davis, B.-C. Chen, *Chem. Soc. Rev.* **1998**, *27*, 13-18.
- [390] "N-tert-Butanesulfinyl Imines: Versatile Intermediates for the Asymmetric Synthesis of Amines" J. A. Ellman, T. D. Owens, T. P. Tang, *Account of Chemical Research* **2002**, *35*, 984-995.
- [391] "Recent advances in asymmetric reactions using sulfinimines (N-sulfinyl imines)" P. Zhou, B.-C. Chen, F. A. Davis, *Tetrahedron* **2004**, *60*, 8003-8030.
- [392] "Total Synthesis of Pinnamine and Anatoxin-a via a Common Intermediate. A Caveat on the Anatoxin-a Endgame" T. Hjelmgaard, I. Sotofte, D. Tanner, *J. Org. Chem.* **2005**, *70*, 5688-5697.
- [393] "2,2,5-Trimethyl-1,3-dioxolane-4-carboxaldehyde as a chiral synthon: synthesis of the two enantiomers of methyl 2,3,6-trideoxy- α -L-threo-hex-2-enopyranoside, key intermediate in the synthesis of daunosamine, and of (+)- and (-)-rhodinoside" S. Servi, *J. Org. Chem.* **1985**, *50*, 5865-5867.
- [394] "Asymmetric Synthesis of Polyhydroxy α -Amino Acids with the Sulfinimine-Mediated Asymmetric Strecker Reaction: 2-Amino 2-Deoxy L-Xylono-1,5-lactone (Polyoxamic Acid Lactone)" F. A. Davis, K. R. Prasad, P. J. Carroll, *J. Org. Chem.* **2002**, *67*, 7802-7806.
- [395] "Highly Diastereoselective Enolate Addition of O-Protected α -Hydroxyacetate to (SR)-tert-Butanesulfinylimines: Synthesis of Taxol Side Chain" Y. Wang, Q.-F. He, H.-W. Wang, X. Zhou, Z.-Y. Huang, Y. Qin, *J. Org. Chem.* **2006**, *71*, 1588-1591.

- [396] "Asymmetric synthesis of the core of AMPTD, the key amino acid of microsclerodermins F-I" C. M. Burnett, R. M. Williams, *Tetrahedron Lett.* **2009**, *50*, 5449-5451.
- [397] "Asymmetric Induction in Methyl Ketone Aldol Additions to α -Alkoxy and α,β -Bisalkoxy Aldehydes: A Model for Acyclic Stereocontrol" D. A. Evans, V. J. Cee, S. J. Siska, *J. Am. Chem. Soc.* **2006**, *128*, 9433-9441.
- [398] "Enantiospecific Synthesis of a Protected Equivalent of APTO, the β -Amino Acid Fragment of Microsclerodermins C and D, by Aziridino- γ -lactone Methodology" A. Tarrade-Matha, M. S. Valle, P. Tercinier, P. Dauban, R. H. Dodd, *Eur. J. Org. Chem.* **2009**, 673-686.
- [399] "Synthesis of Optically Pure 3,4-Disubstituted L-Glutamates from a Novel 2,3-Aziridino- γ -lactone 4-Carboxylate Derivative" P. Dauban, A. Chiaroni, C. Riche, R. H. Dodd, *J. Org. Chem.* **1996**, *61*, 2488-2496.
- [400] "Synthesis of 2,3-aziridino-2,3-dideoxy-D-lyxono- γ -lactone 5-phosphonate from D-ribose, a new member of the 2,3-aziridino- γ -lactone family of synthons" P. Dauban, B. Hofmann, R. H. Dodd, *Tetrahedron* **1997**, *53*, 10743-10752.
- [401] "2,3-Aziridino-2,3-dideoxy-D-ribo- γ -lactone 5-Phosphonate: Stereocontrolled Synthesis from D-Lyxose and Unusual Aziridine Ring Opening" P. Dauban, R. H. Dodd, *J. Org. Chem.* **1997**, *62*, 4277-4284.
- [402] "Application of 2,3-aziridino- γ -lactone methodology toward the enantiospecific synthesis of the (3S,4S)-isomer of dihydroxy-L-glutamic acid" P. Dauban, C. De Saint-Fuscien, R. H. Dodd, *Tetrahedron* **1999**, *55*, 7589-7600.
- [403] "A new straightforward synthesis of 2,3-aziridino- γ -lactones" C. de Saint-Fuscien, A. Tarrade, P. Dauban, R. H. Dodd, *Tetrahedron Lett.* **2000**, *41*, 6393-6397.
- [404] "First enantiospecific synthesis of a 3,4-dihydroxy-L-glutamic acid [(3S,4S)-DHGA], a new mGluR1 agonist" P. Dauban, C. De Saint-Fuscien, F. Acher, L. Prezeau, I. Brabet, J.-P. Pin, R. H. Dodd, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 129-133.
- [405] "Enantiospecific Total Synthesis of (-)-Polyoxamic Acid Using 2,3-Aziridino- γ -lactone Methodology" A. Tarrade, P. Dauban, R. H. Dodd, *J. Org. Chem.* **2003**, *68*, 9521-9524.
- [406] "Enantiospecific synthesis of 3,4-disubstituted glutamic acids via controlled stepwise ring-opening of 2,3-aziridino- γ -lactone" Z. Yan, R. Weaving, P. Dauban, R. H. Dodd, *Tetrahedron Lett.* **2002**, *43*, 7593-7595.
- [407] "Regioselective electrophilic substitution of 2,3-aziridino- γ -lactones: preliminary studies

- aimed at the synthesis of α,α -disubstituted α - or β -amino acids” M. S. Valle, A. Tarrade-Matha, P. Dauban, R. H. Dodd, *Tetrahedron* **2008**, *64*, 419-432.
- [408] “Reactivity of 2,3-Aziridino-2,3-dideoxy-D-lyxono- γ -lactone Derivatives, Rigid Analogs of Aziridine-2-carboxylic Esters, toward Soft and Hard Nucleophiles: Control of Lactone vs Aziridine Ring Opening and C-2 vs C-3 Regioselectivity” P. Dauban, L. Dubois, M. E. Tran Huu Dau, R. H. Dodd, *J. Org. Chem.* **1995**, *60*, 2035-2043.
- [409] “A modified synthesis of (+)-biotin from D-glucose” T. Ravindranathan, S. V. Hiremath, D. R. Reddy, A. V. Rama Rao, *Carbohydr. Res.* **1984**, *134*, 332-336.
- [410] “Practical synthesis of deoxymannojirimycin and mannonolactam from L-gulonolactone. Synthesis of L-deoxymannojirimycin and L-mannonolactam from D-gulonolactone” G. W. J. Fleet, N. G. Ramsden, D. R. Witty, *Tetrahedron* **1989**, *45*, 319-326.
- [411] “Synthesis of, and lack of inhibition of a rhamnosidase by, both enantiomers of deoxyrhamnojirimycin and rhamnonolactam: β -mannosidase inhibition by δ -lactams” A. J. Fairbanks, N. C. Carpenter, G. W. J. Fleet, N. G. Ramsden, I. Cenci de Bello, B. G. Winchester, S. S. Al-Daher, G. Nagahashi, *Tetrahedron* **1992**, *48*, 3365-3376.
- [412] “Preparation of enantiomerically pure mono- and diepoxylactones from aldonolactones” I. Lundt, C. Pedersen, *Synthesis* **1992**, 669-672.
- [413] “Enantiopure hydroxylactones from L-ascorbic and D-isoascorbic acids. Part II. Synthesis of (-)-(5R,6S)-6-acetoxy-5-hexadecanolide and its diastereomers” C. Gravier-Pelletier, Y. Le Merrer, J.-C. Depezay, *Tetrahedron* **1995**, *51*, 1663-1674.
- [414] “Specific removal of O-methoxybenzyl protection by DDQ oxidation” Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 885-888.
- [415] “Protection of hydroxy groups by intramolecular oxidative formation of methoxybenzylidene acetals with DDQ” Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 889-892.
- [416] “Tetrapropylammonium perruthenate, Pr₄N⁺RuO₄⁻, TPAP: a catalytic oxidant for organic synthesis” S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639-666.
- [417] “Tributylphosphine-catalyzed ring-opening reaction of epoxides and aziridines with acetic anhydride” R.-H. Fan, X.-L. Hou, *Tetrahedron Lett.* **2003**, *44*, 4411-4413.
- [418] “Asymmetric syntheses of APTO and AETD: the β -Amino acid fragments within microsclerodermins C, D, and E” S. G. Davies, A. M. Fletcher, E. M. Foster, J. A. Lee, P. M.

- Roberts, J. E. Thomson, *J. Org. Chem.* **2013**, *78*, 2500-2510.
- [419] "Asymmetric synthesis of syn- and anti- α -deuterio- β 3-phenylalanine derivatives" S. G. Davies, E. M. Foster, C. R. McIntosh, P. M. Roberts, T. E. Rosser, A. D. Smith, J. E. Thomson, *Tetrahedron: Asymmetry* **2011**, *22*, 1035-1050.
- [420] "The directed dihydroxylation of allylic alcohols" T. J. Donohoe, P. R. Moore, M. J. Waring, *Tetrahedron Lett.* **1997**, *38*, 5027-5030.
- [421] "Directed Dihydroxylation of Allylic Trichloroacetamides" T. J. Donohoe, K. Blades, M. Helliwell, P. R. Moore, J. J. G. Winter, G. Stemp, *J. Org. Chem.* **1999**, *64*, 2980-2981.
- [422] "Directed Dihydroxylation of Cyclic Allylic Alcohols and Trichloroacetamides Using OsO₄/TMEDA" T. J. Donohoe, K. Blades, P. R. Moore, M. J. Waring, J. J. G. Winter, M. Helliwell, N. J. Newcombe, G. Stemp, *J. Org. Chem.* **2002**, *67*, 7946-7956.
- [423] "Development of the directed dihydroxylation reaction" T. J. Donohoe, *Synlett* **2002**, 1223-1232.
- [424] "Total synthesis of microsclerodermin E" J. Zhu, D. Ma, *Angew. Chem., Int. Ed.* **2003**, *42*, 5348-5351.
- [425] "Lewis acid-mediated addition of lithiated alkyl phenyl sulfones and oxiranes. A method for synthesis of α,β -unsaturated ketones" S. Marczak, J. Wicha, *Synth. Commun.* **1990**, *20*, 1511-1520.
- [426] "Synthetic studies in the brefeldin series: asymmetric enamine-enal cycloaddition and intramolecular Nozaki reactions" S. L. Schreiber, H. V. Meyers, *J. Am. Chem. Soc.* **1988**, *110*, 5198-5200.
- [427] "1-Aminoalkanephosphonates. Part II. A facile conversion of 1-aminoalkanephosphonic acids into O,O-diethyl 1-aminoalkanephosphonates" Z. Kudzin, P. Lyzwa, J. Luczak, G. Andrijewski, *Synthesis* **1997**, 44-46.
- [428] "On the synthesis of glucagon. X. Preparation of sequence 22-29" E. Wunsch, F. Drees, *Chem. Ber.* **1966**, *99*, 110-120.
- [429] "Synthesis of N-protected γ -amino- β -keto esters from urethane N-carboxyanhydrides (UNCAs)" M. Paris, J.-A. Fehrentz, A. Heitz, A. Loffet, J. Martinez, *Tetrahedron Lett.* **1996**, *37*, 8489-8492.
- [430] "Total synthesis of avermectins. Part 2: Enantioselective synthesis of the C10-C25 northern fragment and final steps for the construction of the 22,23-dihydroavermectin B1b aglycon"

- J.-P. Ferezou, M. Julia, Y. Li, L. W. Liu, A. Pancrazi, *Bull. Soc. Chim. Fr.* **1995**, *132*, 428-452.
- [431] “Optical purity of peptide active esters prepared by N,N'-dicyclohexylcarbodiimide and complexes of N,N'-dicyclohexylcarbodiimide-pentachlorophenol and N,N'-dicyclohexylcarbodiimide-pentafluorophenol” J. Kovacs, L. Kisfaludy, M. Q. Ceprini, *J. Am. Chem. Soc.* **1967**, *89*, 183-184.
- [432] “Preparation and applications of pentafluorophenyl esters of 9-fluorenylmethoxycarbonyl amino acids for peptide synthesis” L. Kisfaludy, I. Schon, *Synthesis* **1983**, 325-327.
- [433] “Total Synthesis of Gypsetin, Deoxybrevianamide E, Brevianamide E, and Tryprostatin B: Novel Constructions of 2,3-Disubstituted Indoles” J. M. Schkeryantz, J. C. G. Woo, P. Siliphaivanh, K. M. Depew, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 11964-11975.
- [434] “New organic compounds of phosphorus. III. Phosphinemethylene derivatives and phosphinimines” H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635-646.
- [435] “Acetylzucker-phosphinimine und -carbodiimide” A. Messmer, I. Pintèr, F. Szegö, *Angew. Chem.* **1964**, *76*, 227-228.
- [436] “Total synthesis of OF4949-III and OF4949-IV: unusual effects of remote substituents on the rate of macrocyclization reactions” D. L. Boger, D. Yohannes, *Tetrahedron Lett.* **1989**, *30*, 5061-5064.
- [437] “Ruthenium-Catalyzed Alkene-Alkyne Coupling: Synthesis of the Proposed Structure of Amphidinolide A” B. M. Trost, J. D. Chisholm, S. J. Wroblewski, M. Jung, *J. Am. Chem. Soc.* **2002**, *124*, 12420-12421.
- [438] “Tethered Aminohydroxylation: Synthesis of the β -Amino Acid of Microsclerodermins A and B” R. D. C. Pullin, A. H. Rathi, E. Y. Melikhova, C. Winter, A. L. Thompson, T. J. Donohoe, *Org. Lett.* **2013**, *15*, 5492-5495.
- [439] “Diastereoselective synthesis of the 5-hydroxy-pyrrolidinone amino acid of the microsclerodermins and model studies for an end-game strategy for microsclerodermin B” C. Winter, R. D. C. Pullin, T. J. Donohoe, *Tetrahedron Lett.* **2016**, *58*, 602-605.
- [440] “Dehydromicrosclerodermin B and Microsclerodermin J: Total synthesis and structural revision” E. Y. Melikhova, R. D. C. Pullin, C. Winter, T. J. Donohoe, *Angew. Chem., Int. Ed.* **2016**, *55*, 9753-9757.
- [441] “The Tethered Aminohydroxylation (TA) of Cyclic Allylic Carbamates” T. J. Donohoe, P. D.

- Johnson, A. Cowley, M. Keenan, *J. Am. Chem. Soc.* **2002**, *124*, 12934-12935.
- [442] "Chemistry of higher order, mixed organocuprates. 1. Substitution reactions at unactivated secondary centers" B. H. Lipshutz, R. S. Wilhelm, D. M. Floyd, *J. Am. Chem. Soc.* **1981**, *103*, 7672-7674.
- [443] "Gilman-Type versus Lipshutz-Type Reagents: Competition in Lithiocuprate Chemistry" J. Haywood, J. V. Morey, A. E. H. Wheatley, C.-Y. Liu, S. Yasuike, J. Kurita, M. Uchiyama, P. R. Raithby, *Organometallics* **2009**, *28*, 38-41.
- [444] "Imidoester, V. Die Umlagerung von Trichloracetimidaten zu N-substituierten Säureamiden" F. Cramer, N. Hennrich, *Chem. Ber.* **1961**, *94*, 976-989.
- [445] "A simple access to trichloroacetimidates" V. J. Patil, *Tetrahedron Lett.* **1996**, *37*, 1481-1484.
- [446] "A useful application of benzyl trichloroacetimidate for the benzylation of alcohols" P. Eckenberg, U. Groth, T. Huhn, N. Richter, C. Schmeck, *Tetrahedron* **1993**, *49*, 1619-1624.
- [447] "Highly practical, enantiospecific synthesis of the cyclohexyl fragment of the immunosuppressant FK-506" H. Kotsuki, H. Nishikawa, Y. Mori, M. Ochi, *J. Org. Chem.* **1992**, *57*, 5036-5040.
- [448] "Cyanogen fluoride: synthesis and properties" F. S. Fawcett, R. D. Lipscomb, *J. Am. Chem. Soc.* **1964**, *86*, 2576-2579.
- [449] "Synthetic methods and reactions. IV. Fluorination of carboxylic acids with cyanuric fluoride" G. A. Olah, M. Nojima, I. Kerekes, *Synthesis* **1973**, 487-488.
- [450] "A Stereoselective Entry into Functionalized 1,2-Diamines by Zinc-Mediated Homologation of α -Aminoacids" C. T. Hoang, V. Alezra, R. Guillot, C. Kouklovsky, *Org. Lett.* **2007**, *9*, 2521-2524.
- [451] "Reactions of 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one with alkenes in the presence of weak bases" M. Tsubota, M. Iso, K. Suzuki, *Bull. Chem. Soc. Jap.* **1972**, *45*, 1252-1253.
- [452] "Selective bromination of polyolefins. XV" Y. Kitahara, T. Kato, I. Ichinose, *Chem. Lett.* **1976**, 283-286.
- [453] "Selective bromination of polyenes with TBCO (2,4,4,6-tetrabromocyclohexadienone)" T. Kato, I. Ichinose, T. Hosogai, *Yuki Gosei Kagaku Kyokaiishi* **1977**, *35*, 491-496.
- [454] "Cyclization of polyenes. Part 32. Selective bromination of polyenes by 2,4,4,6-tetrabromocyclohexa-2,5-dienone" T. Kato, I. Ichinose, *J. Chem. Soc., Perkin Trans.*

- I* **1980**, 1051-1056.
- [455] “Enantiomeric synthesis of polysubstituted furans by stereoselective intramolecular bromoetherification” C. E. Tonn, J. M. Palazon, C. Ruiz-Perez, M. L. Rodriguez, V. S. Martin, *Tetrahedron Lett.* **1988**, 29, 3149-3152.
- [456] “Hydrolysis of the GlcNAc oxazoline: deamidation and acyl rearrangement” R. Jha, J. T. Davis, *Carbohydr. Res.* **1995**, 277, 125-134.
- [457] “Boron: a key element in radical reactions” P. Renaud, A. Beauseigneur, A. Brecht-Forster, B. Becattini, V. Darmency, S. Kandhasamy, F. Montermini, C. Ollivier, P. Panchaud, D. Pozzi, E. M. Scanlan, A.-P. Schaffner, V. Weber, *Pure Appl. Chem.* **2007**, 79, 223-233.
- [458] “A General Model for Selectivity in Olefin Cross Metathesis” A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, 125, 11360-11370.
- [459] “Ruthenium-catalysed Z-selective cross metathesis of allylic-substituted olefins” B. L. Quigley, R. H. Grubbs, *Chem. Sci.* **2014**, 5, 501-506.
- [460] “Convenient synthesis of chiral tryptophan derivatives using Negishi cross-coupling” M. Tanaka, H. Hikawa, Y. Yokoyama, *Tetrahedron* **2011**, 67, 5897-5901.
- [461] “Tris(dialkylamino)sulfonium enolates” R. Noyori, I. Nishida, J. Sakata, M. Nishizawa, *J. Am. Chem. Soc.* **1980**, 102, 1223-1225.
- [462] “Tris(dialkylamino)sulfonium enolates. Synthesis, structure, and reactions” R. Noyori, I. Nishida, J. Sakata, *J. Am. Chem. Soc.* **1983**, 105, 1598-1608.
- [463] “Total Synthesis of (+)-Damavaricin D” W. R. Roush, D. S. Coffey, D. J. Madar, *J. Am. Chem. Soc.* **1997**, 119, 11331-11332.
- [464] “Total synthesis of cyclotheonamide C using a tandem backbone-extension-coupling methodology” S. P. Roche, S. Faure, D. J. Aitken, *Angew. Chem., Int. Ed.* **2008**, 47, 6840-6842.
- [465] “Total synthesis of cyclotheonamide C by use of an α -keto cyanophosphorane methodology for peptide assembly” S. P. Roche, S. Faure, L. El Blidi, D. J. Aitken, *Eur. J. Org. Chem.* **2008**, 5067-5078, S5067/5061-S5067/5014.
- [466] “Passerini Reaction-Amine Deprotection-Acyl Migration Peptide Assembly: Efficient Formal Synthesis of Cyclotheonamide C” S. Faure, T. Hjelmgaard, S. P. Roche, D. J. Aitken, *Org. Lett.* **2009**, 11, 1167-1170.
- [467] “A solution to the component instability problem in the preparation of peptides containing

- C2-substituted cis-cyclobutane β -aminoacids: synthesis of a stable rhodopeptin analog” O. Roy, S. Faure, D. J. Aitken, *Tetrahedron Lett.* **2006**, *47*, 5981-5984.
- [468] “An efficient synthesis of (R)-GABOB and of (\pm)-GABOB” E. Sahin, N. Kishali, L. Kelebekli, E. Mete, H. Secen, R. Altundas, Y. Kara, *Org. Prep. Proced. Int.* **2007**, *39*, 509-513.
- [469] “Total synthesis of (+)-negamycin and its 5-epi-derivative” S. Nishiguchi, M. O. Sydnes, A. Taguchi, T. Regnier, T. Kajimoto, M. Node, Y. Yamazaki, F. Yakushiji, Y. Kiso, Y. Hayashi, *Tetrahedron* **2010**, *66*, 314-320.
- [470] “Design, Synthesis, and Biological Evaluation of Simplified Side Chain Hybrids of the Potent Actin Binding Polyketides Rhizopodin and Bistramide” D. Herkommer, S. Dreisigacker, G. Sergeev, F. Sasse, H. Gohlke, D. Menche, *ChemMedChem* **2015**, *10*, 470-489.
- [471] “Synthesis of amphiphilic fullerene derivatives and their incorporation in Langmuir and Langmuir-Blodgett films” D. Felder, M. G. Nava, M. Del Pilar Carreon, J.-F. Eckert, M. Luccisano, C. Schall, P. Masson, J.-L. Gallani, B. Heinrich, D. Guillon, J.-F. Nierengarten, *Helv. Chim. Acta* **2002**, *85*, 288-319.
- [472] “A Stereoselective and Practical Synthesis of (E)- α,β -Unsaturated Ketones from Aldehydes” E. Balducci, E. Attolino, M. Taddei, *Eur. J. Org. Chem.* **2011**, 311-318, S311/311-S311/369.
- [473] “Synthesis of (-)-dihydropinidine, (2S,6R)-isosolenopsin and (+)-monomorine via a chiral synthon from L-aspartic acid” C. R. Reddy, B. Latha, *Tetrahedron: Asymmetry* **2011**, *22*, 1849-1854.
- [474] “Formal syntheses of (-)- and (+)-aphanorphine from (2S,4R)-4-hydroxyproline” Z. Ma, H. Hu, W. Xiong, H. Zhai, *Tetrahedron* **2007**, *63*, 7523-7531.
- [475] “Rearrangement of 6 β -bromo-4-cholesten-3-one to 2 α -acetoxy-4-cholesten-3-one” L. F. Fieser, M. A. Romero, *J. Am. Chem. Soc.* **1953**, *75*, 4716-4719.
- [476] “Preparation of ethylenethioketals” L. F. Fieser, *J. Am. Chem. Soc.* **1954**, *76*, 1945-1947.
- [477] “Boron trifluoride promoted cleavage of benzyl carbamates” D. S. Bose, D. E. Thurston, *Tetrahedron Lett.* **1990**, *31*, 6903-6906.
- [478] “Total synthesis of (\pm)-elwesine, (\pm)-epielwesine, and (\pm)-oxocrinine” I. H. Sanchez, F. J. Lopez, J. J. Soria, M. I. Larraza, H. J. Flores, *J. Am. Chem. Soc.* **1983**, *105*, 7640-7643.
- [479] “Design and preparation of serine-threonine protein phosphatase inhibitors based upon the

- nodularin and microcystin toxin structures. Part 3” K. L. Webster, A. B. Maude, M. E. O'Donnell, A. P. Mehrotra, D. Gani, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1673-1695.
- [480] “Positional scanning for peptide secondary structure by systematic solid-phase synthesis of amino lactam peptides” A. G. Jamieson, N. Boutard, K. Beauregard, M. S. Bodas, H. Ong, C. Quiniou, S. Chemtob, W. D. Lubell, *J. Am. Chem. Soc.* **2009**, *131*, 7917-7927.
- [481] “MSc E” J. Zhu, Shanghai University, **2003**.
- [482] “Urethane-protected N-carboxyanhydrides (UNCAs) as unique reactants for the study of intrinsic racemization tendencies in peptide synthesis” T. T. Romoff, M. Goodman, *J. Pept. Res.* **1997**, *49*, 281-292.
- [483] “Synthesis and pharmacological activity of angiotensin-converting enzyme inhibitors: N-(mercaptoacyl)-4-substituted-(S)-prolines” E. M. Smith, G. F. Swiss, B. R. Neustadt, E. H. Gold, J. A. Sommer, A. D. Brown, P. J. S. Chiu, R. Moran, E. J. Sybertz, T. Baum, *J. Med. Chem.* **1988**, *31*, 875-885.
- [484] “Angiotensin converting enzyme inhibitors: spirapril and related compounds” E. M. Smith, G. F. Swiss, B. R. Neustadt, P. McNamara, E. H. Gold, E. J. Sybertz, T. Baum, *J. Med. Chem.* **1989**, *32*, 1600-1606.
- [485] “Structure-activity studies of fluoroalkyl-substituted γ -butyrolactone and γ -thiobutyrolactone modulators of GABAA receptor function” D. J. Canney, H.-F. Lu, A. C. McKeon, K.-W. Yoon, K. Xu, K. D. Holland, S. M. Rothman, J. A. Ferrendelli, D. F. Covey, *Bioorg. Med. Chem.* **1998**, *6*, 43-55.
- [486] “Synthesis of a Smoothened Cholesterol: 18,19-Di-nor-cholesterol” L. Mydock-McGrane, N. P. Rath, D. F. Covey, *J. Org. Chem.* **2014**, *79*, 5636-5643.
- [487] “Synthesis of a Smoothened Cholesterol: 18,19-Di-nor-cholesterol - Corrections” L. Mydock-McGrane, N. P. Rath, D. F. Covey, *J. Org. Chem.* **2015**, *80*, 6000.
- [488] “Peptide α -keto ester, α -keto amide, and α -keto acid inhibitors of calpains and other cysteine proteases” Z. Li, G. S. Patil, Z. E. Golubski, H. Hori, K. Tehrani, J. E. Foreman, D. D. Eveleth, R. T. Bartus, J. C. Powers, *J. Med. Chem.* **1993**, *36*, 3472-3480.
- [489] “Novel Peptidyl α -Keto Amide Inhibitors of Calpains and Other Cysteine Proteases” Z. Li, A.-C. Ortega-Vilain, G. S. Patil, D.-L. Chu, J. E. Foreman, D. D. Eveleth, J. C. Powers, *J. Med. Chem.* **1996**, *39*, 4089-4098.
- [490] “ α -Keto Amide Peptides: A Synthetic Strategy to Resin-Bound Peptide Isosteres for Protease

- Inhibitor Screening on Solid Support” A. Papanikos, M. Meldal, *J. Comb. Chem.* **2004**, *6*, 181-195.
- [491] “Preservation of the Fmoc protective group under alkaline conditions by using CaCl₂. Applications in peptide synthesis” R. Pascal, R. Sola, *Tetrahedron Lett.* **1998**, *39*, 5031-5034.
- [492] “Proteolytic stability of cyclic α -hydrazino acid containing peptides: a qualitative study” I. Duttagupta, J. Bhadra, S. K. Das, S. Sinha, *Tetrahedron Lett.* **2016**, *57*, 3858-3861.
- [493] “Synthesis of Fmoc-protected amino alcohols via the Sharpless asymmetric aminohydroxylation reaction using FmocNHCl as the nitrogen source” R. Moreira, M. Diamandas, S. D. Taylor, *J. Org. Chem.* **2019**, *84*, 15476-15485.
- [494] “Iodide dealkylation of benzyl, PMB, PNB, and t-butyl N-acyl amino acid esters via lithium ion coordination” J. W. Fisher, K. L. Trinkle, *Tetrahedron Lett.* **1994**, *35*, 2505-2508.
- [495] “Discovery of (1R,5S)-N-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide (SCH 503034), a Selective, Potent, Orally Bioavailable Hepatitis C Virus NS3 Protease Inhibitor: A Potential Therapeutic Agent for the Treatment of Hepatitis C Infection” S. Venkatraman, S. L. Bogen, A. Arasappan, F. Bennett, K. Chen, E. Jao, Y.-T. Liu, R. Lovey, S. Hendrata, Y. Huang, W. Pan, T. Parekh, P. Pinto, V. Popov, R. Pike, S. Ruan, B. Santhanam, B. Vibulbhan, W. Wu, W. Yang, J. Kong, X. Liang, J. Wong, R. Liu, N. Butkiewicz, R. Chase, A. Hart, S. Agrawal, P. Ingravallo, J. Pichardo, R. Kong, B. Baroudy, B. Malcolm, Z. Guo, A. Prongay, V. Madison, L. Broske, X. Cui, K.-C. Cheng, T. Y. Hsieh, J.-M. Brisson, D. Prelusky, W. Korfmacher, R. White, S. Bogdanowich-Knipp, A. Pavlovsky, P. Bradley, A. K. Saksena, A. Ganguly, J. Piwinski, V. Girijavallabhan, F. G. Njoroge, *J. Med. Chem.* **2006**, *49*, 6074-6086.
- [496] “Potent ketoamide inhibitors of HCV NS3 protease derived from quaternized P1 groups” S. Venkatraman, F. Velazquez, W. Wu, M. Blackman, V. Madison, F. G. Njoroge, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2151-2155.
- [497] “Dehydration of threonine esters during tosylation” C. Somlai, S. Lovas, P. Forgo, R. F. Murphy, B. Penke, *Synth. Commun.* **2001**, *31*, 3633-3640.
- [498] “Highly enantioselective enzymatic resolution of aromatic β -amino acid amides with Pd-catalyzed racemization” E. Choi, Y. Kim, Y. Ahn, J. Park, M.-J. Kim, *Tetrahedron:*

- Asymmetry* **2013**, *24*, 1449-1452.
- [499] "Synthesis of 1,n-dicarbonyl derivatives using carbanions from 1,3-dithianes" E. J. Corey, D. Seebach, *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1077-1078.
- [500] "Organic Chemistry of Bivalent Sulfur, Vol. VI"; E. E. Emmet; Chem. Pub. Co., 1966.
- [501] "Methods and possibilities of nucleophilic acylation" D. Seebach, *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 639-649.
- [502] "Oxidative hydrolysis of 1,3-dithiane derivatives to carbonyl compounds using N-halosuccinimide reagents" E. J. Corey, B. W. Erickson, *J. Org. Chem.* **1971**, *36*, 3553-3560.
- [503] "Umpolung of the reactivity of carbonyl compounds through sulfur-containing reagents" B. T. Groebel, D. Seebach, *Synthesis* **1977**, 357-402.
- [504] "Synthetic methods and reactions; part 105. Cleavage of ethanediyl S,S-acetals with tert-butyl bromide(iodide)/dimethyl sulfoxide reagent" G. A. Olah, A. K. Mehrotra, S. C. Narang, *Synthesis* **1982**, 151-152.
- [505] "Developments in the deprotection of thioacetals" T. E. Burghardt, *J. Sulfur Chem.* **2005**, *26*, 411-427.
- [506] "Enantioselective Total Synthesis of (+)-Brefeldin A and 7-epi-Brefeldin A" Y. Wu, X. Shen, Y.-Q. Yang, Q. Hu, J.-H. Huang, *J. Org. Chem.* **2004**, *69*, 3857-3865.
- [507] "Further explorations on bridged 1,2,4-trioxanes" Q. Zhang, Y. Wu, *Tetrahedron* **2007**, *63*, 10189-10201.
- [508] "Second-generation probes for biosynthetic intermediate capture: towards a comprehensive profiling of polyketide assembly" I. Wilkening, S. Gazzola, E. Riva, J. S. Parascandolo, L. Song, M. Tosin, *Chem. Commun. (Cambridge, U. K.)* **2016**, *52*, 10392-10395.
- [509] "Ueber die Verbindungen der Zuckerarten mit den Mercaptanen" E. Fischer, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 673-679.
- [510] "L.(+)-2,3-Butanedithiol: Synthesis and application to the resolution of racemic carbonyl compounds" E. J. Corey, R. B. Mitra, *J. Am. Chem. Soc.* **1962**, *84*, 2938-2941.
- [511] "1,3-Dithienium- and 1,3-dithiolanium salts. VI. N,N-Disubstituted 4-aminobenzophenones from 1,3-dithian- and 1,3-dithiolan-2-ylum tetrafluoroborates, respectively" I. Stahl, *Chem. Ber.* **1987**, *120*, 135-139.
- [512] "Identification of amides through the mercury derivatives" J. W. Williams, W. T. Rainey, Jr.,

- R. S. Leopold, *J. Am. Chem. Soc.* **1942**, *64*, 1738-1739.
- [513] “Two tests for detecting nitriles and amides” S. Trofimenko, J. W. Sease, *Anal. Chem.* **1958**, *30*, 1432-1434.
- [514] “Mild and Reversible Dehydration of Primary Amides with PdCl₂ in Aqueous Acetonitrile” S. I. Maffioli, E. Marzorati, A. Marazzi, *Org. Lett.* **2005**, *7*, 5237-5239.
- [515] “Stereoselective synthesis of the optically active functionalized 1,3,5-all-anti-triol” T. Nakata, S. Nagao, T. Oishi, *Tetrahedron Lett.* **1985**, *26*, 75-78.
- [516] “Ueber die Einwirkung des Broms in alkalischer Lösung auf Amide” A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2725-2736.
- [517] “Hofmann Rearrangement of Carboxamides Mediated by N-Bromoacetamide” I. I. Jevtic, L. Dosen-Micovic, E. R. Ivanovic, M. D. Ivanovic, *Synthesis* **2016**, *48*, 1550-1560.
- [518] “Highly Stereoselective Syntheses of syn- and anti-1,2-Amino Alcohols” R. V. Hoffman, N. Maslouh, F. Cervantes-Lee, *J. Org. Chem.* **2002**, *67*, 1045-1056.
- [519] “Reversible Ketomethylene-Based Inhibitors of Human Neutrophil Proteinase 3” A. Budnjo, S. Narawane, C. Grauffel, A.-S. Schillinger, T. Fossen, N. Reuter, B. E. Haug, *J. Med. Chem.* **2014**, *57*, 9396-9408.
- [520] “Cross-Claisen condensation of N-Fmoc-amino acids - a short route to heterocyclic γ -amino acids” L. Mathieu, C. Bonnel, N. Masurier, L. T. Maillard, J. Martinez, V. Lisowski, *Eur. J. Org. Chem.* **2015**, *2015*, 2262-2270.
- [521] “Condensationen von Ketonen mit Aldehyden” L. Claisen, A. Claparède, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2460-2468.
- [522] “Synthesis of Optically Active α -Aminoalkyl α' -Halomethyl Ketone: A Cross-Claisen Condensation Approach” Y. Honda, S. Katayama, M. Kojima, T. Suzuki, K. Izawa, *Org. Lett.* **2002**, *4*, 447-449.
- [523] “An efficient synthesis of γ -amino β -ketoester by cross-Claisen condensation with α -amino acid derivatives” Y. Honda, S. Katayama, M. Kojima, T. Suzuki, K. Izawa, *Tetrahedron Lett.* **2003**, *44*, 3163-3166.
- [524] “Efficient and simple one-pot conversion of resin-bound N-Fmoc amino acids and dipeptides into N-Boc derivatives” R. L. E. Furlan, E. G. Mata, *ARKIVOC (Gainesville, FL, U. S.)* **2003**, 32-40.
- [525] “Synthesis of chiral nitrones from N-Fmoc amino acids and N-Fmoc dipeptides” M. L. Di

- Gioia, A. Leggio, A. Le Pera, A. Liguori, A. Napoli, F. Perri, C. Siciliano, *Synth. Commun.* **2004**, *34*, 3325-3334.
- [526] "Evaluation of Solution and Solid-Phase Approaches to the Synthesis of Libraries of α,α -Disubstituted- α -acylaminoketones" J. Garcia, E. G. Mata, C. M. Tice, R. E. Hormann, E. Nicolas, F. Albericio, E. L. Michelotti, *J. Comb. Chem.* **2005**, *7*, 843-863.
- [527] "Solid-phase synthesis of a combinatorial library of dihydroceramide analogues and its activity in human alveolar epithelial cells" G. Villorbina, D. Canals, L. Carde, S. Grijalvo, R. Pascual, O. Rabal, J. Teixido, G. Fabrias, A. Llebaria, J. Casas, A. Delgado, *Bioorg. Med. Chem.* **2007**, *15*, 50-62.
- [528] "1,2,3-Triazoles as Amide Bond Mimics: Triazole Scan Yields Protease-Resistant Peptidomimetics for Tumor Targeting" I. E. Valverde, A. Bauman, C. A. Kluba, S. Vomstein, M. A. Walter, T. L. Mindt, *Angew. Chem., Int. Ed.* **2013**, *52*, 8957-8960.
- [529] "Advances in Fmoc solid-phase peptide synthesis" R. Behrendt, P. White, J. Offer, *J. Pept. Sci.* **2016**, *22*, 4-27.
- [530] "Amino acids and peptides. 65. Cyclopeptides. 12. Total synthesis of the didemnins. 1. Synthesis of the peptolide ring" U. Schmidt, M. Kroner, H. Griesser, *Tetrahedron Lett.* **1988**, *29*, 3057-3060.
- [531] "Amino acids and peptides. 71. Total synthesis of the didemnins. III. Synthesis of protected (2R,3S)-alloisoleucine and (3S,4R,5S)-isostatine derivatives - amino acids from hydroxy acids" U. Schmidt, M. Kroner, H. Griesser, *Synthesis* **1989**, 832-835.
- [532] "(Fluoren-9-ylmethoxy)carbonyl (Fmoc) amino acid chlorides. Synthesis, characterization, and application to the rapid synthesis of short peptide segments" L. A. Carpino, B. J. Cohen, K. E. Stephens, Jr., S. Y. Sadat-Aalae, J. H. Tien, D. C. Langridge, *J. Org. Chem.* **1986**, *51*, 3732-3734.
- [533] "An efficient synthesis of optically active α -(t-butoxycarbonylamino)-aldehydes from α -amino acids" J. A. Fehrentz, B. Castro, *Synthesis* **1983**, 676-678.
- [534] "A Practical Approach to the Synthesis of 2,4-Disubstituted Oxazoles from Amino Acids" T. Morwick, M. Hrapchak, M. DeTuri, S. Campbell, *Org. Lett.* **2002**, *4*, 2665-2668.
- [535] "Paecilopeptin, a new cathepsin S inhibitor produced by *Paecilomyces carneus*" K. Shindo, H. Suzuki, T. Okuda, *Biosci., Biotechnol., Biochem.* **2002**, *66*, 2444-2448.
- [536] "Influence of acid surrogates toward potency of VLA-4 antagonist" S. Venkatraman, J. Lim,

- M. Cramer, M. F. Gardner, J. James, K. Alves, R. B. Lingham, R. A. Mumford, B. Munoz, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4053-4056.
- [537] "Evaluation of α,β -unsaturated ketone-based probes for papain-family cysteine proteases" Z. Yang, M. Fonovic, S. H. L. Verhelst, G. Blum, M. Bogyo, *Bioorg. Med. Chem.* **2009**, *17*, 1071-1078.
- [538] "Stereoselective synthesis of 4-(acetylamino)-2,4,6-trideoxy-L-ribo-hexose from ethyl (S)- β -hydroxybutyrate" G. Guanti, L. Banfi, E. Narisano, S. Thea, *Synlett* **1992**, 311-312.
- [539] "A Formal Total Synthesis of (\pm)-Cephalotaxine Using Sequential N-Acyliminium Ion Reactions" Y. Koseki, H. Sato, Y. Watanabe, T. Nagasaka, *Org. Lett.* **2002**, *4*, 885-888.
- [540] "N-Methoxy-N-methylamides as effective acylating agents" S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815-3818.
- [541] "Tosylhydrazide-Promoted Diastereoselective Intramolecular 1,3-Dipolar Cycloadditions: Synthesis of Tetrahydropyrrolo[3,4-c]pyrazoles" R. Barroso, M. Escribano, M.-P. Cabal, C. Valdes, *Eur. J. Org. Chem.* **2014**, *2014*, 1672-1683.
- [542] "A New Family of Small Molecules To Probe the Reactivation of Mutant p53" M. C. Myers, J. Wang, J. A. Iera, J.-k. Bang, T. Hara, S. i. Saito, G. P. Zambetti, D. H. Appella, *J. Am. Chem. Soc.* **2005**, *127*, 6152-6153.
- [543] "Asymmetric substitutions of 2-lithiated N-boc-piperidine and N-noc-azepine by dynamic resolution" I. Coldham, S. Raimbault, D. T. E. Whittaker, P. T. Chovatia, D. Leonori, J. J. Patel, N. S. Sheikh, *Chem. - Eur. J.* **2010**, *16*, 4082-4090, S4082/4081-S4082/4023.
- [544] "Discovery of a Novel Oral Glucocorticoid Receptor Modulator (AZD9567) with Improved Side Effect Profile" L. Ripa, K. Edman, M. Dearman, G. Edenro, R. Hendrickx, V. Ullah, H.-F. Chang, M. Lepistoe, D. Chapman, S. Geschwindner, L. Wissler, P. Svanberg, K. Lawitz, J. Malmberg, A. Nikitidis, R. I. Olsson, J. Bird, A. Llinas, T. Hegelund-Myrbaeck, M. Berger, P. Thorne, R. Harrison, C. Koehler, T. Drmota, *J. Med. Chem.* **2018**, *61*, 1785-1799.
- [545] "Acylation of ester enolates by N-methoxy-N-methylamides: an effective synthesis of β -keto esters" J. A. Turner, W. S. Jacks, *J. Org. Chem.* **1989**, *54*, 4229-4231.
- [546] "Meldrum's acid in organic synthesis. 2. A general and versatile synthesis of β -keto esters" Y. Oikawa, K. Sugano, O. Yonemitsu, *J. Org. Chem.* **1978**, *43*, 2087-2088.
- [547] "Stereospecific synthesis of N-protected statine and its analogs via chiral tetramic acid" P.

- Jouin, B. Castro, D. Nisato, *J. Chem. Soc., Perkin Trans. 1* **1987**, 1177-1182.
- [548] “A β -lactam approach to γ -amino- β -keto acid derivatives” C. Palomo, F. P. Cossio, G. Rubiales, D. Aparicio, *Tetrahedron Lett.* **1991**, 32, 3115-3118.
- [549] “Synthesis of chiral urethane N-alkoxycarbonyl tetramic acids from urethane N-carboxyanhydrides (UNCAs)” J. A. Fehrentz, E. Bourdel, J. C. Califano, O. Chaloin, C. Devin, P. Garrouste, A.-C. Lima-Leite, M. Llinares, F. Rieunier, a. et, *Tetrahedron Lett.* **1994**, 35, 1557-1560.
- [550] “Facile synthesis of N-protected γ - and δ -amino- β -keto-esters” B. Li, R. W. Franck, *Bioorg. Med. Chem. Lett.* **1999**, 9, 2629-2634.
- [551] “Investigation of the synthetic route to pepstatin analogues by SPPS using O-protected and O-unprotected statine as building blocks” C. D. Cadicamo, V. Asante, A. M. Abu, C. Borelli, H. C. Korting, B. Kokschi, *J. Pept. Sci.* **2009**, 15, 272-277.
- [552] “Stereoselective synthesis of chiral α -amino- β -lactams through palladium(II)-catalyzed sequential monoarylation/amidation of C(sp³) -H bonds” Q. Zhang, K. Chen, W. Rao, Y. Zhang, F.-J. Chen, B.-F. Shi, *Angew Chem Int Ed Engl* **2013**, 52, 13588-13592.
- [553] “Stereoselective formation of a functionalized dipeptide isostere by zinc carbenoid-mediated chain extension” W. Lin, C. R. Theberge, T. J. Henderson, C. K. Zercher, J. Jasinski, R. J. Butcher, *J. Org. Chem.* **2009**, 74, 645-651.
- [554] “Completely Stereocontrolled Aldol Reaction of Chiral β -Amino Acids” M. Gazvoda, K. Hoferl-Prantz, R. Barth, W. Felzmann, A. Pevec, J. Kosmrlj, *Org. Lett.* **2015**, 17, 512-515.
- [555] “Glycocluster synthesis by native chemical ligation” J. W. Wehner, T. K. Lindhorst, *Synthesis* **2010**, 3070-3082.
- [556] “Facile reduction of ethyl thiol esters to aldehydes: application to a total synthesis of (+)-neothramycin A methyl ether” T. Fukuyama, S. C. Lin, L. Li, *J. Am. Chem. Soc.* **1990**, 112, 7050-7051.
- [557] “Facile palladium-mediated conversion of ethanethiol esters to aldehydes and ketones” H. Tokuyama, S. Yokoshima, T. Yamashita, S.-C. Lin, L. Li, T. Fukuyama, *J. Braz. Chem. Soc.* **1998**, 9, 381-387.
- [558] “Reduction of ethanethiol esters to aldehydes” H. Tokuyama, S. Yokoshima, S.-C. Lin, L. Li, T. Fukuyama, *Synthesis* **2002**, 1121-1123.
- [559] “Palladium-mediated synthesis of aldehydes and ketones from thiol esters” T. Fukuyama, H.

- Tokuyama, *Aldrichimica Acta* **2004**, *37*, 87-96.
- [560] “New odorless protocols for the synthesis of aldehydes and ketones from thiol esters” T. Miyazaki, Y. Han-ya, H. Tokuyama, T. Fukuyama, *Synlett* **2004**, 477-480.
- [561] “Synthesis of a PNA-encoded cysteine protease inhibitor library” F. Debaene, L. Mejias, J. L. Harris, N. Winssinger, *Tetrahedron* **2004**, *60*, 8677-8690.
- [562] “Synthesis of triamino acid building blocks with different lipophilicities” J. Maity, D. Honcharenko, R. Stroemberg, *PLoS One* **2015**, *10*, e0124046/0124041-e0124046/0124014.
- [563] “New cross-aldol reactions. Reactions of silyl enol ethers with carbonyl compounds activated by titanium tetrachloride” T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503-7509.
- [564] “The directed aldol reaction” T. Mukaiyama, *Org. React. (N. Y.)* **1982**, *28*, 203-331.
- [565] “Mukaiyama reactions of a silyl enol ether with heteroatom-substituted β -formyl esters” H. Angert, R. Czerwonka, H. U. Reissig, *Liebigs Ann./Recl.* **1997**, 2215-2220.
- [566] “Mechanism of metal chloride-promoted Mukaiyama aldol reactions” C. T. Wong, M. W. Wong, *J. Org. Chem.* **2007**, *72*, 1425-1430.
- [567] “Investigations into transition-state geometry in the Mukaiyama directed aldol reaction” S. E. Denmark, W. Lee, *Chem. - Asian J.* **2008**, *3*, 327-341.
- [568] “Lewis Base Catalysis of the Mukaiyama Directed Aldol Reaction: 40 Years of Inspiration and Advances” G. L. Beutner, S. E. Denmark, *Angew. Chem., Int. Ed.* **2013**, *52*, 9086-9096.
- [569] “Asymmetric total synthesis of iedomycin B” S. Lin, J. Zhang, Z. Zhang, T. Xu, S. Huang, X. Wang, *Mar. Drugs* **2017**, *15*, 17/11-17/19.
- [570] “A concise synthesis of tubuphenylalanine and epi-tubuphenylalanine via a diastereoselective Mukaiyama aldol reaction of silyl ketene acetal” Y. Park, M. Sim, T.-S. Chang, J.-S. Ryu, *Org. Biomol. Chem.* **2016**, *14*, 913-919.
- [571] “Protecting-Group-Free and Catalysis-Based Total Synthesis of the Ecklonialactones” V. Hickmann, M. Alcarazo, A. Fuerstner, *J. Am. Chem. Soc.* **2010**, *132*, 11042-11044.
- [572] “An efficient synthesis of an exo-enone analogue of LL-Z1640-2 and evaluation of its protein kinase inhibitory activities” S. Q. Wang, S. S. Goh, C. L. L. Chai, A. Chen, *Org. Biomol. Chem.* **2016**, *14*, 639-645.
- [573] “A selective method for the direct conversion of aldehydes into β -keto esters with ethyl diazoacetate catalyzed by tin(II) chloride” C. R. Holmquist, E. J. Roskamp, *J. Org. Chem.*

- 1989**, 54, 3258-3260.
- [574] "Tin(II) chloride assisted synthesis of N-protected γ -amino β -keto esters through semipinacol rearrangement" A. Bandyopadhyay, N. Agrawal, S. M. Mali, S. V. Jadhav, H. N. Gopi, *Org. Biomol. Chem.* **2010**, 8, 4855-4860.
- [575] "A facile transformation of amino acids to functionalized coumarins" A. Bandyopadhyay, H. N. Gopi, *Org. Biomol. Chem.* **2011**, 9, 8089-8095.
- [576] "Exploring β -hydroxy γ -amino acids (statines) in the design of hybrid peptide foldamers" A. Bandyopadhyay, A. Malik, M. G. Kumar, H. N. Gopi, *Org. Lett.* **2014**, 16, 294-297.
- [577] "Synthesis of tetrasubstituted symmetrical pyrazines from β -keto γ -amino esters: A mild strategy for self-dimerization of peptides" M. Ganesh Kumar, V. J. Thombare, R. D. Bhaire, A. Adak, H. N. Gopi, *Eur. J. Org. Chem.* **2015**, 2015, 135-141.
- [578] "Helices with Additional H-bonds: Crystallographic Conformations of α,γ -Hybrid Peptides Helices Composed of β -Hydroxy γ -Amino acids (Statines)" A. Malik, M. Ganesh Kumar, A. Bandyopadhyay, H. N. Gopi, *Biopolymers* **2017**, 108, n/a.
- [579] "Enantioselective synthesis of α -alkyl- β -ketoesters: Asymmetric Roskamp reaction catalyzed by an oxazaborolidinium ion" L. Gao, B. C. Kang, G.-S. Hwang, D. H. Ryu, *Angew. Chem., Int. Ed.* **2012**, 51, 8322-8325, S8322/8321-S8322/8364.
- [580] "Enantioselective Synthesis of syn- α -Aryl- β -hydroxy Weinreb Amides: Catalytic Asymmetric Roskamp Reaction of α -Aryl Diazo Weinreb Amides" S. H. Shin, E. H. Baek, G.-S. Hwang, D. H. Ryu, *Org. Lett.* **2015**, 17, 4746-4749.
- [581] "Catalytic Asymmetric Roskamp Reaction of Silyl Diazoalkane: Synthesis of Enantioenriched α -Silyl Ketone" J. Y. Kim, B. C. Kang, D. H. Ryu, *Org. Lett.* **2017**, 19, 5936-5939.
- [582] "Glycinecarboxylic acid" H. Leuchs, *Ber. Dtsch. Chem. Ges.* **1906**, 39, 857-861.
- [583] "Isomerism of Carboethoxy Glycylglycine Esters" H. Leuchs, W. Manasse, *Ber. Dtsch. Chem. Ges.* **1907**, 40, 3235-3249.
- [584] "The Anhydrides of α -Amino-N-Carboxylic and α -Amino Acids" H. Leuchs, W. Geiger, *Ber. Dtsch. Chem. Ges.* **1908**, 41, 1721-1726.
- [585] "Isomerism of Carboethoxydiglycylglycine Ester and the Stability of N-Carboxylic Acids" H. Leuchs, F. B. LaForge, *Ber. Dtsch. Chem. Ges.* **1908**, 41, 2586-2596.
- [586] " α -Amino acid N-carboxy anhydrides and related heterocycles: syntheses, properties,

- peptide synthesis, polymerization”; H. R. Kricheldorf; Springer-Verlag, 1987.
- [587] “Urethane protected amino acid N-carboxyanhydrides and their use in peptide synthesis” W. D. Fuller, M. P. Cohen, M. Shabankareh, R. K. Blair, M. Goodman, F. R. Naider, *J. Am. Chem. Soc.* **1990**, *112*, 7414-7416.
- [588] “Reactivity of UNCAs with Grignard reagents” C. Pothion, J. A. Fehrentz, P. Chevallet, A. Loffet, J. Martinez, *Lett. Pept. Sci.* **1997**, *4*, 241-244.
- [589] “Polypeptides and 100 years of chemistry of α -amino acid N-carboxyanhydrides” H. R. Kricheldorf, *Angew. Chem., Int. Ed.* **2006**, *45*, 5752-5784.
- [590] “The use of N-urethane-protected N-carboxyanhydrides (UNCAs) in amino acid and peptide synthesis” J. A. Fehrentz, C. Genu-Dellac, M. Amblard, F. Winternitz, A. Loffet, J. Martinez, *J. Pept. Sci.* **1995**, *1*, 124-131.
- [591] “Synthesis of pyrrolidine-2,4-diones from urethane N-carboxyanhydrides (UNCAs)” C. Pothion, J.-A. Fehrentz, A. Aumelas, A. Loffet, J. Martinez, *Tetrahedron Lett.* **1996**, *37*, 1027-1030.
- [592] “Synthesis of chiral N-protected amino acid esters by the use of UNCAs” P. Chevallet, J. A. Fehrentz, K. Kiec-Kononowicz, C. Devin, J. Castel, A. Loffet, J. Martinez, *Lett. Pept. Sci.* **1996**, *2*, 297-300.
- [593] “Solvent-free synthesis of peptides” V. Declerck, P. Nun, J. Martinez, F. Lamaty, *Angew. Chem., Int. Ed.* **2009**, *48*, 9318-9321, S9318/9311-S9318/9331.
- [594] “Urethane-protected alpha-amino acid N-carboxyanhydrides and peptide synthesis” W. D. Fuller, M. Goodman, F. R. Naider, Y. F. Zhu, *Biopolymers* **1996**, *40*, 183-205.
- [595] “Kinetics of the formation of polypeptides from N-carboxy- α -amino-acid anhydrides” D. G. H. Ballard, C. H. Bamford, *Nature (London, U. K.)* **1953**, *172*, 907-908.
- [596] “New observations on the chemistry of N-carboxy- α -amino acid anhydrides” D. G. H. Ballard, C. H. Bamford, F. J. Weymouth, *Nature (London, U. K.)* **1954**, *174*, 173-175.
- [597] “Polymerization. VII. The polymerization of N-carboxy- α -amino acid anhydrides” D. G. H. Ballard, C. H. Bamford, *Proc. R. Soc. London, Ser. A* **1954**, *223*, 495-520.
- [598] “The initiation step in the polymerization of N-carboxy- α -amino acid anhydrides. I. Catalysis by tertiary bases” C. H. Bamford, H. Block, *J. Chem. Soc.* **1961**, 4989-4991.
- [599] “The polymerization of N-carboxy- α -amino acid anhydrides” C. H. Bamford, H. Block 1976; Elsevier: Vol. 15, p 583-637.

- [600] "Preparation of N-carboxy- α -amino acid anhydrides by the reaction of copper(II)-amino acid complexes with phosgene" R. D. Hamilton, D. J. Lyman, *J. Org. Chem.* **1969**, *34*, 243-244.
- [601] "A procedure for the facile synthesis of amino-acid N-carboxyanhydrides" W. D. Fuller, M. S. Verlander, M. Goodman, *Biopolymers* **1976**, *15*, 1869-1871.
- [602] "The use of triphosgene in preparation of N-carboxy α -amino acid anhydrides" R. Wilder, S. Mobashery, *J. Org. Chem.* **1992**, *57*, 2755-2756.
- [603] S. Nishida, H. Shio, K. Goto, "Preparation of amino acid N-carboxylic acid anhydrides" *JP11029560A*, **1999**; *Chem. Abstr.*
- [604] "Large-scale synthesis of α -amino acid-N-carboxyanhydrides" J. E. Semple, B. Sullivan, K. N. Sill, *Synth. Commun.* **2017**, *47*, 53-61.
- [605] S. Ishida, C. Oizumi, "Purification of N-carboxy- α -amino acid anhydrides" *JP43020181B*, **1968**; *Chem. Abstr.*
- [606] K. Yamaguchi, C. Oizumi, K. Yatsuno, J. Takeda, "Purification of α -amino acid N-carboxylic acid anhydrides" *JP47018109B*, **1972**; *Chem. Abstr.*
- [607] K. Togo, I. Maeda, O. Hiwatashi, H. Mitsutake, "Purification of α -amino acid-N-carboxylic acid anhydrides" *JP49024957A*, **1974**; *Chem. Abstr.*
- [608] " α -Amino-N-carboxylic acid anhydrides. II" F. Sigmund, F. Wessely, *Z. physiol. Chem.* **1926**, *157*, 91-105.
- [609] "The Mechanism of polymerization of N-carboxy- α -amino acid anhydrides" M. Sela, A. Berger, *J. Am. Chem. Soc.* **1953**, *75*, 6350-6351.
- [610] "Synthesis of biomimetic co-polypeptides with tunable degrees of phosphorylation" V. Lipik, L. Zhang, A. Miserez, *Polym. Chem.* **2014**, *5*, 1351-1361.
- [611] "Complex coacervates of oppositely charged co-polypeptides inspired by the sandcastle worm glue" L. Zhang, V. Lipik, A. Miserez, *J. Mater. Chem. B* **2016**, *4*, 1544-1556.
- [612] "Benefits of bovine colostrum in nutraceutical products" M. Ahmadi, A.-B. Velciov, M. Scurtu, T. Ahmadi, L. Olariu, *J. Agroaliment. Processes Technol.* **2011**, *17*, 42-45.
- [613] "Chapter 13 - Niacin" G. F. Combs, J. P. McClung Dans *The Vitamins (Fifth Edition)*; Academic Press: 2017, p 331-350.
- [614] "CHAPTER 6 - Auxins" L. M. Srivastava Dans *Plant Growth and Development*; Academic Press: San Diego, 2002, p 155-169.

- [615] "C-Alkylation with quaternary ammonium salts. A new approach to the synthesis of compounds containing the β -indolemethylene group" H. R. Snyder, C. W. Smith, J. M. Stewart, *J. Am. Chem. Soc.* **1944**, *66*, 200-204.
- [616] "Application of a new alkylation reaction to the synthesis of tryptophan" E. E. Howe, A. J. Zambito, H. R. Snyder, M. Tishler, *J. Am. Chem. Soc.* **1945**, *67*, 38-39.
- [617] "A Convenient Synthesis of dl-Tryptophan" H. R. Snyder, C. W. Smith, *J. Am. Chem. Soc.* **1944**, *66*, 350-351.
- [618] "A synthesis of tryptophan and tryptophan analogs" H. R. Snyder, J. A. MacDonald, *J. Am. Chem. Soc.* **1955**, *77*, 1257-1259.
- [619] "A new synthesis of tryptophan" N. F. Albertson, S. Archer, C. M. Suter, *J. Am. Chem. Soc.* **1944**, *66*, 500.
- [620] "The synthesis of tryptophan from gramine" N. F. Albertson, S. Archer, C. M. Suter, *J. Am. Chem. Soc.* **1945**, *67*, 36-37.
- [621] "Condensations of indoles with aldehydes and secondary amines. I. A new gramine synthesis" H. Kuhn, O. Stein, *Ber. Dtsch. Chem. Ges. B* **1937**, *70B*, 567-569.
- [622] "Benz[f]tryptophan, a bathochromic analog of tryptophan, synthesis of its N- α -Boc derivative" T. S. Yokum, P. K. Tungaturghi, M. L. McLaughlin, *Tetrahedron Lett.* **1997**, *38*, 5111-5114.
- [623] "Catalytic and asymmetric Friedel-Crafts alkylation of indoles with nitroacrylates. Application to the synthesis of tryptophan analogues" Y. Sui, L. Liu, J.-L. Zhao, D. Wang, Y.-J. Chen, *Tetrahedron* **2007**, *63*, 5173-5183.
- [624] "A convenient one-step synthesis of L-aminotryptophans and improved synthesis of 5-fluorotryptophan" M. Winn, A. D. Roy, S. Grueschow, R. S. Parameswaran, R. J. M. Goss, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4508-4510.
- [625] "Efficient asymmetric synthesis of important tryptophan analogs for biological research via the Schollkopf chiral auxiliary" C. Ma, S. Yu, X. He, X. Liu, J. M. Cook, *Tetrahedron Lett.* **2000**, *41*, 2781-2785.
- [626] "Efficient Asymmetric Synthesis of Tryptophan Analogues Having Useful Photophysical Properties" P. Talukder, S. Chen, P. M. Arce, S. M. Hecht, *Org. Lett.* **2014**, *16*, 556-559.
- [627] "An efficient one-pot reaction of indoles, nitroacetate, and paraformaldehyde for the synthesis of tryptophan derivatives" Y. Sui, L. Liu, J.-L. Zhao, D. Wang, Y.-J. Chen,

- Tetrahedron Lett.* **2007**, *48*, 3779-3782.
- [628] “Enantioselective Synthesis of Tryptophan Derivatives by a Tandem Friedel-Crafts Conjugate Addition/Asymmetric Protonation Reaction” M. E. Kieffer, L. M. Repka, S. E. Reisman, *J. Am. Chem. Soc.* **2012**, *134*, 5131-5137.
- [629] “A facile approach to tryptophan derivatives for the total synthesis of argyrin analogues” C.-H. Chen, S. Genapathy, P. M. Fischer, W. C. Chan, *Org. Biomol. Chem.* **2014**, *12*, 9764-9768.
- [630] “Fmoc-Trp(Boc)-OH: A new derivative for the synthesis of peptides containing tryptophan” P. White 1992; ESCOM, p 537-538.
- [631] C. E. Boville, D. K. Romney, P. J. Almhjell, M. M. Sieben, “Improved method for the synthesis of tryptophan analogs in aqueous solvents at reduced temperatures” *WO2019169334A1*, **2019**; *Chem. Abstr.*
- [632] “An improved synthesis of tryptophan” H. Hellmann, *Hoppe-Seyler's Z. Physiol. Chem.* **1949**, *284*, 163-167.
- [633] “One-pot enantioselective synthesis of tryptophan derivatives via phase-transfer catalytic alkylation of glycine using a cinchona-derived catalyst” R. Todd, M. Huisman, N. Uddin, S. Oehm, M. M. Hossain, *Synlett* **2012**, *23*, 2687-2691.
- [634] “Syntheses of substituted L- and D-tryptophans” K. Irie, A. Ishida, T. Nakamura, T. Oh-Ishi, *Chem. Pharm. Bull.* **1984**, *32*, 2126-2139.
- [635] “Synthesis of 5-fluoro-DL-tryptophan” H. Rinderknecht, C. Niemann, *J. Am. Chem. Soc.* **1950**, *72*, 2296-2297.
- [636] “Synthesis of 5-hydroxy-L-tryptophan utilizing N-acetyl-L-glutamic γ -semialdehyde, an intermediate in the metabolism of L-glutamic acid to L-ornithine” S. Iriuchijima, G. Tsuchihashi, *Agric. Biol. Chem.* **1978**, *42*, 843-845.
- [637] “Synthesis of alanine, phenylalanine, and tryptophan from their keto analogs in chicks” N. G. Grigor'ev, T. M. Truzhnikova, *Tr. Vses. Nauch.-Issled. Inst. Fiziol. Biokhim. Sel'skokhoz. Zhivotn.* **1971**, *10*, 63-72.
- [638] “Synthesis of L-tryptophan from L-glutamic acid” F. Masumi, H. Takeuchi, S. Kondo, K. Suzuki, S. Yamada, *Chem. Pharm. Bull.* **1982**, *30*, 3831-3833.
- [639] “Synthesis of tryptophan” C.-H. Liang, C.-M. Cheng, K. u.-H. Wang, P.-H. Li, T.-K. Wang, S.-L. Liu, H.-C. a. Liu, *Yao Hsueh Hsueh Pao* **1966**, *13*, 518-519.

- [640] "A synthesis of tryptophan" H. Plieninger, *Chem. Ber.* **1950**, 83, 268-271.
- [641] R. G. Jones, E. C. Kornfeld, "Synthesis of tryptophan and derivatives thereof" *US2621187*, **1952**; *Chem. Abstr.*
- [642] O. A. Moe, D. T. Warner, "Synthesis of tryptophan and related compounds" *US2516332*, **1950**; *Chem. Abstr.*
- [643] "Synthesis of tryptophan from chorismate: comparative aspects" I. P. Crawford, *Methods Enzymol.* **1987**, 142, 293-300.
- [644] "Synthesis of tryptophan from glutamic acid" Y. Komachiya, *Nippon Nogei Kagaku Kaishi* **1961**, 35, 845-848.
- [645] "Synthesis of tryptophan N-glucoside" M. Schnabel, B. Rompp, D. Ruckdeschel, C. Unverzagt, *Tetrahedron Lett.* **2004**, 45, 295-297.
- [646] "Practical catalytic enantioselective synthesis of α,α -dialkyl- α -amino acids by chiral phase-transfer catalysis" T. Ooi, M. Takeuchi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2000**, 122, 5228-5229.
- [647] "Efficient Asymmetric Synthesis of Biologically Important Tryptophan Analogues via a Palladium-Mediated Heteroannulation Reaction" C. Ma, X. Liu, X. Li, J. Flippen-Anderson, S. Yu, J. M. Cook, *J. Org. Chem.* **2001**, 66, 4525-4542.
- [648] "The synthesis of tryptophan derivatives, 2- and/or 3-substituted indoles, progress toward dilemmaones A-C, and synthetic studies towards fistulosin via palladium-catalyzed reductive N-heteroannulation" C. A. Dacko, **2009**.
- [649] P. Decottignies, R. Azerad, J. P. Vandecasteele, "Continuous enzymic synthesis of tryptophan" *FR2379603A1*, **1978**; *Chem. Abstr.*
- [650] S. Miyahara, M. Yanaka, T. Matsumoto, T. Miyahara, A. Sakaguchi, K. Nitta, "Enzymic process for preparing L-tryptophan and process for preparing a stable aqueous enzyme solution" *EP299715A2*, **1989**; *Chem. Abstr.*
- [651] "Enzyme synthesis of L-tryptophan" R. Zeman, J. Plachy, H. Bulantova, B. Sikyta, E. Pavlasova, E. Stejskalova, *Folia Microbiol. (Prague)* **1990**, 35, 200-204.
- [652] "TrpB2 enzymes are O-phospho-L-serine dependent tryptophan synthases" F. Busch, C. Rajendran, O. Mayans, P. Loeffler, R. Merkl, R. Sterner, *Biochemistry* **2014**, 53, 6078-6083.
- [653] "Unlocking Reactivity of TrpB: A General Biocatalytic Platform for Synthesis of Tryptophan Analogues" D. K. Romney, J. Murciano-Calles, J. E. Wehrmuller, F. H. Arnold,

- J. Am. Chem. Soc.* **2017**, *139*, 10769-10776.
- [654] "The synthesis of tryptophan by strains of typhoid bacilli to which it is essential" W. Burrows, *Rept. Proc. 3rd Intern. Congr. Microbiol.* **1940**, 492.
- [655] "Synthesis of tryptophan from indole and serine by *Neurospora*" E. L. Tatum, D. M. Bonner, *J. Biol. Chem.* **1943**, *151*, 349.
- [656] "The synthesis of niacin from tryptophan in rat-liver slices" W. W. Hurt, B. T. Scheer, H. J. Deuel, Jr., *Arch. Biochem.* **1949**, *21*, 87-94.
- [657] "Synthesis of tryptophan by isolated plantlets. Comparison with the synthetic power of *Sterigmatocystis nigra*" F. Charconnet-Harding, R. Jacquot, *Compt. rend.* **1949**, *228*, 498-500.
- [658] "Tryptophan synthesis from indolylpyruvic acid in plants" V. L. Kretovich, O. L. Polyanovskii, *Biokhimiya (Moscow)* **1959**, *24*, 995-1001.
- [659] "Biosynthesis of tryptophan in *Saccharomyces cerevisiae*" F. Lingen, W. Lueck, *Hoppe-Seyler's Z. Physiol. Chem.* **1963**, *333*, 190-198.
- [660] "Vitamin K and protein synthesis. I. Induced synthesis of tryptophan pyrrolase in rats deprived of vitamin K" A. M. Paolucci, S. Gaetani, B. C. Johnson, *Quaderni Nutr.* **1964**, *24*, 275-280.
- [661] "Aromatic biosynthesis in yeast. I. Synthesis of tryptophan and the regulation of this pathway" C. H. Doy, J. M. Cooper, *Biochim. Biophys. Acta, Gen. Subj.* **1966**, *127*, 302-316.
- [662] "Synthesis of tryptophan from 3-indolepyruvic acid by a healthy woman" P. Richards, C. L. Brown, S. M. Lowe, *J. Nutr.* **1972**, *102*, 1547-1549.
- [663] "Synthesis of tryptophan operon RNA in a cell-free system" D. McGeoch, J. McGeoch, D. Morse, *Nature (London), New Biol.* **1973**, *245*, 137-140.
- [664] "Synthesis of tryptophan from indoleacetic acid by mixed rumen bacteria and a mixture of rumen bacteria and protozoa" K. Okuuchi, Y. Tomita, R. Onodera, *Anim. Sci. Technol.* **1993**, *64*, 1182-1186.
- [665] "Alkylation of carbon with tertiary amines and quaternary ammonium salts. The condensation reactions of tertiary Mannich bases" H. Hellmann, *Angew. Chem.* **1953**, *65*, 473-485.
- [666] "Biosynthesis of violacein, structure and function of L-tryptophan oxidase VioA from *Chromobacterium violaceum*" J. J. Fuller, R. Ropke, J. Krausze, K. E. Rennhack, N. P.

- Daniel, W. Blankenfeldt, S. Schulz, D. Jahn, J. Moser, *J. Biol. Chem.* **2016**, *291*, 20068-20084.
- [667] "Amino acids. VIII. Specificity of mold acylase" I. Chibata, A. Watanabe, S. Yamada, *Bull. Agric. Chem. Soc. Jpn.* **1957**, *21*, 304-307.
- [668] "Preparation of 5-hydroxy-L- and D-tryptophan" A. J. Morris, M. D. Armstrong, *J. Org. Chem.* **1957**, *22*, 306-308.
- [669] "Resolution of optical isomers of 5-hydroxy-DL-tryptophan" H. Rinderknecht, *Helv. Chim. Acta* **1964**, *47*, 2403-2404.
- [670] Y. Mori, M. Sato, "5-Hydroxy-L- and 5-Hydroxy-DL-tryptophan" *DE2152088A*, **1972**; *Chem. Abstr.*
- [671] "Reversibility of the tryptophanase reaction. Synthesis of tryptophan from indole, pyruvate, and ammonia" T. Watanabe, E. E. Snell, *Proc. Nat. Acad. Sci. U. S. A.* **1972**, *69*, 1086-1090.
- [672] "Mimics of tryptophan synthetase and of biochemical dehydroalanine formation" W. Weiner, J. Winkler, S. C. Zimmerman, A. W. Czarnik, R. Breslow, *J. Am. Chem. Soc.* **1985**, *107*, 4093-4094.
- [673] B. Besnainou, G. Geniaut, A. Le Cocguen, P. Lessart, "Recovery of tryptophan or its derivatives and enzymic synthesis of tryptophan" *FR2581654A1*, **1986**; *Chem. Abstr.*
- [674] "Construction of optically pure tryptophans from serine derived aziridine-2-carboxylates" K. Sato, A. P. Kozikowski, *Tetrahedron Lett.* **1989**, *30*, 4073-4076.
- [675] "Synthesis of enantiomerically pure protected β -aryl alanines" R. F. W. Jackson, M. J. Wythes, A. Wood, *Tetrahedron Lett.* **1989**, *30*, 5941-5944.
- [676] "A new direct method for the synthesis of enantiomerically pure protected α -amino acids" R. F. W. Jackson, K. James, M. J. Wythes, A. Wood, *J. Chem. Soc., Chem. Commun.* **1989**, 644-645.
- [677] "Total Synthesis of Kapakahine E and F" V. R. Espejo, J. D. Rainier, *Org. Lett.* **2010**, *12*, 2154-2157.
- [678] "Total syntheses of kapakahines E and F" J. D. Rainier, V. R. Espejo, *Isr. J. Chem.* **2011**, *51*, 473-482.
- [679] "Synthesis and Biological Characterization of Argyrin F" L. Buelow, I. Nickeleit, A.-K. Girbig, T. Brodmann, A. Rentsch, U. Eggert, F. Sasse, H. Steinmetz, R. Frank, T. Carlomagno, N. P. Malek, M. Kalesse, *ChemMedChem* **2010**, *5*, 832-836.

- [680] "Optically Active Total Synthesis of Clavicipitic Acid" Y. Yokoyama, T. Matsumoto, Y. Murakami, *J. Org. Chem.* **1995**, *60*, 1486-1487.
- [681] "Synthetic studies on indole and related compounds. 42. Total synthesis of optically active chanoclavine-I" Y. Yokoyama, K. Kondo, M. Mitsuhashi, Y. Murakami, *Tetrahedron Lett.* **1996**, *37*, 9309-9312.
- [682] "Synthetic studies on indoles and related compounds. Part 46. First total syntheses of 4,8-dioxygenated β -carboline alkaloids" H. Suzuki, M. Unemoto, M. Hagiwara, T. Ohyama, Y. Yokoyama, Y. Murakami, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1717-1724.
- [683] "Synthetic studies of indoles and related compounds Part 48. Total synthesis of optically active costaclavine" K. Osanai, Y. Yokoyama, K. Kondo, Y. Murakami, *Chem. Pharm. Bull.* **1999**, *47*, 1587-1590.
- [684] "A study for palladium-catalyzed chemoselective vinylation at C-3 position of 4-bromo-1-tosylindole" Y. Yokoyama, K. Tsuruta, Y. Murakami, *Heterocycles* **2002**, *56*, 525-529.
- [685] "Syntheses without protection: a three-step synthesis of optically active clavicipitic acid by utilizing biomimetic synthesis of 4-bromotryptophan" Y. Yokoyama, H. Hikawa, M. Mitsuhashi, A. Uyama, Y. Murakami, *Tetrahedron Lett.* **1999**, *40*, 7803-7806.
- [686] "Total synthesis without protection: three-step synthesis of optically active clavicipitic acids by a biomimetic route" Y. Yokoyama, H. Hikawa, M. Mitsuhashi, A. Uyama, Y. Hiroki, Y. Murakami, *Eur. J. Org. Chem.* **2004**, 1244-1253.
- [687] "Enantioselective synthesis of nonproteinogenic amino acids" U. Schölkopf, *Top. Curr. Chem.* **1983**, *109*, 65-84.
- [688] "Concise synthesis of optically active ring-A substituted tryptophans" C. Ma, X. Liu, S. Yu, S. Zhao, J. M. Cook, *Tetrahedron Lett.* **1999**, *40*, 657-660.
- [689] "Catalytic Asymmetric Synthesis of the Central Tryptophan Residue of Celogentin C" S. L. Castle, G. S. C. Srikanth, *Org. Lett.* **2003**, *5*, 3611-3614.
- [690] "Synthesis of tryptophan derivatives via a palladium-catalyzed N-heteroannulation" C. A. Dacko, N. G. Akhmedov, B. C. G. Soederberg, *Tetrahedron: Asymmetry* **2008**, *19*, 2775-2783.
- [691] "Asymmetric synthesis of α -amino acids by the Strecker synthesis" K. Harada, *Nature (London, U. K.)* **1963**, *200*, 1201.

- [692] "Synthesis of tryptophans by alkylation of chiral glycine enolate equivalents with quaternary gramines" M. Reinfelds, K. Kalinins, D. Katkevica, R. Zemribo, M. Katkevics, *Tetrahedron Lett.* **2015**, *56*, 5882-5885.
- [693] "Ag-Catalyzed Diastereo- and Enantioselective Synthesis of β -Substituted Tryptophans from Sulfonylindoles" B.-H. Zheng, C.-H. Ding, X.-L. Hou, L.-X. Dai, *Org. Lett.* **2010**, *12*, 1688-1691.
- [694] "Asymmetric synthesis of α -amino-acid derivatives by alkylation of a chiral Schiff base" S. Yamada, T. Oguri, T. Shioiri, *J. Chem. Soc., Chem. Commun.* **1976**, 136-137.
- [695] S. Yamada, T. Shioiri, T. Oguri, "Optically active α -alkyl- α -amino acid derivatives" JP51110502A, **1976**; *Chem. Abstr.*
- [696] "2-Hydroxy-3-pinanone as chiral auxiliary in the asymmetric synthesis of α -amino acids" A. El Achqar, M. Boumzebra, M. L. Roumestant, P. Viallefont, *Tetrahedron* **1988**, *44*, 5319-5332.
- [697] "Synthesis of enantiomerically pure aminophosphonic acids" R. Jacquier, F. Ouazzani, M. L. Roumestant, P. Viallefont, *Phosphorus Sulfur* **1988**, *36*, 73-77.
- [698] "Alkylation and protonation of chiral Schiff bases: diastereoselectivity as a function of the nature of reactants" M. Tabcheh, A. El Achqar, L. Pappalardo, M. L. Roumestant, P. Viallefont, *Tetrahedron* **1991**, *47*, 4611-4618.
- [699] "Computational studies of effective asymmetric alkylation utilizing a chiral Schiff base derived from 2-hydroxy-3-pinanone. Part 1" T. Matsumoto, T. Shiori, E. Osawa, *Tetrahedron* **1996**, *52*, 5961-5970.
- [700] "Computational studies of effective asymmetric alkylation utilizing a chiral Schiff base derived from 2-hydroxy-3-pinanone. Part 2" T. Matsumoto, T. Shiori, E. Osawa, *Tetrahedron* **1996**, *52*, 5971-5982.
- [701] "Axially chiral bis(α -amino acid)s and dioxopiperazines. Synthesis and configurational assignment" L. Ridvan, M. Budesinsky, M. Tichy, P. Malon, J. Zavada, J. Podlaha, I. Cisarova, *Tetrahedron* **1999**, *55*, 12331-12348.
- [702] "A novel enantioselective synthesis of (S)-(-)- and (R)-(+)-nornicotine via alkylation of a chiral 2-hydroxy-3-pinanone ketimine template" J. H. Swango, B. S. Bhatti, M. M. Qureshi, P. A. Crooks, *Chirality* **1999**, *11*, 316-318.
- [703] "Efficient total synthesis of pentosidine, an advanced glycation endproduct" H. Sugiyama, F.

- Yokokawa, T. Shioiri, N. Katagiri, O. Oda, H. Ogawa, *Tetrahedron Lett.* **1999**, *40*, 2569-2572.
- [704] “Stereoselective synthesis of γ -fluorinated α -amino acids using 2-hydroxy-3-pinanone as an auxiliary” K. W. Laue, S. Kroger, E. Wegelius, G. Haufe, *Eur. J. Org. Chem.* **2000**, 3737-3743.
- [705] “An expeditious synthesis of pentosidine, an advanced glycation end product” F. Yokokawa, H. Sugiyama, T. Shioiri, N. Katagiri, O. Oda, H. Ogawa, *Tetrahedron* **2001**, *57*, 4759-4766.
- [706] “New approaches to stereoselective synthesis of fluorinated amino acids” K. Uneyama, T. Katagiri, H. Amii, *Yuki Gosei Kagaku Kyokaiishi* **2002**, *60*, 1069-1075.
- [707] “Diastereoselective alkylation of Schiff bases for the synthesis of lipidic unnatural Fmoc-protected α -amino acids” A. M. Papini, E. Nardi, F. Nuti, J. Uziel, M. Ginanneschi, M. Chelli, A. Brandi, *Eur. J. Org. Chem.* **2002**, 2736-2741.
- [708] “Enantioselective synthesis of new 4-substituted glutamic acid derivatives” J. Wehbe, V. Rolland, A. Fruchier, M.-L. Roumestant, J. Martinez, *Tetrahedron: Asymmetry* **2004**, *15*, 851-858.
- [709] “A general, efficient and stereospecific route to sphingosine, sphingamines, phytosphingosines and their analogs” Y. Cai, C.-C. Ling, D. R. Bundle, *Org. Biomol. Chem.* **2006**, *4*, 1140-1146.
- [710] “Towards development of new reagents for organic syntheses” T. Shioiri, *Farumashia* **2006**, *42*, 411-414.
- [711] L. Guilloneau, S. Dufour, O. Guerret, “Preparation of novel beta-hydroxy amino acid derivatives via enantioselective aldolization using (1R,2R,5R)-(+)-2-hydroxy-3-pinanone as a chiral auxiliary and their use as synthesis intermediates for obtaining derivatives of sphingosines, ceramides and sphingomyelins with high yields” *WO2014108564A1*, **2014**; *Chem. Abstr.*
- [712] “Synthesis and physical chemical properties of 2-amino-4-(trifluoromethoxy)butanoic acid - a CF₃O-containing analog of natural lipophilic amino acids” I. S. Kondratov, I. G. Logvinenko, N. A. Tolmachova, R. N. Morev, M. A. Kliachyna, F. Clausen, C. G. Daniliuc, G. Haufe, *Org. Biomol. Chem.* **2017**, *15*, 672-679.
- [713] “Diastereoselective monoalkylation of lithium and potassium enolates of a chiral imine of ethyl glycinate: the role of added salts” A. Solladié-Cavallo, M.-C. Simon-Wermeister, J.

- Schwarz, *Organometallics* **1993**, *12*, 3743-3747.
- [714] “Hydroxypinanone: solute/solute interactions and non-linear chiroptical properties” A. Solladie-Cavallo, R. Andriamiadanarivo, *Tetrahedron Lett.* **1997**, *38*, 5851-5852.
- [715] “Enantioselective synthesis of optically pure natural S-(+) or unnatural R-(-)-DABA” A. Solladie-Cavallo, M. C. Simon, *Tetrahedron Lett.* **1989**, *30*, 6011-6014.
- [716] “Structure and reactivity of lithium enolates from pinacolone for the selective C-alkylation of peptides. Difficulties and possibilities through complex structures” D. Seebach, *Angew. Chem.* **1988**, *100*, 1685-1715.
- [717] “Influences of halogen atoms on indole-3-acetonitrile (IAN): Crystal structure and Hirshfeld surfaces analysis” Y.-H. Luo, L.-J. Yang, G. Han, Q.-L. Liu, W. Wang, Y. Ling, B.-W. Sun, *J. Mol. Struct.* **2014**, *1076*, 679-686.
- [718] “Stereoselective synthesis of unsaturated α -amino acids” R. Fanelli, L. Jeanne-Julien, A. Rene, J. Martinez, F. Cavelier, *Amino Acids* **2015**, *47*, 1107-1115.
- [719] “Access to α,α -Disubstituted Disilylated Amino Acids and Their Use in Solid-Phase Peptide Synthesis” R. Fanelli, K. Ben Haj Salah, N. Inguibert, C. Didierjean, J. Martinez, F. Cavelier, *Org. Lett.* **2015**, *17*, 4498-4501.
- [720] “Total synthesis of myxovirescin A1” A. Fürstner, M. Bonnekessel, J. T. Blank, K. Radkowski, G. Seidel, F. Lacombe, B. Gabor, R. Mynott, *Chem. - Eur. J.* **2007**, *13*, 8762-8783.
- [721] “A new synthesis of (+)-negamycin and its derivatives as a potential therapeutic agent for duchenne muscular dystrophy treatment” Y. Hayashi, S. Nishiguchi, M. O. Sydnés, T. Regnier, J.-y. Hasegawa, T. Katoh, T. Kajimoto, M. Node, Y. Kiso, *Adv. Exp. Med. Biol.* **2009**, *611*, 137-138.
- [722] “Revisiting nucleophilic substitution reactions: microwave-assisted synthesis of azides, thiocyanates, and sulfones in an aqueous medium” Y. Ju, D. Kumar, R. S. Varma, *J. Org. Chem.* **2006**, *71*, 6697-6700.
- [723] “Fast and efficient synthesis of the complete LL-Z1640-2 framework” N. Henry, M. N. Robertson, R. Marquez, *Tetrahedron Lett.* **2007**, *48*, 6088-6091.
- [724] “Oxygenated Stereotriads with Definite Absolute Configuration by Lipase-Mediated Kinetic Resolution: De Novo Synthesis of Imino Sugars and 6-Deoxy-C-glycosides” D. Acetti, E. Brenna, F. G. Gatti, *Eur. J. Org. Chem.* **2010**, 4468-4475.

- [725] “Modular Total Syntheses of the Marine-Derived Resorcylic Acid Lactones Cochliomycins A and B Using a Late-Stage Nozaki-Hiyama-Kishi Macrocyclization Reaction” B. Bolte, J. A. Basutto, C. S. Bryan, M. J. Garson, M. G. Banwell, J. S. Ward, *J. Org. Chem.* **2015**, *80*, 460-470.
- [726] “Studies Towards a Fast and Efficient Total Synthesis of LL-Z1640-2” M. N. Robertson, PhD thesis, University of Glasgow, **2009**.
- [727] “Catalysis-Based and Protecting-Group-Free Total Syntheses of the Marine Oxylipins Hybridalactone and the Ecklonialactones A, B, and C” V. Hickmann, A. Kondoh, B. Gabor, M. Alcarazo, A. Furstner, *J. Am. Chem. Soc.* **2011**, *133*, 13471-13480.
- [728] “Practical Asymmetric Synthesis of α -Branched 2-Piperazinylbenzylamines by 1,2-Additions of Organometallic Reagents to N-tert-Butanesulfinyl Imines” W. Jiang, C. Chen, D. Marinkovic, J. A. Tran, C. W. Chen, L. M. Arellano, N. S. White, F. C. Tucci, *J. Org. Chem.* **2005**, *70*, 8924-8931.
- [729] “Intramolecular Tandem Isomerization-Mannich Reaction as a New Route Towards Aminocyclopentitols” H. T. Cao, T. Roisnel, R. Gree, *Eur. J. Org. Chem.* **2011**, *2011*, 6405-6408, S6405/6401-S6405/6408.
- [730] “The fate of the tert-butylsulfinyl auxiliary after acid-promoted cleavage-a method for recycling t-BuSONH₂” V. K. Aggarwal, N. Barbero, E. M. McGarrigle, G. Mickle, R. Navas, J. R. Suarez, M. G. Unthank, M. Yar, *Tetrahedron Lett.* **2009**, *50*, 3482-3484.

EXPERIMENTAL PART

General Conditions

All reagents and solvents were of commercial grade and were used without further purification, with the exception of CH_2Cl_2 which was dried over activated alumina, THF which was distilled from sodium/benzophenone, DIEA and DIPA which were distilled on CaH_2 and PPTS which was recrystallized in acetone. LDA was prepared and freshly used.

All reactions requiring anhydrous conditions were performed under argon in oven drying glassware. Organic extraction was dried over MgSO_4 or NaSO_4 before evaporation under reduced pressure.

Flash chromatography was performed on columns of silica gel (40-63 μm) or Aluminium oxide (neutral activated, 50-200 mesh). Analytical thin-layer chromatography (TLC) was carried out on commercial 0.25 mm silica gel plates which were visualized by UV fluorescence at 254 nm then revealed using a phosphomolybdic acid solution (10% in EtOH), ninhydrin solution (0.3% in *n*-BuOH), acidic *p*-anisaldehyde solution (5% in EtOH) or KMnO_4 solution (7.5% in water). Retention factors (R_f) are given for such TLC analyses.

Melting points were measured in open capillary tubes on a Büchi B-560 apparatus and are uncorrected.

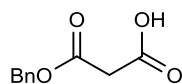
Routine nuclear magnetic resonance (NMR) data were recorded on Bruker spectrometers operating at Bruker AV 400/360/300 MHz for ^1H NMR, at 100/90/75 MHz for ^{13}C NMR. For ^1H NMR spectra, chemical shifts (δ) are reported in parts per million (ppm) with reference to tetramethylsilane ($\delta = 0.00$ ppm) or residual protonated solvents ($\delta_{\text{H}} = 7.26$ ppm for CHCl_3 , $\delta_{\text{H}} = 2.50$ ppm for $\text{DMSO}-d_6$, $\delta_{\text{H}} = 3.31$ ppm for $\text{MeOD}-d_3$, $\delta_{\text{H}} = 4.79$ ppm for D_2O) as internal standards. Splitting patterns for ^1H signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), brs (broad single) and coupling constants (J) are reported in Hz. For ^{13}C NMR spectra, chemical shifts (δ) are reported in parts per million (ppm) with reference to the deuterated solvents ($\delta_{\text{C}} = 77.16$ ppm for CDCl_3 , $\delta_{\text{C}} = 39.52$ ppm for $\text{DMSO}-d_6$, $\delta_{\text{C}} = 49.0$ ppm for $\text{MeOD}-d_3$) as an internal standard.

Fourier-transform infrared (IR) spectra were recorded for neat liquid or solid samples on a FT-IR Perkin Elmer Spectrum using an ATR diamond accessory; maximum absorbances (ν) are given in cm^{-1} .

High-resolution mass spectrometry (HRMS) data were recorded using a Bruker MicroTOF-Q spectrometer equipped with an electrospray ionization mass spectrometry (ESI-MS) in positive mode or negative mode (ESI (+) or ESI (-)).

Optical rotation was measured using a 10 cm quartz cell; values for $[\alpha]_D^T$ were obtained with the D-line of sodium at the indicated temperature T, using solutions of concentration (c) in units of $\text{g}\cdot 100\text{ mL}^{-1}$.

High performance liquid chromatography (HPLC) analysis was performed on a commercial Agilent 1260 Infinity apparatus equipped with diode array detector. All solvents were HPLC grade and were filtered through a $0.45\ \mu\text{m}$ PTFE membrane. Injected solutions were filtered through a $0.22\ \mu\text{m}$ PTFE membrane.

3-(Benzyloxy)-3-oxopropanoic acid 173⁴⁷²

C₁₀H₁₀O₄
 Exact M = 194.0579
 M = 194.19 g·mol⁻¹

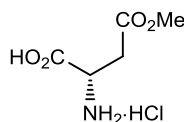
To a flask containing **Meldrum's acid** (20.0 g, 138.8 mmol) was added benzyl alcohol (15.0 g, 14.4 mL, 138.8 mmol). The mixture was refluxed for 6 h (oil bath, 120 °C), then cooling down. After concentrated to remove acetone, monobenzylmalonate **173** (26.2 g, 98%) was obtained as a light colorless oil (stored in fridge into a waxy solid) and used without further purification.

TLC: $R_f = 0.10$ (EtOAc = 100%)

IR (ATR) ν 2989, 1701, 1497, 1456, 1432, 1401, 1381, 1333, 1307, 1200, 1166, 1082 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 3.45 (s, 2H), 5.17 (s, 2H), 7.33-7.35 (m, 5H).

¹³C NMR (90 MHz, CDCl₃) δ 40.99, 67.58, 128.38, 128.56, 128.64, 135.0, 166.5, 172.0.

(S)-2-Amino-4-methoxy-4-oxobutanoic acid hydrochloride 175

C₅H₁₀ClNO₄
 Exact M. = 183.0298
 M = 183.59 g·mol⁻¹

Following Reddy's Procedure⁴⁷⁴

To an ice cold solution of L-aspartic acid (5.0 g, 37.50 mmol, 1 eq.) in MeOH (25 mL) was added dropwise thionyl chloride (SOCl₂, 3.87 mL, 53.30 mmol, 1.4 eq.) over 5 min. The ice bath was then removed and the resulting solution was warmed to room temperature stirred for 25 min at room temperature, and poured into an ice cold ether (25 mL). Upon cooling in ice bath and shaking, a white solid was precipitated. The white solid was filtered immediately, and the filtered solid was washed with ice cold diethyl ether (10 mL), collected and dried to give the desired L-Asp(β -OMe)-hydrochloride **175** (5.352 g, 78%) as a white solid.

Mp. 190-191 °C

$[\alpha]_D^{23}$ = +4.8 (*c* 0.50, D₂O)

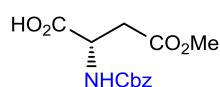
IR (ATR) ν 3435, 3125, 2821, 1731, 1567, 1498, 1446, 1418, 1386, 1286, 1228, 1200, 1181, 1101, 998, 851 cm^{-1}

^1H NMR (360 MHz, D_2O) δ 2.87 (dd, 1H, $J = 6.1, 1.8$ Hz, *ABX*), 3.71 (s, 3H), 4.34 (ddd pseudo td, 1H, $J = 6.1, 1.8$ Hz, *ABX*).

^{13}C NMR (90 MHz, D_2O) δ 33.7, 49.2, 52.8, 170.8, 171.8.

HRMS (ESI+) Calcd for $\text{C}_5\text{H}_{10}\text{NO}_4$ $[\text{M} + \text{H}]^+$: 148.0605, found 148.0604.

(*S*)-2-(((Benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutanoic acid **176²**



$\text{C}_{13}\text{H}_{15}\text{NO}_6$
Exact M = 281.0899
M = 281.26 $\text{g}\cdot\text{mol}^{-1}$

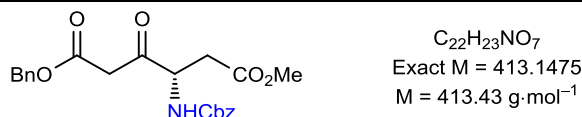
Following Reddy's procedure⁴⁷⁴

To an ice cold solution of L-Asp(β -OMe)-hydrochloride **175** (5.33 g, 36.26 mmol, 1 eq.) in water (60 mL) and dioxane (30 mL) were added Na_2CO_3 (3.48 g, 36.26 mmol, 1 eq.) at 0 °C, then followed by a solution of benzyl chloroformate (CbzCl, 6.25 g, 36.62 mmol, 1.01 eq.) in dioxane (30 mL) dropwise over 30 min. The resulting mixture was slowly warmed to room temperature and stirred for overnight (16 h). The solution was extracted with ethyl acetate (25 mL \times 3). The aqueous layer was then acidified to pH = 2-3 with 4 M HCl, as white solid precipitated was extracted with ethyl acetate (25 mL \times 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give a pale-yellow semid-solid. Short flash chromatography on silica gel (EtOAc = 100%) gave the desired L-(*S*)-Cbz-Asp(β -OMe)-H **176** (5.512 g, 68%) as a white waxy solid.

TLC: $R_f = 0.11$ (EtOAc = 100%)

^1H NMR (360 MHz, CDCl_3) δ 2.87 (dd, 1H, $J = 17.3, 4.7$ Hz, *ABX*), 3.05 (dd, 1H, $J_1 = 17.3, 4.7$ Hz, *ABX*), 3.66 (s, 3H), 4.66-4.70 (m, 1H, *ABX*), 5.11 (s, 2H), 5.96 (d, 1H, $J = 8.8$ Hz), 7.29-7.33 (m, 5H), 9.69 (s, 1H).

^{13}C NMR (90 MHz, CDCl_3) δ 36.3, 50.2, 52.3, 67.4, 128.2, 128.3, 128.6, 136.0, 156.3, 171.6, 175.1.

1-Benzyl 6-methyl (S) 4-(((benzyloxy)carbonyl)amino)-3-oxohexanedioate 177


To a solution of L-(S)-Cbz-Asp(β-OMe)-H **176** (2.8126 g, 10.0 mmol, 1 eq.) in anhydrous THF (20 mL) at room temperature under argon were added CDI (1.7836 g, 11.0 mmol, 1.1 eq.). Stirring for 3 h at room temperature provided *solution A*

Preparation of magnesium salt **174**: In a separated flask, to an ice cold solution of monobenzyl malonate **173** (2.3292 g, 12.0 mmol, 1.2 eq.) in anhydrous THF (24 mL) under argon was dropwise added isopropylmagnesium chloride (2.0 M in THF, 6.0 mL, 12.0 mmol, 1.2 eq.). After stirred for 30 min at 0 °C, then heating at 50 °C for 30 min, giving *solution B*.

To an ice cold *solution B* was then slowly added *solution A* over 30 min. The resulting mixture was stirred for overnight (16-18 h) and slowly warmed to room temperature. The reaction was quenched with 1 M HCl (10 mL) at 0 °C and extracted with Et₂O (25 mL × 3). The combined organic layer was washed with 1 M HCl (25 mL × 3), sat. NaHCO₃ (25 mL × 3) and brine (25 mL × 3), then dried over MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 75/25, 70/30) gave a L-(S)-N-Cbz-β-ketoester **177** (3.3864 g, 82%, *ee* undetermined) as a colorless oil, which was stored in the fridge into a white solid).

TLC: $R_f = 0.45$ (petroleum ether/EtOAc = 75/25)

Mp. 52-54 °C

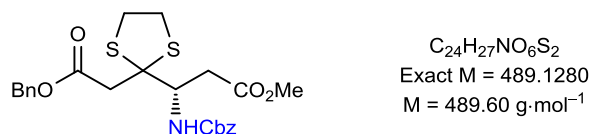
IR (ATR) ν 3292, 2951, 1743, 1720, 1688, 1538, 1443, 1367, 1339, 1252, 1211, 1066, 973, 746, 694 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 2.78 (dd, 1H, $J = 17.3, 5.0$ Hz, ABX), 2.99 (dd, 1H, $J = 17.3, 4.7$ Hz, ABX), 3.63 (s, 3H), 3.67 (s, 2H), 4.64 (ddd, 1H, $J = 9.0, 5.0, 4.7$ Hz, ABX), 5.11-5.16 (m, 4H), 5.97 (d, 1H, $J = 9.0$ Hz), 7.28-7.39 (m, 10H).

¹³C NMR (90 MHz, CDCl₃) δ 35.2, 46.0, 52.2, 56.5, 67.3, 67.5, 128.2, 128.4 (4C), 128.5, 128.6 (4C), 135.3, 136.0, 156.0, 166.8, 171.8, 200.9.

HRMS (ESI+) Calcd for C₂₂H₂₃NNaO₇ [M + Na]⁺: 436.1355, found 436.1366.

Methyl

(S)-3-(2-(2-(benzyloxy)-2-oxoethyl)-1,3-dithiolan-2-yl)-3-(((benzyloxy)carbonyl)amino)propanoate **178**

To a solution of *N*-Cbz- β -ketoester **177** (83.0 mg, 0.20 mmol, 1 eq.) in AcOH (2 mL) were added 1,2-ethanedithiol (56.5 mg, 2.26 mL, 0.60 mmol, 3 eq.) at room temperature under argon, followed by addition of $BF_3 \cdot Et_2O$ (141.9 mg, 1.00 mmol, 36 μ L \times 5, 5 eq.) during 5 days in 5 portions, and the resulting mixture was stirred for 7 days at room temperature. The reaction was diluted with EtOAc (20 mL) and washed with water (10 mL \times 3), sat. $NaHCO_3$ (10 mL \times 3) and brine (10 mL \times 3), respectively. The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 80/20, 70/30) gave a *N*-CBz-dithioketal **178** (33.0 mg, 34%) as a white solid.

TLC: R_f = 0.45 (petroleum ether//EtOAc = 70/30)

¹H NMR (360 MHz, $CDCl_3$) δ 2.63 (dd, 1H, J = 21.2, 14.0 Hz, *ABX*), 3.05-3.15 (m, 2H), 3.24-3.31 (m, 5H), 3.61 (s, 2H), 4.85-4.92 (m, 1H), 4.84-4.91 (m, 1H, *ABX*), 5.03-5.09 (m, 2H), 5.17 (s, 2H), 5.35 (d, 1H, J = 14.0 Hz), 7.26-7.38 (m, 10H).

¹³C NMR (90 MHz, $CDCl_3$) δ 37.6, 39.8, 40.7, 46.9, 52.1, 55.7, 66.9, 67.1, 71.3, 128.2 (2C), 128.3 (2C), 128.5, 128.6 (4C), 128.7, 135.7, 136.5, 156.0, 169.9, 171.5.

HRMS (ESI+) Calcd for $C_{24}H_{27}NNaO_6S_2$ [$M + Na$]⁺: 512.1172, found 512.1191.

(S)-2-(((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-4-methoxy-4-oxobutanoic acid (S)-179**⁴⁸¹**

To an ice cold solution of L-Asp(β -OMe)-hydrochloride **175** (9.60 g, 52.29 mmol, 1 eq.) in water (250 mL) and dioxane (50 mL) were added Na_2CO_3 (11.56 g, 83.68 mmol, 1.6 eq.) at 0 °C, then

followed by a solution of FmocCl (14.88 g, 57.53 mmol, 1.01 eq.) in dioxane (200 mL) dropwise over 30 min. The resulting mixture was slowly warmed to room temperature and stirred for overnight (16 h). The solution was evaporated under reduced pressure to remove most of dioxane, then extracted with ether (25 mL \times 3) to give the aqueous phase, which was then acidified with 4 M HCl until pH = 2-3. The acidified solution was then extracted with ether (80 mL \times 3), and the combined organic layer was washed with brine (50 mL \times 3), dried over MgSO₄ and concentrated under reduced pressure to give the pure desired L-N-Fmoc Asp(β -OMe)-H (S)-**179** (17.56 g, 91%) as a white solid and used without further purification.

TLC: R_f = 0.28 (CH₂Cl₂/MeOH = 85/15)

Mp. 124-125 °C (lit.⁴⁸¹ 122-125 °C)

$[\alpha]_D^{26}$ = +34.3 (*c* 1.05, CHCl₃), (lit.⁴⁸¹ $[\alpha]_D^{23}$ = +14.6 (*c* 1.05, CHCl₃))

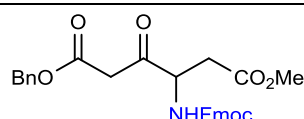
IR (ATR) ν 3377, 3352, 3063, 2974, 1762, 1738, 1673, 1531, 1442, 1376, 1357, 1323, 1282, 1253, 1236, 11207, 1189, 1167, 1087, 1041, 991, 836, 737, 541 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 2.61-2.66 (m, rotamer, ABX) and 2.92 (dd, 1H, J = 17.3, 4.3 Hz, ABX), 2.76-2.80 (m, rotamer, ABX) and 3.10 (dd, 1H, J = 17.3, 4.3 Hz, ABX), 3.71 (s, 3H), 4.23 (t, 1H, J = 6.8 Hz), 4.36-4.48 (m, 2H), 4.54 (pseudo m, rotamer, ABX) and 4.72-4.76 (ddd, 1H, J = 17.3, 8.6, 4.3 Hz, ABX), 6.01 (d, 1H, J = 8.6 Hz) and 6.38 (brs, rotamer), 7.30-7.34 (m, 2H), 7.38-7.42 (m, 2H), 7.60-7.62 (m, 2H), 7.75-7.77 (m, 2H), 10.11 (s, 1H).

¹³C NMR (90 MHz, CDCl₃) δ 36.3, 47.1, 50.3, 52.3, 67.5, 120.0, 125.5, 127.1, 127.8, 141.3, 143.7, 143.8, 156.3, 171.7, 175.3.

HRMS (ESI+) Calcd for C₂₀H₁₉NNaO₆ [M + Na]⁺: 392.1105, found 392.1107.

6-Benzyl 1-methyl 3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-oxohexanedioate **180**



C₂₉H₂₇NO₇
Exact M = 501.1788
M = 501.54 g·mol⁻¹

To a solution of L-N-Fmoc-Asp(β -OMe)-H (S)-**179** (3.10 g, 8.39 mmol, 1 eq.) in anhydrous THF (25 mL) at room temperature under argon was added CDI (1.50 g, 9.24 mmol, 1.1 eq.). The mixture

was stirred for 3 h as *solution A*.

Preparation of magnesium salt **174**: In a separated flask, to an ice cold solution of monobenzyl malonate of monobenzyl malonate (2.45 g, 12.59 mmol 1.5 eq.) in anhydrous THF (24 mL) under argon was dropwise added a solution of 2.0 M isopropylmagnesium chloride in THF (7.8 mL, 12.59 mmol, 1.5 eq). After stirred for 30 min at 0 °C, then heating at 50 °C for 30 min as *solution B*.

To the ice cold *solution B* was slowly added *solution A* over 30 min. The resulting mixture was stirred for overnight (16-18 h) and slowly warmed to room temperature. The reaction was quenched with 1 M HCl (10 mL) at 0 °C and extracted with Et₂O (25 mL × 3). The combined organic layer was washed with 1 M HCl (25 mL × 3), sat. NaHCO₃ (25 mL × 3) and brine (25 mL), then dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 75/25, 70/30) to give a partially racemic *N*-Fmoc-β-ketoester **180** (3.46 g, 82%, extensive racemization 0-28% *ee*) as a colorless oil, which was stored in the fridge into a waxy solid.

TLC: $R_f = 0.43$ (petroleum ether/EtOAc = 70/30)

Mp. 52-55 °C

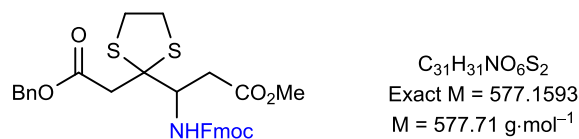
IR (ATR) ν 3354, 3035, 2952, 1716, 1501, 1450, 1405, 1368, 1317, 1216, 1177, 1104, 1047, 992, 757, 738, 697 cm^{-1}

¹H NMR (360 MHz, CDCl₃) δ 2.79 (dd, 1H, $J = 17.3, 4.3$ Hz, *ABX*), 3.00 (dd, 1H, $J = 17.3, 5.0$ Hz, *ABX*), 3.60 (s, 2H), 3.68 (s, 3H), 4.20 (t, 1H, $J = 6.5$ Hz), 4.44 (dd, 1H, $J = 10.6, 6.5$ Hz), 4.54 (dd, 1H, $J = 10.6, 6.5$ Hz), 4.63 (ddd, 1H, $J = 9.0, 5.0, 4.7$ Hz, *ABX*), 5.13-5.21 (m, 2H), 5.93 (d, 1H, $J = 9.0$ Hz), 7.29-7.43 (m, 9H), 7.59 (d, 2H, $J = 7.6$ Hz), 7.76 (dd, 2H $J = 7.6, 3.2$ Hz).

¹³C NMR (90 MHz, CDCl₃) δ 35.1, 45.9, 47.3, 52.2, 56.6, 67.1, 67.3, 120.1 (2C), 125.0, 125.1, 127.2 (2C), 127.9 (2C), 128.5 (2C), 128.7 (2C), 135.3, 141.4 (2C), 143.6, 143.7, 156.0, 166.8, 171.8, 200.8.

HRMS (ESI+) Calcd for C₂₉H₂₇NNaO₇ [M + Na]⁺: 524.1680, found 524.1678.

Methyl

3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-(2-(benzyloxy)-2-oxoethyl)-1,3-dithiolan-2-yl)propanoate **181**

To a solution of *N*-Fmoc- β -ketoester **180** (4.50 g, 8.97 mmol, 1 eq.) in AcOH (50 mL) was added 1,2-ethanedithiol (2.54 g, 2.26 mL, 9.24 mmol, 3 eq.) at room temperature under argon, followed by addition of $BF_3 \cdot Et_2O$ (2.3 mL \times 3, 53.84 mmol, 6 eq.) was added every 2 days in 3 portions. The resulting mixture was stirred for 6-7 days at room temperature. Then diluted with EtOAc (100 mL), washed with water (50 mL \times 3), sat. $NaHCO_3$ (50 mL \times 3) and brine (50 mL \times 3), respectively. The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 80/20, 70/30) gave a partially racemic *N*-Fmoc-dithioketal **181** (3.88 g, 75%, 0-28% *ee*) as a white solid.

TLC: R_f = 0.45 (petroleum ether/EtOAc = 70/30)

Mp. 54-56 °C

$[\alpha]_D^{27} = -10.2$ (*c* 0.52, $CHCl_3$)

IR (ATR) ν 3340, 3032, 2950, 1727, 1505, 1450, 1437, 1333, 1283, 1220, 1166, 1050, 756, 740, 698 cm^{-1}

¹H NMR (360 MHz, $CDCl_3$) δ 2.65 (dd, 1H, J = 14.8, 9.7 Hz, *ABX*), 3.05-3.12 (m, 2H), 3.18-3.28 (m, 5H), 3.63 (s, 3H), 4.20 (t, 1H, J = 6.8 Hz), 4.34-4.43 (m, 2H), 4.84-4.91 (ddd pseudo td, 1H, J = 9.7, 9.7, 3.2 Hz *ABX*), 5.15 (s, 2H), 5.35 (d, 1H, J = 9.7 Hz), 7.24-7.38 (m, 9H), 7.56-7.57 (m, 2H), 7.73-7.75 (m, 2H).

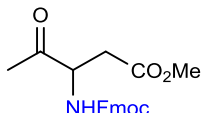
¹³C NMR (90 MHz, $CDCl_3$) δ 37.4, 39.6, 40.6, 46.8, 47.2, 52.0, 55.5, 66.7, 66.8, 71.3, 119.9 (2C), 125.0 (2C), 127.1 (2C), 127.6 (2C), 128.2, 128.4 (2C), 128.5 (2C), 135.6, 141.2 (2C), 143.7, 143.9, 155.9, 169.8, 171.4.

HRMS (ESI+) Calcd for $C_{31}H_{31}NNaO_6S_2$ [$M + Na$]⁺: 600.1485, found 600.1498.

HPLC: 28% *ee*. sample preparation: 1 mg/mL in MeOH, Column 1: A_NP_ChiralpakIC (250 mm \times 4.6 mm), normal phase: hexane/EtOH = 60/40, flow: 1 mL/min, 30 °C; injection: 5 μ L; results: RT

= 22.51 (*S*, Area: 63.8%), 16.044 (*R*, Area: 36.2%).

Methyl 3-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-oxopentanoate **185**



C₂₁H₂₁NO₅
Exact M = 367.1420
M = 367.40 g·mol⁻¹

To a solution of *N*-Fmoc- β -ketoester **180** (200.6 mg, 0.40 mmol, 1 eq.) in EtOAc (10 mL) with a balloon of Hydrogen (1 atm.) was added Pd/C (10% wt., 40.0 mg, 0.08 mmol, 0.2 eq.). After the resulting mixture was stirred for 3 h at room temperature, completed. The reaction solution was filtered through a celite pad, washed with EtOAc (10 mL). The filtered liquid was then concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 70/30) gave a methyl ketone **185** (106.0 g, 73%) as a colorless oil.

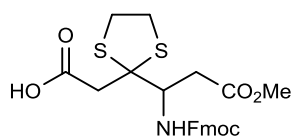
TLC: R_f = 0.50 (petroleum ether/EtOAc = 60/40)

¹H NMR (360 MHz, CDCl₃) δ 2.23(s, 2H), 2.79 (dd, 1H, J = 17.1, 4.7 Hz, *ABX*), 2.99 (dd, 1H, J_1 = 17, 4.3 Hz, *ABX*), 3.69 (s, 3H), 4.20 (t, 1H, J = 6.8 Hz), 4.40-4.53 (m, 3H), 5.90 (d, 1H, J = 8.6 Hz), 7.30-7.34 (m, 2H), 7.38-7.43 (m, 2H), 7.58-7.60 (m, 2H), 7.76-7.78 (m, 2H),

¹³C NMR (90 MHz, CDCl₃) δ 26.8, 35.5, 47.4, 52.3, 56.9, 67.2, 120.2 (2C), 125.1, 125.2, 127.2 (2C), 127.9 (2C), 141.5 (2C), 143.8 (2C), 156.1, 172.0, 205.9.

HRMS (ESI+) Calcd for C₂₁H₂₁NNaO₅ [M + Na]⁺: 390.1312, found 390.1308.

2-(2-(1-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl)-1,3-dithiolan-2-yl)acetic acid **186**



C₂₄H₂₅NO₆S₂
Exact Mass: 487.1123
M. = 487.58 g·mol⁻¹

To an ice cold solution of *N*-Fmoc-dithioacetal benzyl ester **181** (580.0 mg, 1.00 mmol, 1 eq.) in HOAc (6 mL) was slowly added a solution of 33% HBr in HOAc (3.5 mL, 20.00 mmol, 20 eq.).

The ice bath was removed and the mixture was stirred for 5 h. The reaction solution was poured into EtOAc (50 mL), then washed water (20 mL × 3) and brine (20 mL) to give the organic layer, which was dried over MgSO₄ and concentrated under reduced pressure. Flash chromatography on silica gel (MeOH/CH₂Cl₂ = 5/95, 10/90) gave β-dithioketal acid **186** (416.7 mg, 85%) as a white solid.

TLC: $R_f = 0.38$ (MeOH/CH₂Cl₂ = 10/90)

Mp. 81-83 °C

IR (ATR) ν 3296, 2950, 1706, 1510, 1451, 1435, 1330, 1282, 1224, 1174, 1050, 739 cm⁻¹

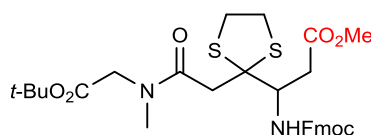
¹H NMR (360 MHz, CDCl₃) δ 2.64 (dd, 1H, $J = 14.8, 9.7$ Hz), 3.01-3.10 (m, 2H), 3.18-3.23 (m, 5H), 3.61 (s, rotamer) and 3.63 (s, 3H), 4.20 (t, $J = 6.8$ Hz), 4.41 (d, $J = 6.8$ Hz), 4.86 (ddd pseudo td, 1 H, $J = 10.1, 9.7, 3.6$ Hz) and 4.97 (pseudo t, rotamer), 5.40 (d, $J = 10.1$ Hz) and 5.80 (d, rotamer), 7.28-7.40 (m, 4H), 7.56-7.66 (m, 4H), 7.73-7.75 (m, 2H).

¹³C NMR (90 MHz, CDCl₃) δ 37.5 and 380.0 (rotamer), 39.7 and 40.1 (rotamer), 40.6 (rotamer) and 40.7, 46.8, 47.1 (rotamer) and 47.3, 52.2, 55.4 and 55.9 (rotamer), 67.1 and 68.6 (rotamer), 71.1, 120.0 (2C), 125.1, 125.2, 127.2 (2C), 127.8 (2C), 141.4 (2C), 143.8, 144.0, 156.3, 171.7, 174.0.

HRMS (ESI+) Calcd for C₂₄H₂₅NNaO₆S₂ [M + Na]⁺: 510.1015, found 510.5992.

Methyl

3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-(2-((2-(tert-butoxy)-2-oxoethyl)(methyl)amino)-2-oxoethyl)-1,3-dithiolan-2-yl)propanoate **187**



C₃₁H₃₈N₂O₇S₂
Exact M. = 614.2120
M. = 614.77 g·mol⁻¹

To a solution of *N*-Fmoc-β-dithioketal acid **186** (80.0 mg, 0.16 mmol, 1 eq.) in CH₂Cl₂ (10 mL) under argon was added H-Sar-*O**t*-Bu·HCl (33.0 mg, 0.18 mmol, 1.1 eq.), PyBroP (84.0 mg, 0.18 mmol, 1.1 eq) and dropwise DIEA (64.0 mg, 0.49 mmol, 4 eq.), respectively. The resulting mixture was stirred at room temperature for overnight (16 h), then diluted with CH₂Cl₂ (10 mL) and subsequently washed with 1 M KHSO₄ (10 mL), sat. NaHCO₃ (10 mL) and brine (10 mL) to give

the organic layer, which was then dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 70/30, 50/50) gave *N*-Fmoc-dipeptide **187** (95.6 mg, 95%) as a white solid.

TLC: $R_f = 0.45$ (petroleum ether/EtOAc = 50/50)

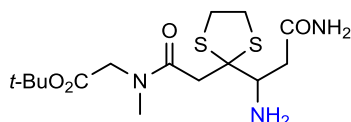
Mp. 68-70 °C

IR (ATR) ν 3331, 2978, 2927, 1732, 1649, 1503, 1450, 1403, 1367, 1327, 1227, 1155, 757, 741 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 1.45 (s, 9H) and 1.47 (s, rotamer), 2.70-2.78 (dd pseudo m, 1H, with rotamer, ABX), 2.98-3.08 (m, 4H), 3.17 (d, 1H, $J = 16.2$ Hz), 3.17 (brs, 4H), 3.29 (d, 1H, $J = 16.2$ Hz), 3.65 (s, 3H), 3.90 (d, 1H, $J = 5.4$ Hz) and 3.93 (d, 1H, $J = 5.4$ Hz, rotamer), 4.14-4.34 (m, 4H), 4.80-4.86 (ddd pseudo m, 1H, ABX), 6.00 (d, 1H, $J = 10.1$ Hz) and 6.04 (d, 1H, $J = 10.1$ Hz), 7.29-7.33 (m, 2H), 7.39 (t, 2H, $J = 7.2$ Hz), 7.61 (d, 2H, $J = 7.2$ Hz), 7.75 (d, 2H, $J = 7.2$ Hz).

HRMS (ESI+) Calcd for C₃₁H₃₈N₂NaO₇S₂ [M + Na]⁺: 637.2013, found 637.2028.

tert*-Butyl *N*-(2-(2-(1,3-diamino-3-oxopropyl)-1,3-dithiolan-2-yl)acetyl)-*N*-methylglycinate **188*



C₁₅H₂₇N₃O₄S₂
Exact M. = 377.1443
M. = 377.52 g·mol⁻¹

To an ice cold solution of *N*-Fmoc-dipeptide **187** (77.0 mg, 125 μ mol, 1 eq.) in ethanol (2 mL) was added a solution of 28% NH₄OH (3 mL). The resulting mixture was stirred at room temperature for 4 days, completed. The reaction solution was then concentrated under reduced pressure, diluted with CH₂Cl₂ (20 mL) and washed with water (20 mL). The separated organic phase was then dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (CH₂Cl₂/MeOH = 95/5, 90/10) gave a dipeptide of free amine **188** (13.5 mg, 52%) as a pale-yellow oil.

TLC: $R_f = 0.19$ (CH₂Cl₂/MeOH = 90/10)

¹H NMR (360 MHz, CDCl₃) δ 1.45 (s, 9H) and 1.48 (s, rotamer), 2.31-2.40 (dd pseudo m, 1H, with

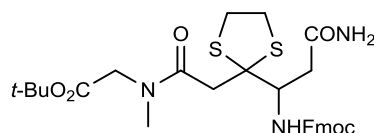
rotamer, *ABX*), 2.31-2.40 (dd pseudo d, 1H, $J = 15.5$ Hz, *ABX*), 2.93 (s, rotamer) and 3.08 (s, 3H), 3.23-3.39 (m, 6H, mixed with brs), 3.92-4.05 (m, 3H), 6.1 (brs, 1H) and 6.16 (brs, rotamer), 7.30 (brs, 1H).

^{13}C NMR (90 MHz, CDCl_3) δ 28.2 (s, 9H), 37.0, 37.3 and (35.4, rotamer), 39.6, 40.1, 45.3, 50.9 and 52.9 (rotamer), 55.6 (rotamer) and 55.8, 72.2, 82.5 and 83.3 (rotamer), 168.1 (rotamer) and 168.3, 170.7 (rotamer) and 170.8, 174.4.

HRMS (ESI+) Calcd for $\text{C}_{15}\text{H}_{28}\text{N}_3\text{O}_4\text{S}_2$ $[\text{M} + \text{H}]^+$: 378.1516, found 378.1514.

tert-Butyl

N-(2-(2-(1-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-amino-3-oxopropyl)-1,3-dithiolan-2-yl)acetyl)-*N*-methylglycinate **189**



$\text{C}_{30}\text{H}_{37}\text{N}_3\text{O}_6\text{S}_2$
Exact Mass: 599.2124
M. = 599.76 $\text{g}\cdot\text{mol}^{-1}$

To an ice cold solution of dipeptide of free amine **187** (18.0 mg, 48 μmol , 1 eq.) in dioxane (1 mL) and water (2 mL) was added K_2CO_3 . (10.5 mg, 76 μmol , 1.6 eq.), and followed by addition of a solution of FmocCl (13.5 mg, 52 μmol , 1.1 eq.) in dioxane (1 mL). The resulting mixture was stirred at room temperature for overnight (16 h). The reaction was diluted with CH_2Cl_2 (20 mL) and washed with water (10 mL) and brine (10 mL). The separated organic phase was then dried over MgSO_4 , filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 70/30, then $\text{CH}_2\text{Cl}_2/\text{MeOH} = 95/5$, 90/10) to give *N*-Fmoc-dipeptide **189** (13.5 mg, 52%) as a white solid.

TLC: $R_f = 0.58$ (EtOAc/MeOH = 90/10)

Mp. 77-79 $^\circ\text{C}$

IR (ATR) ν 3447, 3332, 3214, 2978, 2927, 1714, 1649, 1510, 1450, 1402, 1368, 1231, 1155, 729 cm^{-1}

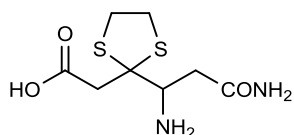
^1H NMR (360 MHz, CDCl_3) δ 1.43 (s, 9H) and 1.46 (s, rotamer), 2.49 (dd, 1H, $J = 14.4, 10.8$ Hz, *ABX*), 2.91-3.04 (m, 4H), 3.17 (d, 1H, $J = 16.9$ Hz), 3.17 (pseudo brs, 4H), 3.30 (d, 1H, $J = 16.9$

Hz), 3.85 (d, 1H, $J = 16.9$ Hz), 4.22 (d, 1H, $J = 16.9$ Hz), 4.18 (t, 1H, $J = 6.8$ Hz), 4.31-4.41(m, 2H), 4.75-4.84 (ddd pseudo m, 1H) and 4.95-5.01 (m, rotamer), 5.63 (brs, rotamer) and 5.75 (brs, 1H), 5.81 (dd, rotamer) and 6.32 (dd, 1H, $J = 10.1$ Hz), 6.55 (brs, 1H) and 6.85 (brs, rotamer), 7.30 (t, 2H, $J = 7.2$ Hz), 7.37 (t, 2H, $J = 7.2$ Hz), 7.60 (t, 2H, $J = 7.2$ Hz), 7.74 (d, 2H, $J = 7.2$ Hz).

^{13}C NMR (90 MHz, CDCl_3) δ 28.2 (3C), 35.4 (rotamer) and 37.2, 39.4 and 39.5 (rotamer), 39.9, 40.3 (2C), 45.4, 47.3, 50.7 and 52.9 (rotamer), 56.4, 67.0, 72.3 and 72.4 (rotamer), 82.0 and 83.0 (rotamer), 120.0 (2C), 125.3, 125.4, 127.2 (2C), 127.7 (2C), 141.3 (2C), 144.0 (2C), 157.0, 167.9 (rotamer) and 168.3, 170.5 (rotamer) and 170.6, 173.1

HRMS (ESI+) Calcd for $\text{C}_{30}\text{H}_{37}\text{N}_3\text{NaO}_6\text{S}_2$ [$\text{M} + \text{Na}$] $^+$: 622.2016, found 622.2032.

2-(2-(1,3-Diamino-3-oxopropyl)-1,3-dithiolan-2-yl)acetic acid **190**



$\text{C}_8\text{H}_{14}\text{N}_2\text{O}_3\text{S}_2$
Exact M = 250.0446
M = 250.33 g·mol $^{-1}$

To a flask containing *N*-Fmoc- β -dithioketal acid **186** (150 mg, 0.31 mmol, 1 eq.) was added a solution of 28% NH_4OH (8.5 mL, 61.40 mmol, ~200 eq.). The mixture was stirred for overnight (18-20 h) at room temperature, then filtered through a filter Buchner funnel to remove dibenzofulvene (DBF) and the solid was washed with 28% NH_4OH (5 mL \times 3) to give the filtrate, which was extracted with Et_2O (10 mL \times 2) to remove the residue of DBF. The aqueous phase was concentrated under reduced pressure to give a pure primary amide **190** (74.0 mg, 100%) as a white solid and used without further purification.

TLC: $R_f = 0.10$ (MeOH/ $\text{CH}_2\text{Cl}_2 = 10/90$)

Mp. 105-108 $^\circ\text{C}$

IR (ATR) ν 3325, 3162, 2921, 1667, 1557, 1378, 1276, 851, 679 cm^{-1}

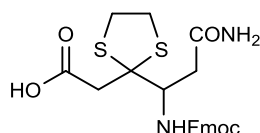
^1H NMR (360 MHz, D_2O) δ 2.56 (dd, 1H, $J = 15.8, 10.4$ Hz, *ABX*), 2.96 (dd, 1H, $J = 15.8, 2.9$ Hz, *ABX*), 3.02 (d, 1H, $J = 16.6$ Hz), 3.13 (d, 1H, $J = 16.6$ Hz), 3.26-3.41 (m, 4H), 4.01 (dd, 1H, $J_1 = 10.4, 2.9$ Hz, *ABX*)

^{13}C NMR (90 MHz, D_2O) δ 35.7, 39.4, 39.5, 49.2, 55.7, 69.3, 174.8, 177.2.

HRMS (ESI+) Calcd for $C_8H_{15}N_2O_3S_2$ $[M + H]^+$: 251.0519, found 251.0516.

HRMS (ESI-) Calcd for $C_8H_{13}N_2O_3S_2$ $[M - H]^-$: 249.0373, found 249.0372.

2-(2-(1-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-amino-3-oxopropyl)-1,3-dithiolan-2-yl)acetic acid **191**



$C_{23}H_{24}N_2O_5S_2$
Exact M. = 472.1127
M. = 472.57 g·mol⁻¹

To an ice cold solution of β -amino primary amide **190** (150.1 mg, 0.60 mmol, 1 eq.) in dioxane (5 mL) and water (10 mL) was added Na_2CO_3 (101.8 mg, 0.96 mmol, 1.6 eq.), then followed by addition of a solution of FmocCl (232.8 mg, 0.90 mmol, 1.5 eq.) in dioxane (5 mL) over 10 min. After the resulting mixture was stirred for overnight (18-24 h) at room temperature, sat. $NaHCO_3$ (10 mL) was added and extracted with EtOAc (20 mL \times 2) to give the aqueous phase. The aqueous phase was then acidified with 4 M HCl until = 2-3, and extracted with EtOAc (20 mL \times 3). The combined organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a pure *N*-Fmoc-mPyrAA **191** (197.5 mg, 70%) as a white solid and used without further purification.

TLC: $R_f = 0.20$ (MeOH/ $CH_2Cl_2 = 20/80$)

Mp. 99 °C, decarboxylation

IR (ATR) ν 3323, 2919, 2853, 1703, 1654, 1520, 1449, 1326, 1242, 1117, 1046, 869, 739 cm^{-1}

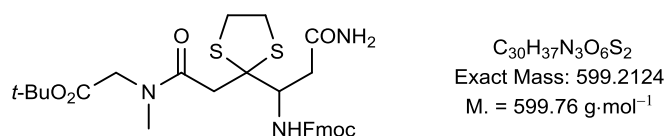
¹H NMR (400 MHz, DMSO- d_6) δ 2.43-2.50 (dd pseudo m, 1H, *ABX*), 2.72 (dd pseudo d, 1H, $J = 13.6$, *ABX*), 2.87 (d, 1H, $J = 17.2$ Hz), 3.06 (d, 1H, $J = 17.2$ Hz), 3.07-3.36 (m, 4H), 4.08-4.23 (m, 2H, with rotamer), 4.26-4.32 (m, 2H), 4.63-4.67 (mt, 1H, *ABX*) and 4.92-4.97 (m, rotamer), 6.80 (brs, 1H) and 6.88 (brs, rotamer), 7.13-7.21 (brs pseudo m, 2H, with rotamer), 7.33 (t, 2H, $J = 7.6$ Hz), 7.41 (t, 2H, $J = 6.5$ Hz), 7.70 (m, 2H), 7.88 (d, 2H, $J = 7.6$ Hz), 11.94 (brs, 1H)

¹³C NMR (90 MHz, DMSO- d_6) δ 37.8, 38.54, 40.0, 46.7, 46.8, 55.2, 65.5, 72.4, 120.1 (2C), 125.3 (2C) 127.1 (2C), 127.6 (2C), 140.6 (2C), 143.7, 143.8, 155.9, 171.3, 172.0.

HRMS (ESI-) Calcd for $C_{23}H_{24}N_2NaO_5S_2$ $[M + Na]^+$: 495.1019, found 495.1009.

tert-Butyl

N*-(2-(2-(1-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-amino-3-oxopropyl)-1,3-dithiolan-2-yl)acetyl)-*N*-methylglycinate **189*



To a solution of *N*-Fmoc-mPyrAA **191** (42.0 mg, 0.89 mmol, 1 eq.) in CH₂Cl₂ (20 mL) under argon was added H-Sar-*O**t*-Bu·HCl (17.8 mg, 0.98 mmol, 1.1 eq.), PyBroP (45.6 mg, 0.98 mmol, 1.1 eq) and dropwise DIEA (46.0 mg, 0.356 mmol, 4 eq.), respectively. The resulting mixture was stirred at room temperature for overnight (16 h). Diluted with CH₂Cl₂ (20 mL) and the solution was subsequently washed with 1 M HCl (20 mL), sat. NaHCO₃ (20 mL) and brine (20 mL), then dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (EtOAc =100, EtOAc/MeOH = 90/10) gave the pure desired dipeptide **189** (48.0 mg, 90%) as a white solid.

tert-Butyl

N*-(4-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-cyano-3-oxopentanoyl)-*N*-methylglycinate **195*

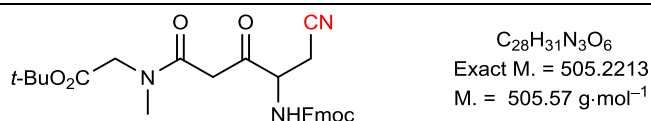


Table 6, entry 7:

To a solution of dipeptide **189** (90.0 mg, 0.15 mmol, 1 eq.) in acetonitrile/water (5/0.5 mL) was added HgO (260.0 mg, 1.20 mmol, 8 eq) and HgCl₂ (488.7 mg, 1.80 mmol, 12 eq.). The mixture was stirred for 24 at room temperature, then filtered through a Celite pad and washed with EtOAc (40mL).The filtrate was washed with water (20 mL) and brine (20mL). The organic layer was dried with Mg₂SO₄, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (EtOAc/petroleum ether = 30/70, 50/50, EtOAc = 100%, then EtOAc/MeOH = 100/1) gave the nitrile **195** (47.0 mg, 60%) as a colorless oil, as well as the dehydrated compound **194** (8.0 mg, 10%)

as a colorless oil.

TLC: $R_f = 0.64$ (EtOAc/petroleum ether = 50/50)

IR (ATR) ν 3316, 2979, 2938, 2247, 1729, 1640, 1502, 1451, 1407, 1369, 1247, 1157, 1045, 760, 742 cm^{-1}

$^1\text{H NMR}$ (400 MHz, CD_3CN) δ 1.42 (rotamer) and 1.44 (s, 9H), 2.77 (dd, 2H, $J = 16.8, 8.4$ Hz, ABX), 2.86-3.00 (m, 4H), 3.46-3.66 (two dd pseudo m, 2H, with rotamer), 3.88-4.00 (m, 2H), 4.27 (t, 1H, $J = 6.8$ Hz), 4.37-4.45 (m, 2H), 4.48-4.59 (m, 1H), 6.36 (d) and 6.6 (d, 1H, $J = 7.2$ Hz), 7.33-7.37 (m, 2H), 7.42 (t, 2H, $J = 7.2$ Hz), 7.67 (d, 2H, $J = 6.0$ Hz), 7.83 (d, 2H, $J = 7.2$ Hz).

$^1\text{H NMR}$ (400 MHz, CD_3CN) δ 1.42 (rotamer) and 1.44 (s, 9H), 2.77 (dd, 2H, $J = 16.8, 8.4$ Hz, ABX), 2.86-3.00 (m, 4H), 3.46-3.66 (two dd pseudo m, 2H, with rotamer), 3.88-4.00 (m, 2H), 4.27 (t, 1H, $J = 6.8$ Hz), 4.37-4.45 (m, 2H), 4.48-4.59 (m, 1H), 6.36 (d) and 6.6 (d, 1H, $J = 7.2$ Hz), 7.33-7.37 (m, 2H), 7.42 (t, 2H, $J = 7.2$ Hz), 7.67 (d, 2H, $J = 6.0$ Hz), 7.83 (d, 2H, $J = 7.2$ Hz).

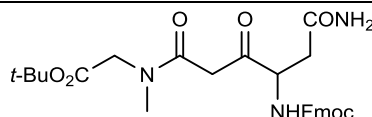
$^{13}\text{C NMR}$ (100 MHz, CD_3CN) δ 19.7 and 22.2 (rotamer), 28.2, 35.0 (rotamer) and 37.0 (rotamer) and 37.6, 45.4 (rotamer) and 45.3, 48.0, 50.7 (rotamer) and 50.9, 52.6 (rotamer) and 53.3, 52.0 (rotamer) and 57.1 and 57.2 (rotamer), 67.7 and 67.8 (rotamer), 82.4 and 83.1 (rotamer), 118.5, 121.2 (2C), 126.2 (2C), 128.2 (2C), 128.8 (2C), 142.2(2C), 144.9 and 145.0 (rotamer) (2C), 157.0, 168.7 and 174.2 (rotamer), 169.2, 201.4 (rotamer) and 201.5.

HRMS (ESI+) : Calcd for $\text{C}_{28}\text{H}_{31}\text{N}_3\text{NaO}_6$ $[\text{M} + \text{Na}]^+$: 528.2105, found 528.2112.

Mixed with enol-form not presented.

tert-Butyl

N-(4-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-6-amino-3,6-dioxohexanoyl)-*N*-methylglycinate **192**



$\text{C}_{28}\text{H}_{33}\text{N}_3\text{O}_7$
Exact M. = 523.2319
M. = 523.59 $\text{g}\cdot\text{mol}^{-1}$

Table 6, entry 9:

To an ice cold solution of dipeptide **189** (120.0 mg, 0.20 mmol, 1 eq.) in acetone (10 mL) was added *N*-Bromosuccinimide (180.0 mg, 1.00 mmol, 5 eq.), and the mixture was stirred for 40 min at

0 °C (from orange red to pale-yellow). Quenched with water (1 mL), then diluted with EtOAc (50 mL), washed with water (30 mL × 3) and brine (30 mL × 2). The organic layer was dried with Mg₂SO₄, filtered, and concentrated under reduced pressure. Flash chromatography on a very short silica gel (EtOAc/petroleum ether = 50/50, EtOAc/MeOH = 95/5, 90/10) gave the γ -keto primary amide **192** (46.4 mg, 44%) as a colorless oil, as well as the dehydrated **194** (5.0 mg, 5%) as a colorless oil.

TLC: R_f = 0.66 (EtOAc/MeOH = 90/10)

IR (ATR) ν 3330, 2978, 2930, 2248, 1713, 1671, 1635, 1479, 1450, 1402, 1368, 1232, 1154, 1046, 910, 760, 737 cm⁻¹

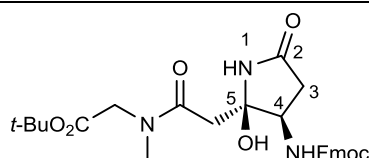
¹H NMR (400 MHz, CDCl₃) δ 1.45 (s, 9H), 2.74-3.04 (m, 5H, ABX + NCH₃), 3.69 (s, rotamer) and 3.75 (s, 1H), 3.90 (s, rotamer) and 4.00 (s, 2H), 4.18-4.23 (m, 1H), 4.36-4.48 (M, 2H), 4.59-4.67 (m, 1H), 5.66 (brs), 5.60 6.14 (brs, 1H), 6.29-6.47 (d pseudo m, 1H, with rotamers, J = 8.0 Hz), 7.30 (t, 2H, J = 7.2 Hz), 7.39 (t, 2H, J = 7.2 Hz), 7.59 (d, 2H, J = 6.0 Hz), 7.75 (d, 2H, J = 7.2 Hz).

¹³C NMR (100 MHz, CDCl₃) δ 28.1 (rotamer) and 28.2, 35.1 (rotamer) and 37.3, 36.4 and 36.5 (rotamer), 45.7, 47.3, 50.4 and 53.0 (rotamer), 57.2, 67.2 and 67.3 (rotamer), 120.0 (rotamer) and 120.1 (2C), 125.2 and 125.4 (rotamer) (2C), 127.8 (rotamer) and 127.9 (2C), 141.4 (2C), 143.8 and 143.9 (rotamer) (2C), 156.4, 167.8 and 168.0 (rotamer), 168.1, 172.6, 202.4 (rotamer) and 202.6.

HRMS (ESI⁺) : Calcd for C₂₈H₃₃N₃NaO₇ [M + Na]⁺: 546.2211, found 546.2212.

tert-Butyl

N*-(2-(3-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-hydroxy-5-oxopyrrolidin-2-ylidene)acetyl)-*N*-methylglycinate **193*



C₂₈H₃₃N₃O₇
Exact M. = 523.2319
M. = 523.59 g·mol⁻¹

Table 6, entry 10:

Step1: To an ice cold solution of dipeptide **189** (120.0 mg, 0.20 mmol, 1 eq.) in acetone (10 mL) was added *N*-Bromosuccinimide (180.0 mg, 1.00 mmol, 5 eq.), and the mixture was stirred for 40

min at 0 °C (from orange red to pale-yellow). Quenched with water (1 mL), then diluted with EtOAc (50 mL), washed with water (30 mL × 3) and brine (30 mL × 2). The organic layer was dried with Mg₂SO₄, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel with a normal speed (EtOAc/petroleum ether = 50/50, EtOAc = 100%, EtOAc/MeOH = 98/2, 95/5, 90/10) gave a mixture of γ -keto primary amide **192** and cyclization product **193** (35.0 mg, 33%) as a colorless oil, as well as the dehydrated **194** (5.0 mg, 5%) as a colorless oil.

Step2: The mixture was stirred with silica (400 mg) in MeOH (5 ml) for 24 h at room temperature, then evaporated. Flash chromatography on silica gel (EtOAc/MeOH = 98/2, 95/5, 90/10) gave a cyclization product **193** (34.0 mg, 33%) as a colorless oil.

TLC: R_f = 0.67 (EtOAc/MeOH = 90/10)

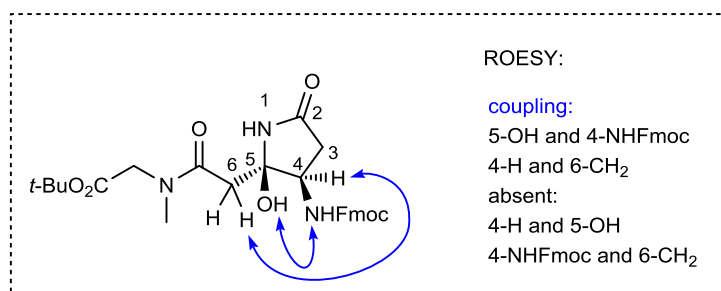
IR (ATR) ν 3300, 2926, 1706, 1658, 1633, 1533, 1450, 1404, 1368, 1232, 1155, 1041, 739 cm⁻¹

¹H NMR (400 MHz, DMSO-*d*₆) δ 1.39 (s, 9H) and 1.40 (rotamer), 2.27-2.36 (m, 2H), 2.54 (d, 0.5 H, J = 16.0 Hz) and 2.68 (d, 0.5 H, J = 16.0 Hz), 2.80 (d, 0.5 H, J = 16.0 Hz) and 2.93 (d, 0.5 H, J = 16.0 Hz), 2.812.97 (s, rotamer, 1H) and 2.97 (s, 2H), 3.96 (dd, 1H, J = 16.8 Hz), 4.03 (d, 0.5H, J = 16.8 Hz) and 4.03 (d, 0.5H, J = 16.8 Hz), 4.22-4.34 (m, 4H), 6.02 (s, 1H) and 6.09 (rotamer), 7.16 (d, 1H, J = 8.4 Hz), 7.33 (t, 2H, J = 7.6 Hz), 7.41 (t, 2H, J = 7.6 Hz), 7.69-7.747.33 (m, 2H), 7.89 (d, 2H, J = 7.6 Hz), 8.01 (d, 1H, J = 1.6 Hz).

¹³C NMR (100 MHz, DMSO-*d*₆) δ 27.6 (rotamer) and 27.7, 34.4 (rotamer) and 36.4, 34.7, 39.6, 46.6 (rotamer) and 46.7, 49.6 and 51.9 (rotamer), 53.4 (rotamer) and 53.4, 65.6 and 65.7 (rotamer), 80.8 and 80.5 (rotamer), 85.9 and 88.8 (rotamer), 120.1 (2C), 120.1 (2C), 125.2 and 125.3 (2C), 127.0 (2C), 1227.6 (2C), 140.7 (2C), 143.7 and 143.8 (2C), 156.0, 168.2 and 168.4 (rotamer), 170.7 and 170.9 (rotamer), 173.1.

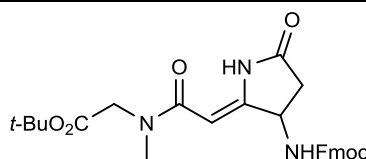
HRMS (ESI+) Calcd for C₂₈H₃₃N₃NaO₇ [M + Na]⁺: 546.2211, found 546.2191.

ROESY



tert-Butyl

(Z)-N-(2-(3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-oxopyrrolidin-2-ylidene)acetyl)-N-methylglycinate **194**



C₂₈H₃₁N₃O₆
 Exact M. = 505.2213
 M. = 505.57 g·mol⁻¹

Table 6, entry 12:

Step1: To an ice cold solution of dipeptide **189** (60.0 mg, 0.10 mol, 1 eq.) in acetone (5 mL) was added *N*-Bromosuccinimide 90.0 mg, 0.20 mmol, 5 eq.), and the mixture was stirred for 40 min at 0 °C. Quenched with water (1 mL), then diluted with EtOAc (50 mL), and washed with water (30 mL× 3) and brine (30 mL× 2). The organic layer was dried with Mg₂SO₄, filtered, and concentrated under reduced pressure to give a pale-yellow oil (55 mg).

Step2: The crude was dissolved in acetone (5 mL) and added 4 M HCl (5 mL). The resulting mixture was stirred for 24 h at room temperature, then diluted with EtOAc (50 mL), then washed with water (30 mL× 3) and brine (30 mL× 2). The organic layer was dried with Mg₂SO₄, filtered, and concentrated under reduced pressure to give a pale-yellow oil (40 mg). Flash chromatography on silica gel with normal speed (EtOAc/petroleum ether = 40/60, 50/50) gave the dehydrated **194** (20.0 mg, 40%) as a colorless oil.

TLC: *R_f* = 0.25 (petroleum ether/EtOAc = 50/50)

IR (ATR) ν 3300, 2932, 1720, 1656, 1595, 1523, 1479, 1368, 1331, 1284, 1247, 1156, 1128, 1046, 758, 741 cm⁻¹

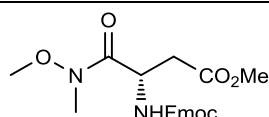
¹H NMR (400 MHz, CDCl₃) δ 1.43 (s, rotamer) and 1.46 (s, 9H), 2.31 (dd, 1H, *J* = 18.0, 4.4 Hz, *ABX*), 2.88 (dd, 1H, *J* = 18.0, 9.6 Hz, *ABX*), 3.00 (s, rotamer) and 3.05 (s, 3H), 3.94 (d, 1H, *J* = 18.4 Hz), 4.13 (d, 1H, *J* = 18.4 Hz), 4.23 (t, 1H, *J* = 6.4 Hz), 4.40-4.53 (m, 2H), 4.94-5.05 (ddd pseudo m, 1H), 5.26 (s, rotamer) and 5.49 (s, 1H, alkene), 5.49 (br, 1H, NHFmoc), 7.31 (t, 2H, *J* = 7.6 Hz), 7.40 (t, 2H, *J* = 7.6 Hz), 7.58 (d, 2H, *J* = 7.2 Hz), 7.76 (d, 2H, *J* = 7.6 Hz), 10.45 (brs, H).

¹³C NMR (100 MHz, CDCl₃) δ 28.2, 36.4, 36.9 (35.2, rotamer), 47.3, 49.4, 50.3 (52.7, rotamer), 67.2, 82.1, 89.2, 120.2 (2C), 125.0, 125.1, 127.2 (2C), 128.0 (2C), 141.5 (2C), 143.7 (2C), 156.1, 168.1, 168.6, 174.1.

HRMS (ESI+) Calcd for $C_{28}H_{31}N_3NaO_6$ $[M + Na]^+$: 528.2105, found 528.2081.

Methyl

(*S*)-3-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-(methoxy(methyl)amino)-4-oxobutanoate **196**



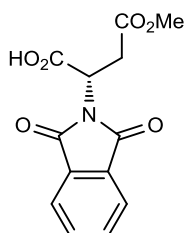
$C_{22}H_{24}N_2O_6$
Exact M. = 412.1634
M. = 412.44 g·mol⁻¹

To a solution of *L-N*-Fmoc-Asp(β -OMe)-H (*S*)-**179** (250.0 g, 0.67 mmol, 1 eq.) in CH_2Cl_2 (8 mL) under argon at room temperature was added *N,O*-dimethylhydroxylamine hydrochloride (17.8 mg, 0.98 mmol, 1.1 eq.), PyBOP (356.0 mg, 0.68 mol, 1 eq) and dropwise DIEA (218.7 mg, 1.69 mmol, 2.5 eq.), respectively. The resulting mixture was stirred at room temperature for overnight (16 h). Then diluted with EtOAc (30 mL) and subsequently washed with 1 M HCl (20 mL), sat. $NaHCO_3$ (20 mL) and brine (20 mL) to give the organic layer, which was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 80/20, 90/10) to give the pure desired Weinreb amide **196** (143.0 mg, 52%) as a white solid.

TLC: R_f = 0.45 (petroleum ether/EtOAc = 80/20)

¹H NMR (30 MHz, $CDCl_3$) δ 2.68 (dd, 1H, J = 15.3, 6.6 Hz, *ABX*), 2.83 (dd, 1H, J = 15.3, 5.4 Hz, *ABX*), 3.21 (s, 3H), 3.67 (s, 3H), 3.75 (s, 3H), 4.20 (t, 1H, J = 6.9 Hz), 4.36 (d, 1H, J = 6.9 Hz), 5.10 (ddd pseudo m, *ABX*), 5.96 (d, 1H, J = 8.7 Hz), 7.28 (t, 2H, J = 7.5 Hz), 7.37 (t, 2H, J = 7.5 Hz), 7.5-7.60 (m, 2H), 7.73 (d, 2H, J = 7.5 Hz).

(*S*)-2-(1,3-Dioxisoindolin-2-yl)-4-methoxy-4-oxobutanoic acid **199**



$C_{13}H_{11}NO_6$
Exact M. = 277.0586
M. = 277.23 g·mol⁻¹

To an ice cold solution of L-H-Asp(β -OMe)-H·HCl **175** (917.9 mg, 5.00 mmol, 1 eq.) in water (15 mL) was added Na₂CO₃ (529.9 mg, 5.00 mmol, 1 eq.). *N*-Carbonylphthalimide (1.096 g, 5.00 mmol, 1 eq.) was then added in 3 portions at 0 °C, and the ice bath was removed. After stirred for 3 h at room temperature, the reaction was diluted with sat. NaHCO₃ (20 mL), extracted with EtOAc (20 mL \times 2) to give the aqueous layer. The aqueous was then acidified with 4 M HCl until pH = 2-3, extracted with EtOAc (30 mL \times 3). The combined organic phase was washed with brine (30 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (MeOH/CH₂Cl₂ = 90/10) gave a phthalimido derivative **199** (1.246 g, 90%) as a white solid.

TLC: R_f = 0.49 ((MeOH/CH₂Cl₂ = 80/20)

Mp. 132-133 °C

$[\alpha]_D^{23}$ = -62.7 (c 0.53, CHCl₃)

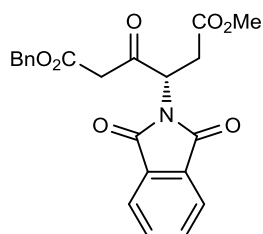
IR (ATR) ν 3176, 2937, 1783, 1755, 1744, 1690, 1405, 1256, 1213, 1169, 1013, 885, 723 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 3.14 (dd, 1H, J = 16.9, 9.0 Hz, ABX), 3.35 (dd, 1H, J = 16.9, 5.8 Hz, ABX), 3.65 (s, 3H), 5.43 (dd, 1H, J = 9.0, 5.8 Hz, ABX), 7.66-7.89 (m, 4H), 10.88 (1H).

¹³C NMR (90 MHz, CDCl₃) δ 33.6, 48.1, 52.4, 123.9 (2C), 131.7 (2C), 134.5 (2C), 167.3, 170.5, 173.8.

HRMS (ESI+) Calcd for C₁₃H₁₁NNaO₆ [M + Na]⁺: 300.0478, found 300.0474

11-Benzyl 6-methyl (*S*)-4-(1,3-dioxisoindolin-2-yl)-3-oxohexanedioate **200**



C₂₂H₁₉NO₇
Exact M. = 409.1162
M. = 409.39 g·mol⁻¹

To an ice cold solution of phthalimido derivative **199** (277.5 mg, 1.00 mmol, 1 eq.) in anhydrous THF (5 mL) under argon were added CDI (178.6 mg, 1.10 mmol, 1.1 eq.). The ice bath was then removed and stirred for 3 h at room temperature as *solution A*

Preparation of magnesium salt **174** as *solution B*: In a separated flask, to an ice cold solution of monobenzyl malonate (233.0mg, 1.20 mmol, 1.2 eq.) in anhydrous THF (5 mL) under argon was dropwise added a solution of 2 M isopropylmagnesium chloride in THF(1.2 mL, 2.40 mmol, 2.4 eq.). After stirred for 30 min at 0 °C, then heating at 50 °C for 30 min.

To an ice cold *solution B* was then slowly added *solution A* over 30 min. The resulting mixture was stirred for overnight (16-18 h) and slowly warmed to room temperature. The reaction was quenched with 1 M HCl (10 mL) at 0 °C and extracted with Et₂O (25 mL × 3). The combined organic layer was washed with 1 M HCl (25 mL), sat. NaHCO₃ (25 mL) and brine (25 mL), then dried over MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 75/25, 70/30) to give a β-keto-γ-phthalimidoester **200** (163.9 mg, 40%, *ee* undetermined) as a colorless oil.

TLC: $R_f = 0.62$ (petroleum ether/EtOAc = 70/30)

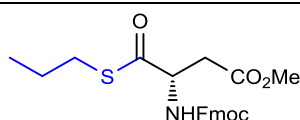
$[\alpha]_D^{24} = -6.0$ (*c* 0.50, CHCl₃)

IR (ATR) ν 2953, 1778, 1713, 1383, 1215, 1173, 721 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 2.78 (dd, 1H, $J = 17.3, 5.0$ Hz, ABX), 2.99 (dd, 1H, $J = 17.3, 4.7$ Hz, ABX), 3.63 (s, 3H), 3.67 (s, 2H), 4.64 (ddd, 1H, $J = 9.0, 5.0, 4.7$ Hz, ABX), 5.11-5.16 (m, 4H), 5.97 (d, 1H, $J = 9.0$ Hz), 7.28-7.39 (m, 10H).

¹³C NMR (90 MHz, CDCl₃) δ 32.6, 45.9, 52.2, 54.7, 67.5, 124.0 (3C), 128.5 (3C), 128.6 (2C), 131.6, 134.7 (2C), 135.1, 166.0, 167.3, 170.6, 196.4.

Methyl (*S*)-3-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-oxo-4-(propylthio)butanoate **201**



C₂₃H₂₅NO₅S
Exact M. = 427.1453
M. = 427.51 g·mol⁻¹

To an ice cold solution of L-*N*-Fmoc-Asp(β-OMe)-H (*S*)-**179** (1.847 g, 5.00 mmol, 1 eq.) in THF/DMF (9:3 mL) under argon was added HATU (2.844 g, 7.50 mmol, 1.5 eq.), propanethiol (4.523 g, 20.00 mol, 4 eq.), respectively. DIEA (5.170 g, 20.00 mmol, 4 eq.) was added dropwise. The resulting mixture was stirred for overnight (17 h). Without work-up, the reaction solution was

directly loaded for flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 80/20, 70/30) to give the desired L-(S)-N-Fmoc thioester **201** (1.846 g, 86%) as a colorless oil.

TLC: $R_f = 0.72$ (petroleum ether/EtOAc = 70/30)

$[\alpha]_D^{25} = +8.3$ (c 0.50, CHCl_3)

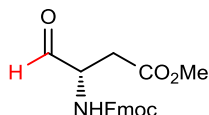
IR (ATR) ν 3332, 2958, 1725, 1683, 1504, 1446, 1438, 1226, 1049, 759, 741 cm^{-1}

^1H NMR (360 MHz, CDCl_3) δ 0.97 (t, 3H, $J = 7.2$ Hz), 1.56-1.65 (m, 2H), 2.79 (dd, 1H, $J = 16.9$, 4.7 Hz, ABX), 2.88 (t, 2H, $J = 7.2$ Hz), 3.14 (dd, 1H, $J = 16.9$, 4.7 Hz, ABX), 3.70 (s, 3H), 4.27 (t, 1H, $J = 6.8$ Hz), 4.37 (dd, 1H,), 4.57 (dd, 1H,), 4.74 (ddd, pseudo dt, 1H, $J = 9.4$, 4.7, 4.7 Hz, ABX), 6.06 (d, 1H, $J = 9.4$ Hz), 7.32 (t, 2H, $J = 77.2$ Hz), 7.41 (t, 2H, $J = 7.2$ Hz), 7.63-7.66 (m 2H), 7.77 (d, 2H, $J = 7.6$ Hz).

^{13}C NMR (90 MHz, CDCl_3) δ 13.4, 22.7, 31.1, 36.1, 47.2, 52.2, 57.2, 67.4, 120.1 (2C), 125.1, 125.2, 127.1 (2C), 127.8 (2C), 141.3, 143.7, 143.8, 155.9, 171.5, 200.2.

HRMS (ESI+) Calcd for $\text{C}_{23}\text{H}_{25}\text{NNaO}_5\text{S}$ $[\text{M} + \text{Na}]^+$: 450.1346, found 450.1328

Methyl (S)-3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-oxobutanoate **202**



$\text{C}_{20}\text{H}_{19}\text{NO}_5$
Exact M. = 353.1263
M. = 353.37 $\text{g}\cdot\text{mol}^{-1}$

To an ice cold solution of L-(S)-N-Fmoc thioester **201** (293.0 mg, 0.68 mmol, 1 eq.) in acetone (6 mL) under argon was added Pd/C (10% wt., 72.4 mg, 0.07 mmol, 0.1 eq.), followed by addition of Et_3SiH (318.6 mg, 2.74 mmol, 4 eq.) dropwise. The ice bath was then removed, and the resulting mixture was stirred for 30 min at room temperature, completed. The reaction solution was filtered through a Celite pad and washed with acetone (5 ml \times 3). The filtered liquid was concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 80/20, 70/30) to give the desired N-Fmoc aldehyde **202** (230.0 mg, 95%) as a white solid.

TLC: $R_f = 0.66$ (petroleum ether/EtOAc = 70/30)

Mp. 108-110 $^\circ\text{C}$

$$[\alpha]_D^{23} = -3.8 \text{ (} c \text{ 0.50, CHCl}_3 \text{)}$$

IR (ATR) ν 3352, 2952, 1728, 1518, 1450, 1250, 1056, 760, 741 cm^{-1}

^1H NMR (360 MHz, CDCl_3) δ 2.87 (dd, 1H, $J = 17.3, 4.7$ Hz, *ABX*), 3.00 (dd, 1H, $J = 17.3, 4.7$ Hz, *ABX*), 3.69 (s, 3H), 4.22 (t, 1H, $J = 6.5$ Hz), 4.41-4.47 (m, 3H), 6.01 (d, 1H, $J = 7.9$ Hz), 7.30-7.34 (m, 2H), 7.41 (t, 2H, $J = 7.2$ Hz), 7.60 (d, 2H, $J = 7.2$ Hz), 7.77 (d, 2H, $J = 7.2$ Hz), 9.63 (s, 1H).

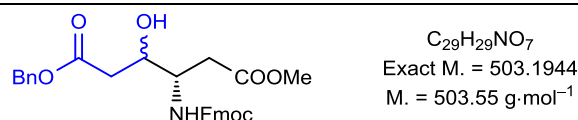
^{13}C NMR (90 MHz, CDCl_3) δ 34.1, 47.1, 52.2, 56.4, 120.1 (2C), 125.0 (2C), 127.1 (2C), 127.8 (2C), 141.3 (2C), 143.6 (2C), 156.2, 171.5, 198.6.

HRMS (ESI+) Calcd for $\text{C}_{20}\text{H}_{19}\text{NNaO}_5$ [$\text{M} + \text{Na}$] $^+$: 376.1155, found 376.1141.

6-Benzyl

1-methyl

(3*S*)-3-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-hydroxyhexanedioate **203**



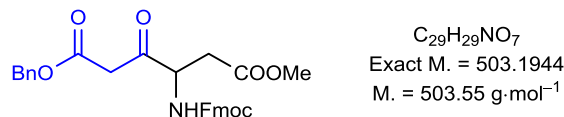
Mukaiyama aldol: To a solution of *N*-Fmoc aldehyde **202** (200.0 mg, 0.57 mmol, 1 eq.) in CH_2Cl_2 (6 mL) under argon was dropwise added $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.21 mL, 1.71 mmol, 3 eq) at -78 °C over 30 min, and followed by addition of ((1-(benzyloxy)vinyl)oxy)trimethylsilane (507.0 mg, 2.28 mmol, 4 eq.). The resulting mixture was stirred for overnight and slowly warmed to room temperature. The reaction was quenched with water (2 mL), filtered through a Celite pad and washed with CH_2Cl_2 (20 mL). The filtered liquid was washed with sat. NaHCO_3 (10 mL), and brine (10 mL). The organic layer was then dried over MgSO_4 , filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 80/20, 70/30, 60/40) gave the desired γ -amino- β -hydroxyester **203** (205.5 mg, 72%) as a colorless oil, with an inseparable mixture of two diastereoisomers (1.4:1, by ^1H NMR).

TLC: $R_f = 0.31$ (petroleum ether/EtOAc = 70/30)

^1H NMR (360 MHz, CDCl_3) δ 2.47-2.83 (m, 4H), 3.67 and 3.69 (s, 3H, two diastereoisomers), 3.50 and 3.61 (brs, 1H, two diastereoisomers), 3.94-4.09 (m, 1H, two diastereoisomers) 4.17-4.21 (m, 1H), 4.39-4.43 (m, 2H), 5.11-5.15 (m, 2H), 5.37 and 5.61 (d, 1H, two diastereoisomers), 7.28-7.41

(m, 9H), 7.55-7.59 (m, 2H), 7.69-7.76 (m, 2H)

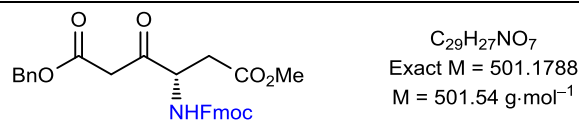
6-Benzyl 1-methyl 3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-oxohexanedioate **180**



Dess–Martin oxidation: To an ice cold solution of γ -amino- β -hydroxyester **203** (50.3 mg, 0.10 mmol, 1 eq.) in acetone (6 mL) under argon was added Dess–Martin periodinane (63.6 mg, 0.15 mmol, 1.5 eq.). The ice bath was then removed, and the resulting mixture was stirred for 20 h at room temperature, completed. The reaction was concentrated under reduced pressure, diluted with EtOAc (20 mL), washed with sat. NaSO₃ (20 mL), sat NaHCO₃ (20 mL) and brine (20 mL), respectively. Flash chromatography on silica gel (petroleum ether/EtOAc = 80/20, 70/30) gave a fully racemic *N*-Fmoc- β -ketoester **180** (50.0 mg, 99%, as racemic, 0% *ee*) as a colorless oil when stored in the fridge in turned into a waxy solid). Data see compound **180**.

One-pot Roskamp reaction: To an ice cold solution of L-(*S*)-*N*-Fmoc thioester **201** (236.3 mg, 0.50 mmol, 1 eq.) in CH₂Cl₂ (5 mL) under argon was added Pd/C (10% wt., 53.2 mg, 0.05 mmol, 0.1 eq.), followed by addition of Et₃SiH (232.5 mg, 2.00 mmol, 4 eq.) dropwise. The ice bath was then removed, and the resulting mixture was stirred for 30 min at room temperature, completed. The reaction solution was filtered through a Celite pad and washed with CH₂Cl₂ (5 ml × 3). The filtered liquid was concentrated under reduced pressure to give the aldehyde **202** crude (300 mg, τ = 100%) as a semi-solid. To a solution of aldehyde **202** crude was directly subjected to Roskamp reaction. To a solution of crude **202** in CH₂Cl₂ (10 mL) under argon at room temperature was added SnCl₂ (37.9 mg, 0.20 mmol, 0.4 eq.). A solution of benzyl diazoacetate in toluene (10% wt., 1.2 mL, 0.60 mmol, 1.2 eq.) was added over 10 min. The resulting mixture was stirred for 8 h at room temperature and quenched with 1 M HCl (1 mL). Then diluted with CH₂Cl₂ (10 mL), washed with 1 M HCl (10 mL), sat. NaHCO₃ (10 mL), and brine (10 mL). The organic layer was then dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 80/20, 70/30) gave the desired benzyl γ -amino- β -ketoester **180** (160.0 mg, 64%, 58% *ee*) as a white solid. Data see compound **180**.

6-Benzyl 1-methyl (S)-3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-oxohexanedioate (S)-180



Fmoc-UNCA (S)-204 formation: To an ice cold solution of L-N-Fmoc-Asp(OMe)-OH (**S**)-**179** (1.108 g, 3.00 mmol, 1 eq.) in anhydrous THF (20 mL) under argon was added triphosgene (356.1 mg, 1.20 mmol, 1.2 eq.). Then *sym*-collidine (727.1 mg, 6.00 mmol, 2 eq.) was added in two portions (~0.8 mL), of which the first portion (~0.4 mL) was added over 10 min at 0 °C (immediately white solid precipitated). The ice bath was then removed, the left portion of *sym*-collidine (~0.4 mL) was added over 20 min at room temperature. The resulting mixture was totally stirred 2 h, then filtered rapidly through a filter Buchner funnel to remove the collidine hydrochloride salt and the solid was washed with anhydrous THF (10 mL × 3) to give the filtered liquid as *solution A* (~50 mL).

Preparation of magnesium enolate salt **174** as *solution B*: In a separated flask, to an ice cold solution of monobenzyl malonate of monobenzyl malonate (815.6 g, 4.20 mmol 1.4 eq.) in anhydrous THF (15 mL) under argon was dropwise added a solution of 2.0 M isopropylmagnesium chloride in THF (4.2 mL, 8.40 mmol, 2.8 eq.). After stirred for 30 min at 0 °C, then heating at 50 °C for 30 min as *solution B*.

Condensation: To the ice cold *solution B* was then slowly added *solution A* at -10 °C over 30 min. The resulting mixture was stirred for overnight (16-18 h) and slowly warmed to room temperature. The reaction was then quenched with 1 M HCl (20 mL) at 0 °C, evaporated under reduced pressure to remove most of THF, then extracted with EtOAc (50 mL × 3). The combined organic layer was washed with sat. NaHCO₃ (50 mL) and brine (50 mL), then dried over MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 80/20, 70/30) to give the desired γ -amino- β -ketoester (**S**)-**180** (797.0 mg, 53%, 93% *ee*) as a colorless oil, when stored in the fridge it turned into a waxy solid.

TLC: $R_f = 0.43$ (petroleum ether/EtOAc = 70/30)

$[\alpha]_D^{26} = -17.8$ (*c* 0.50, CHCl₃)

IR (ATR) ν 3360, 2953, 1722, 1514, 1451, 1316, 1248, 756, 742 cm^{-1}

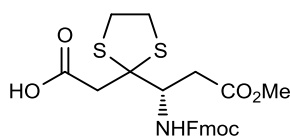
^1H NMR (360 MHz, CDCl_3) δ 2.80 (dd, 1H, $J = 17.3, 4.7$ Hz, ABX), 2.99 (dd, 1H, $J = 17.3, 5.0$ Hz, ABX), 3.62 (s, 2H), 3.66 (s, 3H), 4.21 (t, 1H, $J = 6.5$ Hz), 4.46 (dd, 1H, $J = 10.8, 6.5$ Hz), 4.55 (dd, 1H, $J = 10.8, 6.5$ Hz), 4.64 (ddd, 1H, $J = 9.0, 5.0, 4.7$ Hz, ABX), 5.11-5.21 (m, 2H), 6.00 (d, 1H, $J = 9.0$ Hz), 7.29-7.43 (m, 9H), 7.59 (d, 2H, $J = 7.2$ Hz), 7.76 (dd, 2H, $J = 7.2, 2.9$ Hz).

^{13}C NMR (90 MHz, CDCl_3) δ 35.0, 45.8, 47.3, 52.2, 56.5, 67.1, 67.3, 120.1 (2C), 125.0 (2C), 127.1 (2C), 127.8 (2C), 128.5 (2C), 128.6 (2C), 135.3, 141.4 (2C), 143.6 (2C), 156.0, 166.7, 171.7, 200.7.

HRMS (ESI+) Calcd for $\text{C}_{29}\text{H}_{27}\text{NNaO}_7$ $[\text{M} + \text{Na}]^+$: 524.1680, found 524.1663.

HPLC: 93% *ee*. sample preparation: 1 mg/mL in MeOH,; column: A_NP_5-AmyCoat (250 mm \times 4.6 mm), normal phase: hexane/EtOH = 60/40, flow: 1 mL/min, 30 $^\circ\text{C}$; injection: 5 μL ; results: RT = 21.822 (*R*, Area: 3.4%), 26.681 (*S*, Area: 96.6%).

(*S*)-2-(2-(1-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl)-1,3-dithiolan-2-yl)acetic acid (*S*)-186



$\text{C}_{24}\text{H}_{25}\text{NO}_6\text{S}_2$
Exact M = 487.1123
M = 487.58 $\text{g}\cdot\text{mol}^{-1}$

To a flask containing L- γ -amino- β -ketoester (*S*)-**180** (1.004 g, 2.00 mmol, 1 eq.) under argon at room temperature was added 1,2-ethanedithiol (1.7 mL, 20.0 mmol, 10 eq.), followed by addition of $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.74 mL, 6.00 mmol, 3 eq.) dropwise. The resulting mixture was stirred for 3 days at room temperature. The reaction was quenched with water (20 mL), extracted with EtOAc (20 mL \times 3). The combined organic phase was washed with brine (20 mL \times 3), then dried over MgSO_4 , filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 80/20, 70/30, 50/50) to give the desired L-*N*-Fmoc- β -dithioketal acid (*S*)-**186** (828.7 mg, 85%) as a white solid.

TLC: $R_f = 0.10$ (petroleum ether/EtOAc = 75/25)

Mp. 59-62 $^\circ\text{C}$

$[\alpha]_D^{25} = -15.5$ (*c* 0.50, CHCl_3)

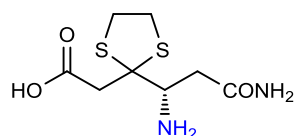
IR (ATR) ν 3321, 2952, 1730, 1513, 1450, 1334, 1243, 1055, 758, 741 cm^{-1}

^1H NMR (400 MHz, 323 K, CDCl_3) δ 2.64 (dd, 1H, $J = 14.8, 10.0$ Hz, *ABX*), 3.04-3.09 (m, 2H), 3.19-3.27 (m, 5H), 3.63 (s, 3H), 4.22 (t, 1H, $J = 6.8$ Hz), 4.41 (d, 2H, $J = 6.8$ Hz), 4.88 (ddd pseudo brs, 1H, *ABX*), 5.43 (brs, 1H) and 5.82 (brs, rotamer), 7.30 (t, 2H, $J = 7.2$ Hz), 7.37 (t, 2H, $J = 7.2$ Hz), 7.59 (m pseudo brs, 2H), 7.73 (t, 2H, $J = 7.2$ Hz), 9.02 (brs, 1H).

^{13}C NMR (100 MHz, 323 K, CDCl_3) δ 37.6, 39.9, 40.6, 46.8, 47.4, 52.1, 55.7, 67.2, 71.3, 120.0 (2C), 125.3 (2C), 127.2 (2C), 127.7 (2C), 141.4 (2C), 143.9, 144.1, 156.3, 171.6, 173.5.

HRMS (ESI+) Calcd for $\text{C}_{24}\text{H}_{25}\text{NNaO}_6\text{S}_2$ [$\text{M} + \text{Na}$] $^+$: 510.1015, found 510.0992.

2-(2-(1,3-Diamino-3-oxopropyl)-1,3-dithiolan-2-yl)acetic acid (*S*)-190



$\text{C}_8\text{H}_{14}\text{N}_2\text{O}_3\text{S}_2$
Exact M = 250.0446
M = 250.33 $\text{g}\cdot\text{mol}^{-1}$

To a flask containing *L*-*N*-Fmoc- β -dithioketal acid (*S*)-**186** (830 mg, 1.70 mmol, 1 eq.) was added a solution of 28% NH_4OH (48 mL, 336 mmol, ~ 200 eq.). The mixture was stirred for overnight (24 h) at room temperature, then filtered through a filter Buchner funnel to remove dibenzofulvene (DBF) and the solid was washed with 28% NH_4OH (3×5 mL) to give the filtered liquid. The filtered liquid was extracted with Et_2O (2×20 mL) to remove the residue of dibenzofulvene, and the aqueous phase was concentrated under reduced pressure to give a pure primary amide (*S*)-**190** (425.9 mg, 100%) as a pale-yellow solid and used without further purification directly in next step.

TLC: $R_f = 0.10$ ($\text{MeOH}/\text{CH}_2\text{Cl}_2 = 10/90$)

Mp. 86-88 $^\circ\text{C}$

$[\alpha]_D^{22} = -13.3$ (c 0.50, CHCl_3)

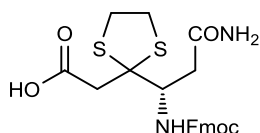
IR (ATR) ν 3321, 3160, 2922, 1667, 1563, 1382, 1278, 1146, 1006, 679 cm^{-1}

^1H NMR (360 MHz, D_2O) δ 2.48 (dd, $J = 16.6, 10.4$ Hz, rotamer, *ABX*) and 2.65 (dd, 1H, $J = 16.6, 10.4$ Hz, *ABX*), 2.78 (dd, $J = 16.6, 2.9$ Hz, rotamer, *ABX*) and 2.99 (dd, 1H, $J = 16.6, 2.9$ Hz, *ABX*), 3.05 (d, 1H, $J = 16.9$ Hz), , 3.16 (d, 1H, $J = 16.9$ Hz), 3.27-3.43 (m, 4H), 4.07 (dd, 1H, $J = 10.4, 2.9$ Hz, rotamer, *ABX*) and 4.12 (dd, 1H, $J = 10.4, 2.9$ Hz, *ABX*).

^{13}C NMR (90 MHz, D_2O) δ 35.7 and 36.6 (rotamer), 39.4, 39.5, 49.2, 55.7 and 56.4 (rotamer), 68.1 (rotamer) and 69.5, 174.9, 177.2.

HRMS (ESI+) Calcd for $\text{C}_8\text{H}_{15}\text{N}_2\text{O}_3\text{S}_2$ $[\text{M} + \text{H}]^+$: 251.0519, found 251.0519.

2-(2-(1-(((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-amino-3-oxopropyl)-1,3-dithiolan-2-yl)acetic acid **191**



$\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_5\text{S}_2$
Exact M. = 472.1127
M. = 472.57 $\text{g}\cdot\text{mol}^{-1}$

To an ice cold solution of L- β -amino primary amide (*S*)-**190** (425.9 mg, 1.70 mmol, 1 eq.) in water (30 mL) was added k_2CO_3 (375.9 mg, 2.72 mmol, 1.6 eq.), then followed by addition of a solution of FmocCl (483.8 mg, 1.87 mmol, 1.1 eq.) over 10 min. The resulting mixture was stirred for overnight (18-24 h) at room temperature, then diluted with sat. NaHCO_3 (10 mL), extracted with Et_2O (50 mL \times 2) to give the aqueous phase. The aqueous phase was acidified with 4 M HCl until = 2-3, then with EtOAc (50 mL \times 3) to give the organic phase. The combined organic phase was dried over MgSO_4 , filtered and concentrated under reduced pressure to give a pure L-*N*-Fmoc-*m*PyrAA (*S*)-**191** (560.7 mg, 70%) as a white solid and used without further purification.

TLC: R_f = 0.20 (MeOH/ CH_2Cl_2 = 20/80)

$[\alpha]_D^{15} = -13.5$ (c 0.50, CHCl_3)

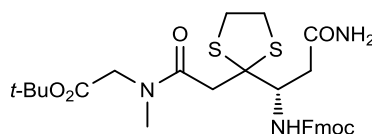
Mp. 99 $^\circ\text{C}$, decarboxylation

IR (ATR) ν 3331, 2926, 1709, 1661, 1514, 1448, 1411, 1334, 1245, 756, 741 cm^{-1}

^1H NMR (360 MHz, $\text{MeOD}-d_4$) δ 2.51-2.59 (dd pseudo m, 1H, *ABX*), 2.93-3.04 (m, 2H), 3.18 (dt, 1H, J = 16.9 Hz), 3.22-3.30 (m, 4H), 4.26 (t, 1H), 5.90 (d, 1H, J = 7.2 Hz), 4.29 (dd, 1H, J = 11.6, 7.2 Hz), 4.41 (dd, 1H, J = 11.6, 7.2 Hz), 4.84-4.91 (m, 1H, combined with water), 7.32-7.34 (t, 2H, J = 8.4 Hz), 7.39 (t, 2H, J = 8.4 Hz), 7.64-7.67 (m, 2H), 7.79 (d, 2H, J = 8.4 Hz).

^{13}C NMR (90 MHz, $\text{MeOD}-d_4$) δ 39.3, 40.4, 41.4, 47.7, 48.4, 57.1, 67.8, 72.9, 120.9 (2C), 126.2 (2C), 128.2 (2C), 128.7 (2C), 142.5 (2C), 145.1, 145.3, 158.5, 173.5, 176.0.

HRMS (ESI+) Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{NaO}_5\text{S}_2$ $[\text{M} + \text{Na}]^+$: 495.1019, found 495.1001.

tert-Butyl**(S)-N-(2-(2-(1-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-amino-3-oxopropyl)-1,3-dithiolan-2-yl)acetyl)-N-methylglycinate (S)-189**

C₃₀H₃₇N₃O₆S₂
 Exact Mass: 599.2124
 M. = 599.76 g·mol⁻¹

To a solution of L-N-Fmoc-mPyrAA (S)-**191** (472.5 mg, 1.00 mmol, 1 eq.) in CH₂Cl₂ (20 mL) under argon was added H-Sar-Ot-Bu·HCl (199.8 mg, 1.10 mmol, 1.1 eq.), PyBroP (512.8 mg, 1.10 mmol, 1.1 eq.) and dropwise DIEA (516.9 mg, 4.00 mmol, 4 eq.), respectively. The resulting mixture was stirred at room temperature for overnight (16 h). Diluted with CH₂Cl₂ (20 mL) and the solution was subsequently washed with 1 M HCl (2 × 20 mL), sat. NaHCO₃ (2 × 20 mL) and brine (20 mL), then dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 50/50, EtOAc = 100, EtOAc/MeOH = 90/10) to give the desired dipeptide L-mPyrAA-Sar (S)-**189** (538.9 mg, 90%) as a white solid.

TLC: $R_f = 0.61$ (EtOAc/MeOH = 90/10)

Mp. 94-97 °C

$[\alpha]_D^{23} = -12.4$ (c 0.50, CHCl₃)

IR (ATR) ν 3446, 3326, 3214, 2977, 2928, 1721, 1661, 1512, 1450, 1403, 1370, 1243, 1157, 758, 742 cm⁻¹

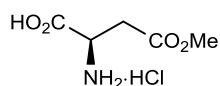
¹H NMR (360 MHz, CDCl₃) δ 1.41 (s, 9H) and 1.43 (s, rotamer), 2.39 (dd, rotamer, ABX) and 2.50 (dd, 1H, $J = 14.4, 10.1$ Hz, ABX), 2.89-3.00 (m, 4H), 3.11 (d, 1H, $J = 16.6$ Hz), 3.17 (pseudo brs, 4H), 3.26 (d, 1H, $J = 16.6$ Hz), 3.82 (d, 1H, $J = 16.9$ Hz), 4.12 (d, 1H, $J = 16.9$ Hz), 4.18 (t, 1H, $J = 7.2$ Hz), 4.24-4.36 (m, 2H), 4.74-4.85 (ddd pseudo m, 1H, ABX) and 5.01-5.07 (m, rotamer), 5.78 (brs, rotamer) and 5.88 (brs, 1H), 6.32 (dd, 1H, $J = 10.1$ Hz), 6.62 (brs, 1H) and 6.64 (brs, rotamer), 7.23-7.26 (m, 2H), 7.34 (t, 2H, $J = 7.2$ Hz), 7.57 (t, 2H, $J = 7.2$ Hz), 7.69 (d, 2H, $J = 7.2$ Hz).

¹³C NMR (90 MHz, CDCl₃) δ 28.0 (3C), 35.2 (rotamer) and 36.9, 39.2 (2C), 40.1, 45.2, 47.1, 50.5 and 52.7 (rotamer), 56.1 (rotamer) and 56.2, 66.8, 72.3 and 72.4 (rotamer), 81.9 and 82.7 (rotamer), 119.8 (2C), 125.2, 125.3, 127.0 (2C), 127.5 (2C), 141.1 (2C), 143.8, 144.0, 156.8, 167.8 (rotamer) and 168.2, 170.4, 170.5, 173.1.

HRMS (ESI+) Calcd for C₃₀H₃₇N₃NaO₆S₂ [M + Na]⁺: 622.2016, found 622.1993.

HPLC: 80% *ee*. sample preparation: 1 mg/mL in MeOH,; column: A_RP_5-CelluloseCoat (250 mm × 4.6 mm), normal phase: CH₃CN = 100%, flow: 1 mL/min, 5 °C; injection: 5 μL; results: RT = 5.265 (*R*, Area: 10%), 6.247 (*S*, Area: 90%).

(*R*)-2-Amino-4-methoxy-4-oxobutanoic acid hydrochloride (*R*)-175



C₅H₁₀ClNO₄
Exact M = 183.0298
M = 183.59 g·mol⁻¹

Following Reddy's procedure⁴⁷⁴

To a solution of D-aspartic acid (6.655 g, 50.00 mmol, 1 eq.) in MeOH (50.0 mL, 1.23 mol, ~24.6 eq.) at -10 °C (ice-salt bath) under argon was dropwise added thionyl chloride (SOCl₂, 5.10 mL, 70.0 mmol, 1.4 eq.). The cooling bath was then removed, and the resulting mixture was slowly warmed to room temperature and stirred for 25-30 min, and then diluted with ice cold diethyl ether (150 mL), upon cooling and shaking, precipitated as a white solid, which was filtered immediately and washed with ice-cold diethyl ether (20 mL). The solid was collected and dried to give the desired pure D-Asp(β-OMe)-hydrochloride (***R***-175 (7.89 g, 86%) a white power and used without further purification.

Mp = 189-191 °C, decarboxylation

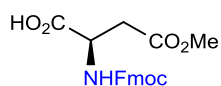
[α]_D²⁴ = -7.8 (*c* 0.50, H₂O)

IR (ATR) ν 2878, 2640, 1739, 1720, 1592, 1499, 1440, 1377, 1352, 1239, 1203, 1142, 1097, 1069, 835, 821 cm⁻¹

¹H NMR (360 MHz, D₂O) δ 3.08-3.12 (pseudo m, 2H), 3.70 (s, 3H) and 3.79 (rotamer), 4.33-4.39 (pseudo m, 1H).

¹³C NMR (90 MHz, D₂O) δ 33.6 (rotamer) and 33.7, 49.2, 52.9 and 53.9 (rotamer), 170.7 and 170.8 (rotamer), 171.8 and 173.1 (rotamer).

HRMS (ESI+) Calcd for C₅H₁₀NO₄⁺ [M]⁺: 148.0583, found 148.0605.

(R)-2-(((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-4-methoxy-4-oxobutanoic acid (R)-179³

C₂₀H₁₉NO₆
 Exact M = 369.1212
 M. = 369.37 g·mol⁻¹

To an ice cold solution of D-Asp(β-OMe)-hydrochloride (**R**)-**175** (1.836 g, 10.0 mmol, 1 eq.) in water (20 mL) and dioxane (10 mL) was added Na₂CO₃ (2.211 g, 16.0 mmol, 1.6 eq.) at 0 °C, then followed by a solution of FmocCl (2.846 g, 11.0 mmol, 1.1 eq.) in dioxane (10 mL) dropwise over 10 min. The resulting mixture was slowly warmed to room temperature and stirred for overnight (16 h). The solution was evaporated under reduced pressure to remove most of dioxane, then extracted with ether (2 × 30 mL) to give the aqueous phase, which was acidified with 4 M HCl until pH = 2-3. The acidified solution was then extracted with ether with Et₂O (3 × 30 mL), and the combined organic layer was washed with brine (50 mL), dried over MgSO₄ and concentrated under reduced pressure gave the pure desired D-Fmoc-Asp(β-OMe)-H (**R**)-**179** (3.68 g, 100%) as a white solid and used without further purification directly in the next step.

TLC: $R_f = 0.11$ (EtOAc = 100), $R_f = 0.28$ (CH₂Cl₂/MeOH = 85/15)

Mp. 62-64 °C

$[\alpha]_D^{24} = -34.5$ (c 0.50, CHCl₃)

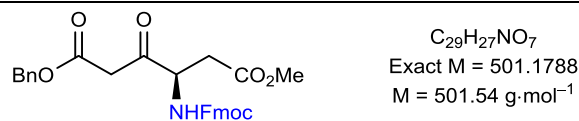
IR (ATR) ν 3334, 2952, 1716, 1517, 1439, 1209, 1178, 1052, 758, 738 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 2.58-2.82 (pseudo m, rotamer, ABX), 2.91 (dd, 1H, $J = 17.3, 4.3$ Hz, ABX), 3.09 (dd, 1H, $J = 17.3, 4.3$ Hz, ABX), 3.71 (s, 3H), 4.22 (t, 1H, $J = 6.8$ Hz), 4.35-4.46 (m, 2H) and 4.53 (pseudo brs, rotamer), 4.69-4.74 (ddd, 1H, $J = 8.3, 4.3, 4.3$ Hz, ABX) and 4.88-4.92 (m, rotamer), 5.99 (d, 1H, $J = 8.3$ Hz) and 6.29 (dd, rotamer), 7.28-7.33 (m, 2H), 7.37-7.41 (m, 2H), 7.55-7.60 (m, 2H), 7.73-7.76 (m, 2H), 9.46 (s, 1H).

¹³C NMR (90 MHz, CDCl₃) δ 36.3, 47.1, 50.3, 52.3, 67.5, 120.1 (2C), 125.2 (2C), 127.2 (2C), 127.8 (2C), 141.4 (2C), 143.7, 143.8, 156.3, 171.7, 175.3.

HRMS (ESI+) Calcd for C₂₀H₁₉NNaO₆ [M + Na]⁺: 392.1105, found 392.1100.

6-Benzyl 1-methyl (S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-oxohexanedioate (R)-180



Fmoc-UNCA (*R*)-**203** formation: To an ice cold solution of D-Fmoc-Asp(β-OMe)-H (*R*)-**179** (1.847 g, 5.00 mmol, 1 eq.) in anhydrous THF (20 mL) under argon was added triphosgene (593.5 mg, 2.00 mmol, 1.2 eq.). Then sym-collidine (1.2118 g, 6.00 mmol, 2 eq.) was added in two portions (~1.3 mL), of which the first portion (~0.6 mL) was added over 10 min at 0 °C (immediately white solid precipitated). The ice bath was then removed, the left portion of sym-collidine (~0.7 mL) was added over 20 min at room temperature. The resulting mixture was totally stirred 2 h, then filtered rapidly through a filter Buchner funnel to remove the collidine hydrochloride salt and the solid was washed with anhydrous THF (10 mL × 3) to give the filtered liquid as *solution A* (~50 mL).

Preparation of magnesium enolate salt **174** as *solution B*: In a separated flask, to an ice cold solution of monobenzyl malonate of monobenzyl malonate (1.359 g, 7.00 mmol 1.4 eq.) in anhydrous THF (20 mL) under argon was dropwise added a solution of 2.0 M isopropylmagnesium chloride in THF (7.0 mL, 14.00 mmol, 2.8 eq.). After stirred for 30 min at 0 °C, then heating at 50 °C for 30 min as *solution B*.

Condensation: To the ice cold *solution B* was then slowly added *solution A* at -10 °C over 30 min. The resulting mixture was stirred for overnight (16-18 h) and slowly warmed to room temperature. The reaction was then quenched with 1 M HCl (20 mL) at 0 °C and concentrated under reduced pressure to remove most of THF, then extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with sat. NaHCO₃ (50 mL) and brine (50 mL), then dried over MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 75/25, 70/30) gave the desired D-*N*-Fmoc-β-ketoester (*R*)-**180** (1.032 g, 42%, 97% *ee*) as a colorless oil, when stored in the fridge it turned into a waxy solid.

TLC: $R_f = 0.43$ (petroleum ether/EtOAc = 70/30)

$[\alpha]_D^{26} = +25.4$ (c 0.53, CHCl₃)

IR (ATR) ν 3321, 2948, 1714, 1692, 1528, 1448, 1315, 1257, 1098, 1005, 756, 738 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 2.81 (dd, 1H, $J = 17.3, 4.7$ Hz, ABX), 2.98 (dd, 1H, $J = 17.3, 5.0$ Hz,

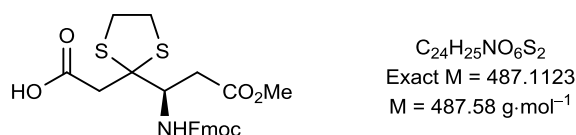
ABX), 3.62 (s, 2H), 3.66 (s, 3H), 4.21 (t, 1H, $J = 6.5$ Hz), 4.46 (dd, 1H, $J = 10.8, 6.5$ Hz), 4.55 (dd, 1H, $J = 10.8, 6.5$ Hz), 4.64 (ddd, 1H, $J = 9.0, 5.0, 4.7$ Hz, ABX), 5.11-5.21 (m, 2H), 6.00 (d, 1H, $J = 9.0$ Hz), 7.29-7.43 (m, 9H), 7.60 (d, 2H, $J = 7.2$ Hz), 7.77 (dd, 2H, $J = 7.2, 2.9$ Hz).

^{13}C NMR (90 MHz, CDCl_3) δ 35.0, 45.8, 47.2, 52.1, 56.5, 67.0, 67.2, 120.0 (2C), 124.9, 125.0, 127.1 (2C), 127.8 (2C), 128.4 (2C), 128.6 (2C), 135.3, 141.3 (2C), 143.6 (2C), 156.0, 166.7, 171.7, 200.7.

HRMS (ESI+) Calcd for $\text{C}_{29}\text{H}_{27}\text{NNaO}_7$ $[\text{M} + \text{Na}]^+$: 524.1680, found 524.1656.

HPLC: 97% *ee*. sample preparation: 1 mg/mL in MeOH; column: A_NP_5-AmyCoat (250 mm \times 4.6 mm), normal phase: hexane/EtOH = 60/40, flow: 1 mL/min, 30 $^\circ\text{C}$; injection: 5 μL ; results: RT = 21.723 (*R*, Area: 98.5%), 26.825 (*S*, Area: 1.5%).

(*R*)-2-(2-(1-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl)-1,3-dithiolan-2-yl)acetic acid (*R*)-186



To a flask containing *N*-Fmoc- β -ketoester (*R*)-**180** (1.004 g, 2.00 mmol, 1 eq.) under argon at room temperature under were added 1,2-ethanedithiol (1.7 mL, 20.0 mmol, 10 eq.) and followed by addition of $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.74 mL, 6.00 mmol, 3 eq.) dropwise. The resulting mixture was stirred for 3 days at room temperature. The reaction was quenched with water (20 mL), extracted with EtOAc (20 mL \times 3). The combined organic phase was washed with brine (20 mL \times 3), then dried over MgSO_4 , filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 80/20, 70/30, 50/50) gave the desired *N*-Fmoc- β -dithioketal acid (*R*)-**186** (823.0 mg, 85%) as a white solid.

TLC: $R_f = 0.10$ (petroleum ether/EtOAc = 75/25)

Mp. 57-60 $^\circ\text{C}$

$[\alpha]_D^{25} = +17.8$ (c 0.50, CHCl_3)

IR (ATR) ν 3667, 3312, 2979, 2966, 2913, 1719, 1511, 1453, 1408, 1333, 1284, 1240, 1227, 1054,

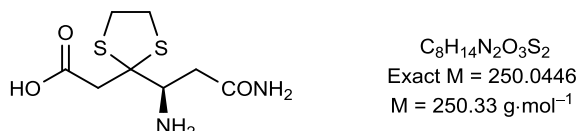
761, 738 cm^{-1}

^1H NMR (400 MHz, 323 K, CDCl_3) δ 2.64 (dd, 1H, $J = 14.8, 10.0$ Hz, ABX), 3.05-3.09 (m, 2H), 3.19-3.29 (m, 5H), 3.63 (s, 3H), 4.22 (t, 1H, $J = 6.8$ Hz), 4.41 (d, 2H, $J = 6.8$ Hz), 4.88 (ddd pseudo brs, 1H, ABX), 5.44 (brs, 1H) and 5.78 (brs, rotamer), 7.30 (t, 2H, $J = 7.2$ Hz), 7.37 (t, 2H, $J = 7.2$ Hz), 7.59 (m pseudo brs, 2H), 7.73 (t, 2H, $J = 7.2$ Hz), 9.09 (brs, 1H).

^{13}C NMR (100 MHz, 323 K, CDCl_3) δ 37.7, 39.9, 40.6, 46.8, 47.4, 52.1, 55.7, 67.2, 71.3, 120.0 (2C), 125.3 (2C), 127.2 (2C), 127.8 (2C), 141.4 (2C), 143.9, 144.1, 156.3, 171.5, 173.4.

HRMS (ESI+) Calcd for $\text{C}_{24}\text{H}_{25}\text{NNaO}_6\text{S}_2$ [$\text{M} + \text{Na}$] $^+$: 510.1015, found 510.1006.

2-(2-(1,3-Diamino-3-oxopropyl)-1,3-dithiolan-2-yl)acetic acid (*R*)-190



To a flask containing *N*-Fmoc- β -dithioketal acid (*R*)-**186** (2.04 g, 4.18 mmol, 1 eq.) was added a solution of 28% NH_4OH (50 mL, 418 mmol, ~ 100 eq.). The mixture was stirred for overnight (24 h) at room temperature, then filtered through a filter Buchner funnel to remove dibenzofulvene (DBF) and the solid was washed with 28% NH_4OH (10 mL \times 3) to give the filtered liquid. The filtered liquid was extracted with Et_2O (20 mL \times 2) to remove the residue of dibenzofulvene, and the aqueous phase was concentrated under reduced pressure to give a pure primary amide (*R*)-**190** (1.05 g, 100%) as a pale-yellow solid and used without further purification directly in the next step.

TLC: $R_f = 0.10$ (MeOH/ $\text{CH}_2\text{Cl}_2 = 10/90$)

Mp. 93-96 $^\circ\text{C}$

$[\alpha]_D^{22} = +21.7$ (c 0.50, CHCl_3)

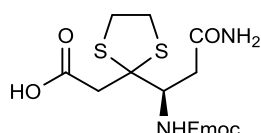
IR (ATR) ν 3339, 3156, 2922, 1667, 1557, 1379, 1277, 1176, 1013, 679 cm^{-1}

^1H NMR (360 MHz, D_2O) δ 2.48 (dd, $J = 16.6, 10.4$ Hz, rotamer, ABX) and 2.66 (dd, 1H, $J = 16.6, 10.4$ Hz, ABX), 2.78 (dd, $J = 16.6, 2.9$ Hz, rotamer, ABX) and 3.00 (dd, 1H, $J = 16.6, 2.9$ Hz, rotamer, ABX), 3.05 (d, 1H, = 16.6 Hz, with rotamer), 3.17 (d, 1H, = 16.6 Hz, with rotamer), 3.25-3.43 (m, 4H), 4.05 ($J = 10.4, 2.9$ Hz, rotamer, ABX) and 4.13 (dd, 1H, $J = 10.4, 2.9$ Hz, ABX).

^{13}C NMR (90 MHz, D_2O) δ 34.6 and 36.5 (rotamer), 39.4, 39.5 (rotamer) and 39.6, 49.3, 55.6 and 56.4 (rotamer), 68.1, 174.1, 177.0.

HRMS (ESI+) Calcd for $\text{C}_8\text{H}_{15}\text{N}_2\text{O}_3\text{S}_2$ $[\text{M} + \text{H}]^+$: 251.0519, found 251.0517.

2-(2-(1-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-amino-3-oxopropyl)-1,3-dithiolan-2-yl)acetic acid (*R*)-191



$\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_5\text{S}_2$
Exact M. = 472.1127
M. = 472.57 $\text{g}\cdot\text{mol}^{-1}$

To an ice cold solution of D- β -amino primary amide (*R*)-**190** (302.6 mg, 1.21 mmol, 1 eq.) in water (30 mL) was added K_2CO_3 (267.5 mg, 1.94 mmol, 1.6 eq.), then followed by addition of a solution of FmocCl (344.3 mg, 1.33 mmol, 1.1 eq.) over 10 min. The resulting mixture was stirred for overnight (18-24 h) at room temperature, then diluted with sat. NaHCO_3 (10 mL), extracted with Et_2O (50 mL \times 2) to give the aqueous phase. The aqueous phase was acidified with 4 M HCl until = 2-3, then with EtOAc (50 mL \times 3) to give the organic phase. The combined organic phase was dried over MgSO_4 , filtered and concentrated under reduced pressure to give the pure D-*N*-Fmoc-mPyrAA (*R*)-**191** (398.0 mg, 70%) as a white solid and used without further purification.

TLC: R_f = 0.20 ($\text{MeOH}/\text{CH}_2\text{Cl}_2$ = 20/80)

$[\alpha]_D^{27} = +6.6$ (c 0.30, MeOH)

Mp. 99 $^\circ\text{C}$, decarboxylation

IR (ATR) ν 3345, 1738, 1693, 1670, 1520, 1451, 1404, 1392, 1258, 1237, 184, 1152, 1144, 970, 845, 763, 743, 724 cm^{-1}

^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ 2.54 (dd, 1H, J = 14.0, 11.2 Hz, ABX), 2.98-3.017 (m, 2H, mixed with 3.0 (d, 1H, J = 16.8 Hz)); 2.98-3.017 (dd 1H, J = 14.0, 2.4 Hz, ABX), 3.16 (d, 1H, J = 16.8 Hz), 3.19-3.29 (m, 4H), 4.20 (dd pseudo t, 1H, J = 7.2, 6.8 Hz), 4.29 (dd, 1H, J = 10.4, 6.8 Hz), 4.40 (dd, 1H, J = 10.4, 7.2 Hz), 4.83 (dd, 1H, J = 11.2, 2.4 Hz, ABX), 7.30 (t, 2H, J = 7.2 Hz), 7.37 (t, 2H, J = 7.2 Hz), 7.64 (t, 2H, J = 6.4 Hz), 7.77 (d, 2H, J = 7.2 Hz)

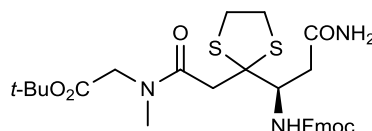
^{13}C NMR (100 MHz, $\text{MeOD}-d_4$) δ 39.3, 40.4, 41.4, 47.7, 48.5, 57.1, 67.8, 72.9, 120.9 (2C), 126.2

(2C), 128.2 (2C), 128.7 (2C), 142.6 (2C), 145.2, 145.4, 158.5, 173.5, 176.0.

HRMS (ESI+) Calcd for $C_{23}H_{24}N_2NaO_5S_2$ $[M + Na]^+$: 495.1019, found 495.1001.

tert-Butyl

(R)-N-(2-(2-(1-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-amino-3-oxopropyl)-1,3-dithiolan-2-yl)acetyl)-N-methylglycinate (R)-189



$C_{30}H_{37}N_3O_6S_2$
 Exact Mass: 599.2124
 M. = 599.76 g·mol⁻¹

To a solution of D-N-Fmoc-mPyrAA (**R**)-**191** (472.6 mg, 1.00 mmol, 1 eq.) in CH_2Cl_2 (20 mL) under argon was added H-Sar-Ot-Bu·HCl (199.8 mg, .110 mmol, 1.1 eq.), PyBroP (512.8 mg, 1.10 mmol, 1.1 eq.) and dropwise DIEA (516.9 mg, 4.00 mmol, 4 eq.), respectively. The resulting mixture was stirred at room temperature for overnight (16 h). Diluted with CH_2Cl_2 (20 mL) and the solution was subsequently washed with 1 M HCl (20 mL × 2), sat. $NaHCO_3$ (20 mL × 2) and brine (20 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 50/50, EtOAc =100, EtOAc/MeOH = 90/10) gave the pure desired dipeptide D-mPyrAA–Sar (**R**)-**189** (539.6 mg, 90%) as a white solid.

TLC: R_f = 0.61 (EtOAc/MeOH = 90/10)

Mp. 93-96 °C

$[\alpha]_D^{23}$ = +13.9 (*c* 0.50, $CHCl_3$)

IR (ATR) ν 3449, 3331, 3205, 2978, 2929, 1721, 1661, 1512, 1450, 1403, 1368, 1244, 1157, 761, 742 cm^{-1}

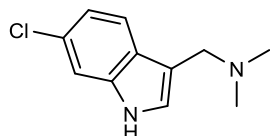
¹H NMR (360 MHz, $CDCl_3$) δ 1.42 (s, 9H) and 1.44 (s, rotamer), 2.38 (dd, rotamer, ABX) and 2.49 (dd, 1H, J = 14.4, 10.1 Hz, ABX), 2.90-3.01 (m, 4H), 3.13 (d, 1H, J = 16.6 Hz), 3.18 (pseudo brs, 4H), 3.27 (d, 1H, J = 16.6 Hz), 3.82 (d, 1H, J = 17.3 Hz), 4.14 (d, 1H, J = 17.3 Hz), 4.20 (t, 1H, J = 7.2 Hz), 4.27-4.38 (m, 2H), 4.74-4.83 (ddd pseudo m, 1H) and 4.98-5.04 (m, rotamer), 5.79 (brs, 1H), 5..29 (dd, 1H, J = 10.1 Hz) and 6.35 (brs, rotamer), 6.60 (brs, 1H) and 6.63 (brs, rotamer), 7.26-7.29 (m, 2H) , 7.35 (t, 2H, J = 7.2 Hz), 7.58 (t, 2H, J = 7.2 Hz), 7.71 (d, 2H, J = 7.2 Hz).

^{13}C NMR (90 MHz, CDCl_3) δ 28.0 (3C), 35.2 (rotamer) and 37.0, 39.2 and 39.3 (rotamer), 39.5, 40.1 (2C), 45.2, 47.1, 50.5 and 52.7 (rotamer), 56.3, 66.8, 72.3 and 72.4 (rotamer), 82.0 and 82.8 (rotamer), 119.8 (2C), 125.2, 125.3, 127.0 (2C), 127.6 (2C), 141.2 (2C), 143.8, 144.0, 156.8, 167.8 (rotamer) and 168.2, 170.4 (rotamer) and 170.5, 173.0

HRMS (ESI+) Calcd for $\text{C}_{30}\text{H}_{37}\text{N}_3\text{NaO}_6\text{S}_2$ $[\text{M} + \text{Na}]^+$: 622.2016, found 622.1992.

HPLC: 90% *ee*. sample preparation: 1 mg/mL in MeOH,; column: A_RP_5-CelluloseCoat (250 mm \times 4.6 mm), normal phase, CH_3CN = 100%, flow: 1 mL/min, 5 $^\circ\text{C}$; injection: 5 μL ; results: RT = 5.249 (*R*, Area: 95%), 6.247 (*S*, Area: 5%).

1-(6-Chloro-1*H*-indol-3-yl)-*N,N*-dimethylmethanamine **211**



$\text{C}_{11}\text{H}_{13}\text{ClN}_2$
Exact M. = 208.0767
M = 208.69 $\text{g}\cdot\text{mol}^{-1}$

To an ice cold solution of 37% HCHO aq. (1.13 mL, 15.00 mmol, 1.5 eq.) in AcOH (10 mL) was added 40% $\text{Me}_2\text{NH}_{\text{aq}}$. (2.14 mL, 17.00 mmol, 1.7 eq.). After stirred for 10 min at 0 $^\circ\text{C}$, a solution of 6-Cl-indole (1.516 g, 10.00 mmol, 1 eq.) in AcOH (5.0 mL) was added. The resulting mixture was stirred for 4 h at 0 $^\circ\text{C}$ until completed. The resulting mixture was poured into ice water (50 mL). Lots of pale-yellow solid was precipitated, filtered and washed with water (3 \times 20 mL). The filtered solid was dissolved in ether, dried over MgSO_4 , filtered, and evaporated under reduced pressure to give the pure desired 6-Cl-gamine **211** without further purification as a white solid (fraction 1, 1.013 mg, 49%). The aqueous phase was basified with 1 M NaOH until pH > 10, extracted with ether (50 mL \times 2), and the combined organic phase was then washed with brine, dried over MgSO_4 , filtered, and evaporated under reduced pressure to give fraction 2, which was purified by flash chromatography on silica gel ($\text{MeOH}/\text{CH}_2\text{Cl}_2$ = 5/95, 10/90, then with $\text{MeOH}/\text{CH}_2\text{Cl}_2/\text{Et}_3\text{N}$ = 10/90/1) to give the pure desired gramine as a pale-yellow solid (fraction 2, 700 mg, 33%). Fraction 1 and 2 were combined to give 82% overall yield.

TLC: R_f = 0.35 (petroleum ether/EtOAc = 60/40)

Mp = 134-137 $^\circ\text{C}$

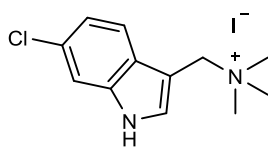
IR (ATR) ν 2938, 2860, 2817, 2775, 1542, 1452, 1341, 1327, 1229, 1167, 995, 9020, 853, 821, 795, 422 cm^{-1}

^1H NMR (360 MHz, CDCl_3) δ 2.29 (s, 6H), 3.60 (s, 2H), 6.95 (d, 1H, $J = 1.8$ Hz), 7.06 (dd, 1H, $J = 10.1, 1.8$ Hz), 7.20 (d, 1H, $J = 1.4$ Hz), 7.57 (d, 1H, $J = 8.3$ Hz), 9.32 (brs, 1H).

^{13}C NMR (90 MHz, CDCl_3) δ 45.3, 54.3, 111.2, 112.8, 120.0, 120.2, 124.8, 126.5, 127.8, 136.7.

HRMS (ESI+) Calcd for $\text{C}_{11}\text{H}_{14}\text{ClN}_2$ [$\text{M} + \text{H}$] $^+$: 209.0840, found 209.0831.

(6-Chloro-1H-indol-3-yl)-N,N,N-trimethylmethanaminium iodide 212



$\text{C}_{12}\text{H}_{16}\text{ClIN}_2$
Exact M. = 350.0047
M = 350.63 $\text{g}\cdot\text{mol}^{-1}$

To an ice cold solution of **6-Cl-gramine 211** (834.7 mg, 4.00 mmol, 1 eq.) in THF (12 mL) was added MeI (851.6 mg, 6.00 mmol, 1.5 eq). The mixture was stirred for 5 min at 0 °C then warmed to room temperature for 1 h, completed. Diluted with 3 times volume of petane (36 mL), precipitated and filtered. The filtered solid was washed with petane (10 mL) to give the quaternary salt **212** (2.10 g) in quantitative yield as a pale-yellow solid after dried. This compound was not stable and decomposed on storage. It was usually prepared and used immediately in the next step.

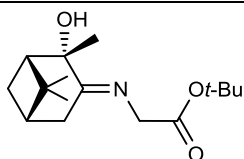
Mp = 154 °C, decomposition.

IR (ATR) ν 3215, 1616, 1535, 1470, 1452, 1408, 1292, 1107, 1060, 906, 807 cm^{-1}

^1H NMR (360 MHz, $\text{DMSO}-d_6$) δ 3.50 (s, 9H), 4.71 (s, 1H), 4.83 (s, 1H), 7.15 (dddd, $J = 10.4, 3.6, 1.8$ Hz), 7.54 (t, 1H, $J = 1.8$ Hz), 7.77 (dd, 1H, $J = 13.7, 2.9$ Hz), 7.90 (dd, 1H, $J = 21.2, 8.6$ Hz), 11.76 (s).

^{13}C NMR (90 MHz, $\text{DMSO}-d_6$) δ 51.3 and 54.5 (t and t, rotamer), 60.3 and 58.7 (rotamer), 101.9 and 102.2 (rotamer), 111.8, 120.2 and 120.3 (rotamer), 120.6, 126.6, 126.7 and 126.8 (rotamer), 131.4 and 131.6 (rotamer), 136.5 and 136.6 (rotamer).

HRMS (ESI+) : found [$\text{C}_9\text{H}_7\text{ClN}^+$] 164.0246, decomposition.

tert-Butyl**2-(((1*S*,2*S*,5*S*,*E*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylidene)amino)acetate **20****

$C_{16}H_{27}NO_3$
 Exact M. = 281.1991
 M = 281.40 g·mol⁻¹

Step (1) Basification of H-Gly-*Ot*-Bu hydrochloride salt: To an ice cold solution of H-Gly-*Ot*-Bu hydrochloride salt (1.2070 g, 7.20 mmol, 1.2 eq.) in toluene (10 mL) was added Et₃N (728.6 mg, 7.20 mmol, 1.2 eq.). After stirred for 1 h at 0 °C, then filtered and washed with toluene (5.0 mL).

Step (2): To a solution of (1*S*,2*S*,5*S*)-(+)-2-hydroxy-3-pinanone (1.0094 g, 6.00 mmol, 1 eq) in toluene (20.0 mL) was added BF₃·Et₂O (80 μL 0.06 mmol, 0.01 eq.), and a filtered solution of step (1). The resulting mixture was refluxed (oil bath, 135 °C) for overnight (16 h), then cooling down and evaporated under reduced pressure. Flash chromatography on silica gel (ether/petroleum ether = 10/90, 20/80, 30/70, 50/50) gave the desired Gly-pinanone imine **20** (950.3 mg, 57%) as a pale-yellow oil.

TLC: R_f = 0.30 (ether/petroleum ether = 30/70)

$[\alpha]_D^{25}$ = +11.1 (c 1.48, CHCl₃)

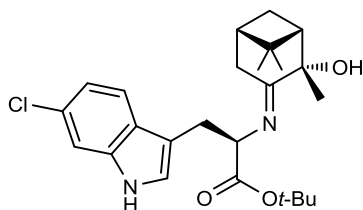
IR (ATR) ν 3434, 2979, 2920, 1737, 1655, 1475, 1368, 1153 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 0.84 (s, 3H), 1.29 (s, 3H), 1.45 (s, 9H), 1.48 (s, 1H), 1.54 (d, 1H), 1.97-2.06 (m, 2H), 2.37-2.34 (m, 1H), 2.38-2.51 (m, 2H), 2.76 (brs, 1H), 4.00-4.10 (m, 2H).

¹³C NMR (90 MHz, CDCl₃) δ 23.0, 27.4, 28.19 (2C), 28.3, 38.3, 38.6, 50.4, 53.5, 76.6, 81.3, 169.3, 179.7

HRMS (ESI+) Calcd for C₁₆H₂₇NNaO₃ [M + Na]⁺: 304.1883, found 304.1872.

tert*-Butyl(*R*)-3-(6-chloro-1*H*-indol-3-yl)-2-(((1*S*,2*S*,5*S*,*E*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylidene)amino)propanoate **213*



C₂₅H₃₃ClN₂O₃
 Exact M. = 444.2180
 M = 445.00 g·mol⁻¹

Step (1) preparation of fresh LDA solution: To a solution of DIPA (178.1 mg, 1.76 mmol, 2.2 eq.) in THF (5 mL) at $-78\text{ }^{\circ}\text{C}$ was added dropwise a solution of 1.6 M *n*-BuLi (1.1 mL, 1.76 mmol, 2.2 eq.). The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min.

Step (2) preparation of Li-enolate: To a solution of Gly-pinanone imine **20** (225.1 mg, 0.80 mmol, 1 eq.) in THF (2 mL) was slowly added to the well-prepared LDA solution of step (2) at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min.

Step (3): To a solution of fresh gramine quaternary ammonium salt **212** (420.7, 1.50 mmol, 1.5 eq.) in THF (10 mL) at $-78\text{ }^{\circ}\text{C}$ was slowly added the solution of Li-enolate from step (2). The resulting mixture was stirred for overnight ($> 12\text{ h}$), slowly warmed to room temperature, then quenched with sat. NH₄Cl (20 mL) in ice bath and extracted with EtOAc (50 mL \times 2), The combined organic phase was then washed with brine and dried over MgSO₄, then filtered and evaporated under reduced pressure (crude **213**, *dr* = 95:5 by ¹H NMR integration). Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 80/20, 70/30, 60/40) gave the desired (*R*)-Trp(6-Cl)-pinanone imine **213** (186.0 mg, 52%, *dr* $> 97:3$ by ¹H NMR integration) as a white solid.

TLC: *R_f* = 0.40 (petroleum ether/EtOAc = 50/50)

Mp = 63-65 $^{\circ}\text{C}$

[α]_D²² = +10.8 (*c* 0.50, CHCl₃)

IR (ATR) ν 3302, 2978, 2920, 1726, 1649, 1456, 1369, 1230, 1154 cm⁻¹

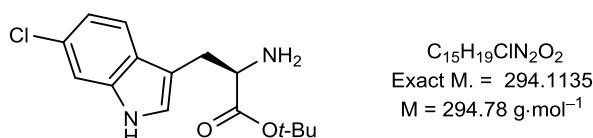
¹H NMR (360 MHz, CDCl₃) δ 0.17 (s, 3H), 1.15 (s, 3H), 1.33 (s, 3H), 1.42-1.45 (m, 10H), 1.76-1.81 (m, 1H), 1.88-1.95 (m, 2H), 2.17-2.23 (m, 1H), 2.42 (dd, 1H, *J* = 14.4, 9.7 Hz, *ABX*), 2.83 (brs, 1H), 3.21 (dd, 1H, *J* = 14.4, 9.7 Hz, *ABX*), 3.41 (dd, 1H, *J* = 14.4, 3.2 Hz, *ABX'*), 4.46 (dd, 1H, *J* = 9.7, 3.9 Hz, *ABX'*), 6.98 (d, 1H, *J* = 2.2 Hz), 7.05 (dd, *J* = 8.3, 1.8 Hz), 7.29 (d, 1H, *J* = 1.4 Hz),

7.52 (d, $J = 8.3$ Hz), 8.41 (brs, 1H).

^{13}C NMR (90 MHz, CDCl_3) δ 21.9, 27.2, 27.9, 28.1 (4C), 28.6, 28.5, 28.6, 33.0, 38.1, 38.2, 50.0, 63.2, 76.6, 81.6, 11.1, 112.3, 119.7, 120.1, 124.0, 126.1, 127.8, 13.6, 170.8.

HRMS (ESI+) Calcd for $\text{C}_{25}\text{H}_{34}\text{ClN}_3\text{O}_3$ [$\text{M} + \text{H}$] $^+$: 445.2252, found 445.2237.

tert-Butyl (*R*)-2-amino-3-(6-chloro-1*H*-indol-3-yl)propanoate **213**



To a solution of Trp(6-Cl)-pinanone imine **213** (111.3 mg, 0.25 mmol, 1 eq.) in THF (2 mL) was added a solution of 15% citric acid (300.0 mg, 1.60 mmol, 6 eq.) in water (2 mL). The mixture was stirred at room temperature for 24 h, then evaporated and diluted with water (5 mL). The aqueous phase was extracted with EtOAc (5 mL \times 2), subsequently then basified with sat. NaHCO_3 until pH > 8, then extracted with EtOAc (5 mL \times 2). The combined organic phase was dried over MgSO_4 , then filtered and evaporated under reduced pressure to give the pure desired H-Trp(6-Cl)-*Ot*-Bu **214** as a colorless oil (70.0 mg, 95%)

TLC: $R_f = 0.54$ (MeOH/ $\text{CH}_2\text{Cl}_2 = 5/95$)

$[\alpha]_D^{22} = -14.8$ (c 0.50, CHCl_3)

IR (ATR) ν 3363, 3161, 2977, 2932, 1722, 1620, 1456, 1368, 1249, 1152, 1062, 906, 845, 803 cm^{-1}

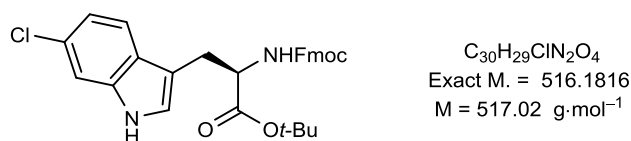
^1H NMR (360 MHz, CDCl_3) δ 1.43 (s, 9H), 1.86 (brs, 2H), 2.93 (dd, 1H, $J = 14.4, 7.9$ Hz, ABX), 3.20 (dd, 1H, $J = 14.4, 4.7$ Hz, ABX), 3.70 (dd, 1H, $J = 7.9, 4.7$ Hz, ABX), 6.95 (s, 1H), 7.05 (dd, 1H, $J = 8.6, 1.8$ Hz), 7.25 (d, 1H, $J = 1.4$ Hz), 7.50 (d, 1H, $J = 8.6$ Hz), 8.94 (brs, 1H).

^{13}C NMR (90 MHz, CDCl_3) δ 28.1 (3C), 30.7, 55.5, 81.4, 111.2, 111.4, 119.7, 120.4, 123.8, 126.2, 127.8, 136.7, 174.6.

HRMS (ESI+) Calcd for $\text{C}_{15}\text{H}_{20}\text{ClN}_2\text{NaO}_2$ [$\text{M} + \text{Na}$] $^+$: 317.1027, found 317.1019.

tert-Butyl

(R)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-chloro-1H-indol-3-yl)propanoate



To an ice cold solution of H-Trp(6-Cl)-Ot-Bu **213** (80 mg, 0.271 mmol, 1 eq.) in THF (5 mL) in ice bath was added FmocCl (77.6 mg, 10.30 mmol, 1.1 eq.), and Na₂CO₃ (46.0 mg, 0.43 mmol, 1.6 eq.) subsequently. The resulting mixture was stirred at room temperature for 24 h, then evaporated and diluted with water, extracted with EtOAc (30 mL × 3). The combined organic phase was washed with brine and dried over MgSO₄, filtered, concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 80/20, 70/30) gave the desired dipeptide Fmoc-Trp(6-Cl)-Ot-Bu (140.2 mg, 100%, > 94% *ee*) as a white solid.

TLC: $R_f = 0.33$ (petroleum ether/EtOAc = 80/20)

Mp = 74-78 °C

$[\alpha]_D^{25} = -9.6$ (*c* 0.50, CHCl₃)

IR (ATR) ν 3413, 3333, 2977, 1699, 1620, 1511, 1450, 1368, 1335, 1226, 1151, 1060, 738 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 1.41 (s, 9H), 3.20-3.32 (m, 2H), 4.19 (t, 1H, $J = 7.2$ Hz), 4.35-4.44 (m, 2H), 4.62-4.67 (m, 1H), 5.46 (d, H, $J = 7.9$ Hz), 6.84 (d, 1H, $J = 1.4$ Hz), 7.09 (dd, 1H, $J = 8.6$ Hz, 1.8 Hz), 7.28-7.32 (m, 3H), 7.39-7.43 (m, 2H), 7.51-7.57 (m, 3H), 7.76-7.78 (m, 2H), 8.36 (brs, 1H).

¹³C NMR (90 MHz, CDCl₃) δ 28.0 (4C), 47.2, 55.1, 67.0, 82.4, 110.5, 111.2, 119.8, 120.1 (2C), 120.4, 123.5, 125.2 (2C), 126.5, 127.2 (2C), 127.8 (2C), 128.0, 136.5, 141.3 (2C), 143.8 (2C), 155.9, 171.1.

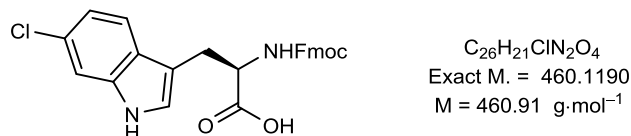
HRMS (ESI+) Calcd for C₃₀H₂₉ClN₂NaO₄ [M + Na]⁺: 539.1708, found 539.1691.

HPLC: >94% *ee*. Fmoc-Trp(6-Cl)-Ot-Bu sample preparation: 1 mg/L in EtOH.; column: A_NP_Lux Cellulose-2 (250 mm × 4.6 mm), normal phase: hexane/EtOH = 80/20, flow: 1 mL/min, 30 °C; injection: 5 μ L; results: RT = 8.025 (*R*, Area: 97%), 9.467 (*S*, Area: 3%).

Racemic one: sample preparation: 1 mg/L in MeOH; column: A_NP_Lux Cellulose-1 (250 mm × 4.6 mm), normal phase: hexane/EtOH = 80/20, flow: 1 mL/min, 30 °C; injection: 5 μ L; results: RT =

15.550 (*R*, Area: 50.1%), 13.706 (*S*, Area: 49.9%).

***R*-2-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-chloro-1*H*-indol-3-yl)propanoic acid
215**



To a solution of Fmoc-Trp(6-Cl)-Ot-Bu (80.0 mg, 0.155 mmol, 1 eq.) in CH₂Cl₂ (5 mL) was added Et₃SiH (36.0 mg, 0.31 mmol, 2 eq.), then followed by addition of TFA (0.48 mL, 6.2 mmol, 40 eq) at room temperature. The resulting mixture was stirred at room temperature for overnight (>18 h), completed. Evaporated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 80/20, 50/50, then MeOH/CH₂Cl₂ = 10/90) gave the desired Fmoc-Trp(6-Cl)-OH **215** (70.0 mg, 98%) as a white solid.

TLC: $R_f = 0.39$ (MeOH/CH₂Cl₂ = 10/90)

Mp = 128 °C, decarboxylation

$[\alpha]_D^{25} = +0.8$ (*c* 0.50, MeOH)

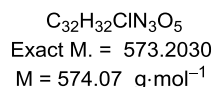
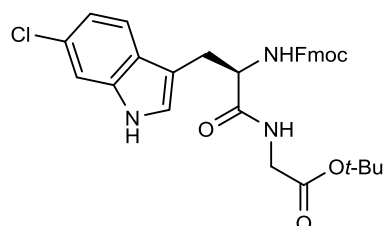
IR (ATR) ν 3418, 3325, 2922, 2852, 1702, 1618, 1515, 1450, 1337, 1215, 1061, 757, 740 cm⁻¹

¹H NMR (360 MHz, MeOD-*d*₃) δ 3.13 (dd, 1H, $J = 16.2, 8.6$ Hz, *ABX*; rotamer: 2.95); 3.32 (dd, 1H, $J = 16.2, 5.0$ Hz, *ABX*), 4.12 (t, 1H, $J = 7.2$ Hz; rotamer: 4.00), 4.19-4.34 (m, 2H), 4.48 (dd, 1H, $J = 8.6, 5.0$ Hz, *ABX*; rotamer: 4.34), 6.97 (dd, 1H, $J = 8.6, 1.8$ Hz), 7.09 (s, rotamer: 7.01), 7.21-7.27 (m, 2H), 7.33-7.37 (m, 3H), 7.43-7.56 (m, 3H), 7.74-7.76 (m, 2H).

¹³C NMR (90 MHz, MeOD-*d*₃) δ 28.5 (rotamer: 29.0), 48.3, 56.3 (rotamer: 56.6), 68.0 (rotamer: 68.2), 111.6, 112.1, 120.4, 120.8, 125.4, 126.2 (2C), 127.6, 128.1, 128.3, 128.7, 138.3, 142.5, 145.1, 145.2, 158.4, 175.4.

HRMS (ESI+) Calcd for C₂₆H₂₂ClN₂O₄ [M + H]⁺: 461.1263, found 461.1239.

HRMS (ESI-) Calcd for C₂₆H₂₀ClN₂O₄ [M - H]⁻: 459.1117, found 459.1089

tert-Butyl**(R)-2-(((9H-fluoren-9-yl)methyl)amino)-3-(6-chloro-1H-indol-3-yl)propanoyl)glycinate 216**

To a solution of Fmoc-Trp(6-Cl)-OH **215** (70.0 mg 0.15 mmol, 1 eq.) in CH₂Cl₂ (3 mL) at room temperature under argon was added PyBroP (77.0 mg, 0.17 mmol, 1.1 eq.) and H-Gly-Ot-Bu hydrochloride (27.6 mg, 0.17 mmol, 1.1 eq.), subsequently. Followed by addition of DIEA (77.5 mg, 0.60 mmol, 4 eq.) dropwise. The resulting mixture was stirred at room temperature for overnight (>16 h). The reaction was then diluted with CH₂Cl₂ (20 mL), and then washed with 1 M HCl (20 mL), sat. NaHCO₃ (20 mL) and sat. NaCl (20 mL), respectively. The combined organic phase was dried over MgSO₄, then filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 80/20, 70/30, 60/40, 50/50) gave peptide Fmoc-Trp(6-Cl)-Gly-Ot-Bu **216** (69.6 mg, 81%, > 94% *ee*) as a white solid.

TLC: R_f = 0.35 (petroleum ether/EtOAc = 60/40)

Mp = 163-166 °C

$[\alpha]_D^{27}$ = +9.5 (*c* 0.50, CHCl₃)

IR (ATR) ν 3437, 3299, 1731, 1695, 1651, 1529, 1451, 1258, 1234, 1161, 808, 757, 739 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 1.42 (s, 9H), 3.17 (dd, 1H, J = 13.3, 6.8 Hz, *ABX*), 3.17 (dd, 1H, J = 13.3, 9.7 Hz, *ABX*), 3.73-3.87 (m, 2H), 4.18 (1H, t, J = 6.8 Hz), 4.39-4.46 (m, 2H), 4.50 (pseudo brs, 1H, *ABX*'), 5.47 (brs, 1H), 6.20 (brs, 1H), 7.06 (s, 1H), 7.08 (dd, 1H, J = 8.6 Hz, J = 1.4 Hz), 7.27-7.31 (m, 2H), 7.33 (d, 1H, J = 1.4 Hz), 7.38-7.42 (m, 2H), 7.51-7.55 (m, 3H), 7.75-7.77 (m, 2H), 8.14 (brs, 1H).

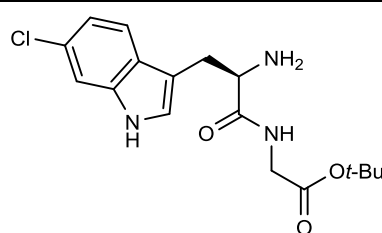
¹³C NMR (90 MHz, CDCl₃) δ 28.1 (3C), 28.4, 42.2, 47.2, 55.6, 67.2, 82.6, 110.6, 111.3, 119.7, 120.1 (2C), 120.6, 124.1, 125.2 (2C), 126.2, 127.2 (2C), 127.8 (2C), 128.2, 136.6, 141.4 (2C), 143.8 (2C), 156.2, 168.6, 171.4.

HRMS (ESI+) Calcd for C₃₂H₃₂ClN₃NaO₅ [M + Na]⁺: 596.1923, found 596.1895.

HPLC: > 94% *ee*. Fmoc-Trp(6-Cl)-Gly-O*t*-Bu **215** sample preparation: 1 mg/mL in MeOH,; column: A_NP_Lux Cellulose-2 (250 mm × 4.6 mm), normal phase: hexane/EtOH = 70/30, flow: 1 mL/min, 30 °C; injection: 2 μL; results: RT = 7.309 (*R*, Area: 97.2%), 13.706 (*S*, Area: 2.8%).

Racemic (±)-**215**: 0% *ee*. sample preparation: 1 mg/L in MeOH: column: A_NP_Lux Cellulose-2 (250 mm × 4.6 mm), normal phase: hexane/EtOH = 70/30, flow: 1 mL/min, 30 °C; injection: 5 μL; results: RT = 7.391 (*R*, Area: 50%), 13.706 (*S*, Area: 50%).

tert-Butyl (*R*)-(2-amino-3-(6-chloro-1*H*-indol-3-yl)propanoyl)glycinate **217**



C₁₇H₂₂ClN₃O₃
Exact M. = 351.1350
M = 351.83 g·mol⁻¹

To a solution of Fmoc-Trp-Gly(6-Cl)-O*t*-Bu **216** (57.4 mg, 0.10 mmol, 1 eq.) in MeOH (5 mL) was added diethylamine (146.2 mg, 2.00 mmol, 20 eq.) dropwise at room temperature. After stirred for 24 h, the mixture was concentrated under reduced pressure. Flash chromatography on silica gel (MeOH/CH₂Cl₂ = 5/95, 10/90) gave the desired H-Trp(6-Cl)-O*t*-Bu **215** (31.0 mg, 90%) as a white solid.

TLC: *R_f* = 0.36 (MeOH/CH₂Cl₂ = 5/95)

Mp = 128-131 °C

[α]_D²⁷ = 21.1 (*c* 0.50, CHCl₃)

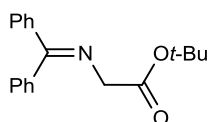
IR (ATR) ν 3311, 2978, 2929, 2854, 1736, 1656, 1524, 1456, 1366, 1234, 1157 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 1.47 (s, 9H), 1.77 (brs, 2H), 2.93 (dd, 1H, *J* = 14.4, 9.0 Hz, *ABX*), 3.34 (dd, 1H, *J* = 14.4, 4.0 Hz, *ABX*), 3.72 (dd, 1H, *J* = 9.0, 4.0 Hz, *ABX*), 3.93 (dd, 2H, *J* = 14.4, 4.0 Hz, *ABX*), 7.08 (d, 1H, *J* = 6.8 Hz), 7.07 (d, 1H, *J* = 6.8 Hz), 7.08 (d, 1H, *J* = 1.8 Hz), 7.35 (d, 1H, *J* = 1.8 Hz), 7.55 (d, 1H, *J* = 8.6 Hz), 7.73 (t, 1H, *J* = 5.0, 4.7 Hz), 8.34 (brs, 1H).

¹³C NMR (90 MHz, CDCl₃) δ 28.2 (3C), 30.7, 41.8, 55.5, 82.3, 111.3, 112.0, 120.0, 120.5, 123.9, 126.2, 128.3, 136.9, 169.2, 175.0.

HRMS (ESI+) Calcd for $C_{17}H_{22}ClN_3NaO_3$ $[M + Na]^+$: 374.1242, found 374.1231.

tert*-Butyl 2-((diphenylmethylene)amino)acetate **218*⁷¹⁷



$C_{19}H_{21}NO_2$
Exact M. = 295.1572
M = 295.38 g·mol⁻¹

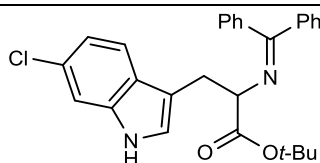
Following Fanelli's procedure⁷¹⁷

To a solution of H-Gly-O*t*-Bu hydrochloride (1.0058 g, 6.00 mmol, 1 eq.) in CH_2Cl_2 (20 mL) was added diphenylmethanimine (1.0874 mg, 6.00 mmol, 1 eq.). After stirred for overnight (16 h), then diluted with CH_2Cl_2 (10 mL), washed with water (30 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 95/5) gave the desired imine **218** (1.7701 g, 100%) as a white solid.

TLC: R_f = 0.26 (petroleum ether/EtOAc = 98/2)

¹H NMR (360 MHz, $CDCl_3$) δ 1.46 (s, 9H), 4.12 (s, 2H), 7.17-7.19 (m, 2H), 7.30-7.39 (m, 6H), 7.65-7.67 (m, 2H).

tert*-Butyl 3-(6-chloro-1*H*-indol-3-yl)-2-((diphenylmethylene)amino)propanoate **219*



$C_{28}H_{27}ClN_2O_2$
Exact M. = 458.1716
M = 458.99 g·mol⁻¹

Step (1) preparation of fresh LDA solution: To a solution of DIPA (202.4 mg, 2.00 mmol, 1 eq.) in THF (5.0 mL) at -78 °C was added dropwise a solution of 1.6 M *n*-BuLi in hexane (1.1 mL, 1.76 mmol, 1 eq.). The mixture was stirred at -78 °C for 30 min.

Step (2): To a solution of imine **218** (591.2 g, 2.00 mmol, 1.0 eq.) in THF (2 mL) was slowly added to the LDA solution of step (1) at -78 °C. The mixture was stirred at -78 °C for 30 min.

Step (3): To a solution of fresh gramine quaternary ammonium salt **211** (420.7, 1.50 mmol, 1.5 eq.) in THF (10 mL) at -78 °C was slowly added the solution of step (2). The resulting mixture was

stirred for overnight (12 h), slowly warmed to room temperature, then quenched with sat. NH_4Cl (25 mL) in ice bath and extracted with EtOAc (20 mL \times 3), The combined organic phase was then washed with brine and dried over MgSO_4 , then filtered and evaporated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 80/20, 70/30, 60/40) gave the desired imine (\pm)-**219** (770.3 mg, 84%) as a white solid.

TLC: R_f = 0.40 (petroleum ether/EtOAc = 50/50)

Mp = 61-63 °C

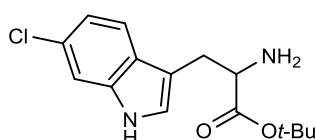
IR (ATR) ν 3422, 3349, 2977, 1717, 1618, 1455 1446, 1367, 1148, 694 cm^{-1}

^1H NMR (360 MHz, CDCl_3) δ 1.39 (s 1H), 3.18 (dd, 1H, J = 14.4, 8.6 Hz, ABX), 3.33 (dd, 1H, J = 14.4, 4.3 Hz, ABX), 4.24 (dd, 1H, J = 8.6, 4.3 Hz, ABX), 6.59 (d, 2H, J = 6.8 Hz), 6.87 (s, 2H), 7.11-7.16 (m, 3H), 7.20-7.37 (m, 5H), 7.55 (d, 2H, J = 7.7 Hz), 8.32 (brs, 1H).

^{13}C NMR (90 MHz, CDCl_3) δ 28.1 (3C), 29.2, 66.6, 81.3, 111.0, 112.2, 119.7, 119.8, 124.0, 126.4, 127.5, 127.6 (2C), 128.1 (2C), 128.2 (2C), 128.3, 128.8 (2C), 130.3, 136.1, 136.4, 139.6, 170.6, 171.4.

HRMS (ESI+) Calcd for $\text{C}_{28}\text{H}_{28}\text{ClN}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$: 459.1834, found 459.1817.

tert*-Butyl 2-amino-3-(6-chloro-1*H*-indol-3-yl)propanoate (\pm)-**214*



$\text{C}_{15}\text{H}_{19}\text{ClN}_2\text{O}_2$
Exact M. = 294.1135
M = 294.78 $\text{g}\cdot\text{mol}^{-1}$

To a solution of racemic imine (\pm)-**219** (651.7 mg, 1.42 mmol, 1 eq.) in THF (11 mL) was added a solution of 15% citric acid (1.637 g, 8.52 mmol, 6 eq.) in water (11.0 mL). The mixture was stirred for 6 h at room temperature. Then evaporated under reduced pressure and diluted with water (10 mL). The aqueous phase was extracted with EtOAc (2 \times 20 mL), subsequently then basified with sat. NaHCO_3 until pH > 8, then extracted with EtOAc (3 \times 20 mL). The combined organic phase was dried over MgSO_4 , then evaporated under reduced pressure to give the racemic H-Trp(6-Cl)-Ot-Bu (\pm)-**214** as a white solid (350 mg, 84%).

TLC: $R_f = 0.54$ (MeOH/CH₂Cl₂ = 5/95)

Mp = 106-108 °C

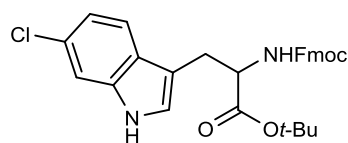
IR (ATR) ν 3360, 3330, 2979, 2933, 1722, 1617, 1457, 1367, 1225, 1151, 1063, 850, 797 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 1.44 (s, 9H), 1.70 (brs, 2H), 2.93 (dd, 1H, $J = 14.4$ Hz, $J = 7.9$ Hz, ABX), 3.21 (dd, 1H, $J = 14.4$, 4.7 Hz, ABX), 3.71 (dd, 1H, $J = 7.9$, 4.7 Hz, ABX), 6.91 (d, 1H, $J = 1.8$ Hz), 7.05 (dd, 1H, $J = 8.6$, 1.8 Hz), 7.22 (d, 1H, $J = 1.4$ Hz), 7.50 (d, 1H, $J = 8.3$ Hz), 9.19 (brs, 1H).

¹³C NMR (90 MHz, CDCl₃) δ 28.0 (3C), 30.7, 55.5, 81.4, 111.1, 111.2, 119.6, 119.8, 123.8, 126.1, 127.7, 136.7, 174.6.

tert-Butyl

2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-chloro-1H-indol-3-yl)propanoate



C₃₀H₂₉ClN₂O₄
Exact M. = 516.1816
M = 517.02 g·mol⁻¹

To an ice cold solution of H-Trp(6-Cl)-Ot-Bu (\pm)-**214** (294.5 mg, 1.00 mmol, 1 eq.) in THF (10 mL) was added FmocCl (284.6 mg, 1.10 mmol, 1.1 eq.), and Na₂CO₃ (169.6 mg, 1.60 mmol, 1.6 eq.). The resulting mixture was stirred at room temperature for overnight (> 18 h). Then concentrated under reduced pressure, diluted with water (20 mL) and extracted with EtOAc (3 \times 30 mL). The combined organic phase was washed with brine and dried over MgSO₄, filtered, concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc (90/10, 80/20, 70/30) gave the racemic dipeptide Fmoc-Trp(6-Cl)-Ot-Bu (517.5 mg, 100%) as a white solid.

TLC: $R_f = 0.33$ (petroleum ether/EtOAc = 80/20)

Mp = 63-67 °C

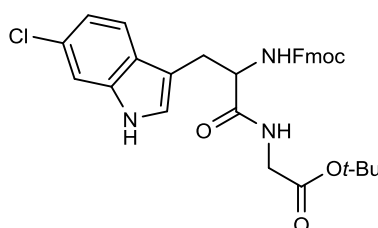
¹H NMR (360 MHz, CDCl₃) δ 1.40 (s, 9H), 3.20-3.32 (m, 2H), 4.19 (t, 1H, $J = 7.2$ Hz), 4.35-4.44 (m, 2H), 4.61-4.66 (m, 1H), 5.41 (d, H, $J = 9.3$ Hz), 6.86 (s, 1H), 7.08 (dd, 1H, $J = 8.3$ Hz, 1.8 Hz), 7.28-7.32 (m, 3H), 7.39-7.43 (m, 2H), 7.51-7.57 (m, 3H), 7.76-7.78 (m, 2H), 8.27 (brs, 1H).

^{13}C NMR (90 MHz, CDCl_3) δ 28.0 (4C), 47.2, 55.1, 67.1, 82.4, 110.6, 111.2, 119.9, 120.1 (2C), 120.4, 123.5, 125.2 (2C), 126.5, 127.2 (2C), 127.8 (2C), 128.1, 136.5, 141.4 (2C), 143.9 (2C), 155.9, 171.1.

tert-Butyl

(*R*)-(2-(((9*H*-fluoren-9-yl)methyl)amino)-3-(6-chloro-1*H*-indol-3-yl)propanoyl)glycinate

(\pm)-**216**



$\text{C}_{32}\text{H}_{32}\text{ClN}_3\text{O}_5$
Exact M. = 573.2030
M = 574.07 $\text{g}\cdot\text{mol}^{-1}$

To a solution of racemic Fmoc-Trp(6-Cl)-*Ot*-Bu (103.4 mg, 0.20 mmol, 1 eq.) in CH_2Cl_2 (2 mL) was added Et_3SiH (46.5 mg, 0.40 mmol, 2 eq.), then followed by addition of TFA (0.62 mL, 8.00 mmol, 40 eq) at room temperature. The resulting mixture was stirred at room temperature for overnight (18 h), completed. Evaporated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 80/20, 50/50, then MeOH/ CH_2Cl_2 = 10/90) gave the desired racemic Fmoc-Trp(6-Cl)-OH (\pm)-**215** (92.0 mg, 98%) as a white solid, then used for coupling.

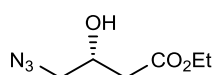
To a solution of racemic Fmoc-Trp(6-Cl)-OH (\pm)-**215** (92.0 mg 0.20 mmol, 1 eq.) in CH_2Cl_2 (5 mL) at room temperature under argon was added PyBroP (102.6 mg, 0.22 mmol, 1.1 eq.) and Gly·HCl (36.9 mg, 0.22 mmol, 1.1 eq.), subsequently. Followed by addition of DIEA (103.4 mg, 0.80 mmol, 4 eq.) dropwise. The resulting mixture was stirred at room temperature for overnight (>16 h). The reaction was then diluted with CH_2Cl_2 (20 mL), and then washed with 1 M HCl (20 mL), sat. NaHCO_3 (20 mL) and sat. NaCl (20 mL), respectively. The combined organic phase was dried over MgSO_4 , then filtered and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 80/20, 70/30, 60/40, 50/50) gave the desired racemic peptide Fmoc-Trp(6-Cl)-Gly-*Ot*-Bu (\pm)-**216** (93.3 mg, 81%) as a white solid.

TLC: R_f = 0.35 (petroleum ether/EtOAc = 60/40)

HPLC: Racemic (\pm)-**216**: 0% *ee*. sample preparation: 1 mg/L in MeOH: column: A_NP_Lux

Cellulose-2 (250 mm × 4.6 mm), normal phase: hexane/EtOH = 70/30, flow: 1 mL/min, 30 °C; injection: 5 µL; results: RT = 7.391 (*R*, Area: 50%), 13.706 (*S*, Area: 50%).

Ethyl (*R*)-4-azido-3-hydroxybutanoate **220**



(+)-**N₃-GABOB-OEt**
C₆H₁₁N₃O₃
M = 173.17 g·mol⁻¹
Exact. M = 173.08 g·mol⁻¹

Ethyl (*R*)-4-chloro-3-hydroxybutanoate (900 mg, 5.41 mmol, 1 eq.) was added to a solution of sodium azide (894 mg, 13.8 mmol, 2.55 eq.) in water (10 mL). The mixture was stirred for 30 min at 120 °C under microwave irradiation. The resulting aqueous mixture was then extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (20 mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure to give the azido ester (+)-**N₃-GABOB-OEt 220** (770 mg, 82%) as a yellow oil.

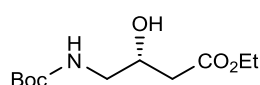
$[\alpha]_D^{26} = +14$ (*c* 1.00, CHCl₃)

IR (ATR) ν 3452, 2099, 1721, 1271, 1164 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 1.29 (t, 3H, ³*J* = 7.1 Hz), 2.53 (dd, 1H, ²*J* = 16.5 Hz, ³*J* = 3.7 Hz, ABX), 2.56 (dd, 1H, ²*J* = 16.5 Hz, ³*J* = 8.8 Hz, ABX), 2.26 (bs, 1H), 3.34 (dd, 1H, ²*J* = 12.5 Hz, ³*J* = 6.1 Hz, A'B'X'), 3.38 (dd, 1H, ²*J* = 12.5 Hz, ³*J* = 4.1 Hz, A'B'X'), 4.19 (q, 1H, ³*J* = 7.2 Hz), 4.18-4.25 (m, 1H, ABX and A'B'X').

¹³C NMR (90 MHz, CDCl₃) δ 14.0, 38.6, 55.6, 61.0, 67.3, 171.9.

Ethyl (*R*)-4-((*tert*-butyloxycarbonyl)amino)-3-hydroxybutanoate **221**



(+)-**Boc-GABOB-OEt**
C₁₁H₂₁NO₅
M = 247.29 g·mol⁻¹
Exact. M = 247.14 g·mol⁻¹

To a solution of (+)-**N₃-GABOB-OEt 220** (710 mg, 4.10 mmol, 1 eq.) in EtOAc (50 mL) was

added Boc_2O (1.34 g, 6.15 mmol, 1.5 eq.) and Pd-C (107 mg, 15% w/w). The resulting mixture was stirred for 24 h under hydrogen atmosphere then filtered through Celite[®] and the solvent was removed under reduced pressure. Flash chromatography of the residue (petroleum ether/EtOAc = 90/10) gave the amino ester (+)-Boc-GABOB-OEt **221** (728 mg, 72%) as a pale-yellow oil.

TLC: $R_f = 0.41$ (petroleum ether/EtOAc = 70/30)

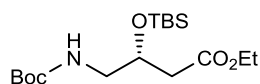
$[\alpha]_D^{26} = +4.0$ (c 1.12, CHCl_3)

IR (ATR) ν 3381, 1711, 1690, 1517, 1273, 1249, 1162 cm^{-1}

^1H NMR (360 MHz, CDCl_3) δ 1.28 (t, 3H, $^3J = 7.1$ Hz), 1.45 (s, 9H), 2.47 (dd, 1H, $^2J = 16.6$ Hz, $^3J = 9.2$ Hz, ABX), 2.50 (dd, 1H, $^2J = 16.6$ Hz, $^3J = 3.4$ Hz, ABX), 3.07-3.17 (m, 1H), 3.27-3.40 (m, 1H), 3.56 (bs, 1H), 4.06-4.15 (m, 1H, ABX), 4.17 (q, 2H, $^3J = 7.1$ Hz), 4.98 (bs, 1H).

^{13}C NMR (90 MHz, CDCl_3) δ 13.8, 28.1, 38.8, 45.4, 60.3, 67.3, 79.0, 156.4, 171.9.

Ethyl (*R*)-4-((*tert*-butyloxycarbonyl)amino)-3-hydroxybutanoate **222**



(+)-Boc-GABOB(TBS)-OEt
 $\text{C}_{17}\text{H}_{35}\text{NO}_5\text{Si}$
 $M = 361.55 \text{ g}\cdot\text{mol}^{-1}$
 Exact. $M = 361.23 \text{ g}\cdot\text{mol}^{-1}$

To a solution of (+)-Boc-GABOB-OEt **221** (571 mg, 2.31 mmol, 1 eq.) in DMF (5 mL) was added imidazole (786 mg, 11.6 mmol, 5 eq.) and TBSCl (696 mg, 4.62 mmol, 2 eq.). The resulting mixture was stirred for 16 h at room temperature and then washed successively with 1 M KHSO_4 (2×15 mL), saturated NaHCO_3 (2×15 mL), water (15 mL) and brine (15 mL). The organic layer was dried over MgSO_4 , filtered and evaporated under reduced pressure. Flash chromatography of the residue (petroleum ether/EtOAc = 95/5) gave the amino ester (+)-Boc-GABOB(TBS)-OEt **222** (734 mg, 72%) as a pale-yellow oil.

TLC: $R_f = 0.62$ (petroleum ether/EtOAc = 90/10)

$[\alpha]_D^{23} = +11$ (c 1.04, CHCl_3)

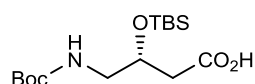
IR (ATR) ν 3382, 1735, 1719, 1504, 1250, 1167 cm^{-1}

¹H NMR (360 MHz, CDCl₃) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 1.26 (t, 3H, ³J = 7.1 Hz), 1.44 (s, 9H), 2.46 (pseudo d, 2H, ³J = 6.0 Hz), 3.13-3.29 (m, 2H), 4.13 (q, 2H, ³J = 7.1 Hz), 4.17-4.27 (m, 1H), 4.80 (bs, 1H).

¹³C NMR (90 MHz, CDCl₃) δ -4.9, -4.6, 14.3, 18.0, 25.8, 28.5, 40.4, 46.1, 60.6, 68.5, 79.3, 156.0, 171.3.

HRMS (ESI+) Calcd for C₁₇H₃₅NNaO₅Si [M + Na]⁺: 384.2177, found 384.2157.

(R)-4-((tert-Butyloxycarbonyl)amino)-3-hydroxybutanoic acid 223



(+)-Boc-GABOB(TBS)-OH

C₁₅H₃₁NO₅Si

M = 333.50 g·mol⁻¹

Exact. M = 333.20 g·mol⁻¹

To a solution of (+)-Boc-GABOB(TBS)-OEt **222** (740 mg, 2.05 mmol, 1 eq.) in ethanol (15 mL) was added a solution of KOH (345 mg, 6.14 mmol, 3 eq.) in water (7.5 mL). The resulting mixture was stirred for 16 h at room temperature and ethanol was removed under reduce pressure. The aqueous residue was then washed with CH₂Cl₂ (3 × 20 mL), acidified with 1 M HCl until pH = 1 and then extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated under reduced pressure to give the amino acid (+)-Boc-GABOB(TBS)-OH **223** (597 mg, 87%) as a white solid.

Mp = 56-62 °C

[α]_D²⁶ = +11 (c 1.01, CHCl₃)

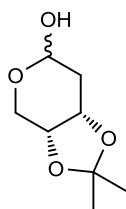
IR (ATR) ν 3398, 3101, 1710, 1649, 1512, 1251, 1165 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 0.07 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 1.45 (s, 9H), 2.42-2.47 (m, 2H), 3.18-3.30 and 2.99-3.13 (m, 2H, rot.), 4.14-4.27 (m, 1H), 4.85 and 5.93 (bs, 1H, rot.), 9.18 (bs, 1H).

¹³C NMR (90 MHz, CDCl₃) δ -4.9, -4.7, 18.0, 25.8, 28.4, 40.2, 46.0 and 47.3 (rot.), 68.3, 79.6 and 81.0 (rot.), 156.2, 176.2.

HRMS (ESI+) Calcd for C₁₅H₃₁NNaO₅Si [M + Na]⁺: 356.1864, found 356.1862.

HRMS (ESI-) Calcd for C₁₅H₃₀NO₅Si [M - H]⁻: 332.1899, found 332.1890.

(3a*R*,7a*S*)-2,2-Dimethyltetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-6-ol **63**⁷²⁵

C₈H₁₄O₄
 Exact M. = 174.0892
 M. = 174.20 g·mol⁻¹

Following Robertson's procedure⁷²⁵

To a stirred solution of 2-deoxy-ribose (200 mg, 1.49 mmol) in EtOAc (7 mL) at -10 °C was added PPTS (37 mg, 0.15 mmol, 0.1 eq.) and 2-methoxypropene (0.19 mL, 1.94 mmol, 1.3 eq.). The resulting mixture was then stirred for overnight (16 h) and warmed up to room temperature. The reaction solution was quenched with triethylamine (0.1 mL), concentrated under reduced pressure. Flash chromatograph on silica gel (petroleum ether/EtOAc = 70/30) gave the desired 2-deoxy-D-ribose acetonide **63** (170.0 mg, 66%, as an inseparable mixture of α and β anomers ratio of 3:1) as a colorless oil.

TLC: R_f = 0.30 (petroleum ether/EtOAc = 60/40)

$[\alpha]_D^{23} = -25.8$ (c 0.60, CHCl₃) (lit.⁷²⁵ $[\alpha]_D^{20} = -28.5$ (c 1.0, CH₂Cl₂))

IR (ATR) ν 3410, 2984, 2936, 1456, 1371, 1243, 1212, 1106, 1056, 1031, 1002 cm⁻¹

Major (α -anomer):

¹H NMR (360 MHz, CDCl₃) δ 1.34 (s, 3H), 1.49 (s, 3H), 1.77 (ddd, 1H, J = 14.8, 7.2, 4.3 Hz), 2.22 (dt, 1H, J = 14.8, 4.3 Hz), 3.68 (dd, 1H, J = 12.6, 3.6 Hz), 3.94 (dd, 1H, J = 12.6, 3.2 Hz), 4.16 (dt, 1H, J = 6.5, 3.2 Hz), 4.47 (dt, 1H, J = 6.5, 4.3 Hz), 5.22 (dd, 1H, J = 7.2, 4.3 Hz).

¹³C NMR (75 MHz, CDCl₃) δ 25.3, 27.2, 32.1, 61.9, 70.5, 71.5, 90.7, 108.7.

Minor (β -anomer):

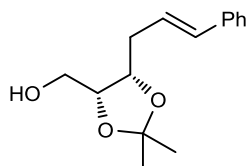
¹H NMR (360 MHz, CDCl₃) δ 1.36 (s, 3H), 1.55 (s, 3H), 1.95-2.02 (m, 1H), 2.09-2.15 (m, 1H), 3.72 (dd, 1H, J = 13.0, 4.7 Hz), 3.99 (dd, 1H, J = 12.6, 5.4 Hz), 4.14-4.18 (m, 1H), 4.37 (dd, 1H, J = 5.8 Hz), 5.00 (t, 1H, J = 4.3 Hz).

¹³C NMR (90 MHz, CDCl₃) δ 25.7, 27.9, 33.4, 60.9, 70.6, 71.2, 91.6, 109.3.

For the synthesis of compounds **64-67**, following in-house procedures previously reported by

Aitken,³⁸⁸ excepting the precursor aldehyde of epimerized aldehyde **65** was synthesized by Dess-Martin oxidation. All analytical data were in good accordance with reported data by NMR and optical rotation.

((4*R*,5*S*)-5-Cinnamyl-2,2-dimethyl-1,3-dioxolan-4-yl)methanol **64**³⁸⁸



C₁₅H₂₀O₃
Exact M. = 248.1412
M. = 248.32 g·mol⁻¹

To a solution of diethyl benzylphosphonate (630 mg, 2.76 mmol, 2 eq.) in THF (10 mL) at 0 °C under argon was added a solution of 1.6 M *n*-BuLi in hexanes (2.65 mL, 2.76 mmol, 2 eq.) and the mixture was stirred for 20 min. A solution of acetonide **63** (240.0 mg, 1.38 mmol, 1 eq.) in THF (10 mL) was then added dropwise and the mixture was stirred for 19 h at approx. 45 °C. The reaction was quenched by addition of sat. NH₄Cl (4 mL). The mixture was diluted with water (20 mL) and EtOAc (20 mL) and the organic phase was isolated. The aqueous phase was extracted with EtOAc (20 mL × 2) and the combined organic phases were dried over MgSO₄, filtered, concentrated and dried in vacuo. Flash chromatography on silica gel (petroleum ether/EtOAc = 70/30, 60/40) gave the desired alcohol **64** (178.0 mg, 52%) as a colorless oil.

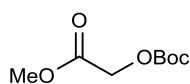
TLC: $R_f = 0.30$ (petroleum ether/EtOAc = 70/30)

$[\alpha]_D^{23} = -15.7$ (c 0.63, CHCl₃) (lit.³⁸⁸ $[\alpha]_D^{22} = -15.7$ (c 0.63, CH₂Cl₂))

IR (ATR) ν 3451, 2985, 2935, 1495, 1449, 1379, 1369, 1246, 1215, 1163, 1037, 965, 846, 743, 692 cm⁻¹

¹H NMR (360 MHz, CDCl₃) δ 1.39 (s, 3H), 1.51 (s, 3H), 2.12 (brs, 1H), 2.40-2.48 (m, 1H), 2.52-2.60 (m, 1H), 3.70 (d, 1H, $J = 5.4$ Hz), 4.22 (dd, 1H, $J = 11.9, 5.8$ Hz), 4.31 (ddd, 1H, $J = 8.3, 5.8, 5.4$ Hz), 6.23 (ddd, 1H, $J = 16.2, 7.6, 6.1$ Hz), 6.49 (d, 1H, $J = 16.2$ Hz).

¹³C NMR (90 MHz, CDCl₃) δ 25.6, 28.2, 33.1, 61.8, 76.7, 77.9, 108.4, 125.9, 126.2 (2C), 127.4 (2C), 128.6 (2C), 132.5, 137.3.

Methyl 2-((tert-butoxycarbonyl)oxy)acetate³⁸⁸

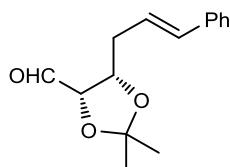
C₈H₁₄O₅
 Exact M. = 190.0841
 M. = 190.19 g·mol⁻¹

To a solution of methyl glycolate (2.70 g, 30.0 mmol) in CH₂Cl₂ (150 mL) at 0 °C under argon was added DMAP (366.5 mg, 2.00 mmol, 0.1 eq.) and Boc₂O (4.82 g, 29.7 mmol, 0.99 eq.). The resulting mixture was then stirred at 0 °C for 3 h and at r.t. for 1 h. The reaction solution was concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 95/5, 90/10) gave the desired Boc- glycolate (4.78 mg, 83%) as a colorless oil.

TLC: R_f = 0.46 (petrum ether/EtOAc = 90/10)

¹H NMR (360 MHz, CDCl₃): δ 1.50 (9H, s), 3.77 (3H, s), 4.58 (2H, s)

¹³C NMR (900 MHz, CDCl₃): δ 27.5 (3C), 52.1, 62.5, 82.9, 152.8, 168.2.

(4*S*,5*S*)-5-Cinnamyl-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **65**³⁸⁸

C₁₅H₁₈O₃
 Exact M. = 246.1256
 M. = 246.31 g·mol⁻¹

To a solution of alcohol **64** (496.7 mg, 2.00 mmol, 1 eq.) in CH₂Cl₂ (20 mL) at room temperature under argon was added DMP (1.272 g, 3.00 mmol, 1.5 eq) in 3 portions. After 5 min, NaHCO₃ (840.1 mg, 10.00 mmol, 5 eq.) was added in portions. The resulting mixture was stirred for 50 min at room temperature. The reaction solution was filtered a Celite pad, then washed with CH₂Cl₂ (10 mL × 3). The filtrate was then washed with sat. NaHCO₃ (20 mL × 3), water (20 mL) and sat (20 mL), respectively. The combined organic phases were dried over MgSO₄, filtered, and concentrated and dried in vacuo. Flash chromatography on silica gel (petroleum ether/EtOAc = 70/30, 60/40) gave the desired aldehyde (492.7 mg, 100%) as a colorless oil.

TLC: R_f = 0.58 (petrum ether/EtOAc = 80/20)

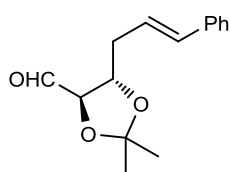
$[\alpha]_D^{27} = -40.5$ (c 0.69, CHCl₃) (lit.³⁸⁸ $[\alpha]_D^{22} = -45.8$ (c 0.69, CH₂Cl₂))

IR (ATR) ν 2988, 2937, 1732, 1495, 1450, 1382, 1245, 1218, 1160, 1069, 968, 693 cm^{-1}

^1H NMR (300 MHz, CDCl_3) δ 1.45 (s, 3H), 1.65 (s, 3H), 2.42-2.60 (m, 2H), 4.38 (dd, 1H, $J = 8.3$, 3.6 Hz), 4.47-4.53 (m, 1H), 6.24 (ddd pseudo dt, 1H, $J = 16.2$, 8.3, 8.3 Hz), 7.22-7.41 (m, 5H), 9.74 (d, $J = 3.6$ Hz).

^{13}C NMR (75 MHz, CDCl_3) δ 25.3, 27.5, 35.5, 78.4, 81.9, 110.7, 124.8, 126.2 (2C), 127.5 (2C), 128.6 (2C), 133.3, 137.0, 202.1.

(4R,5S)-5-Cinnamyl-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 65³⁸⁸



$\text{C}_{15}\text{H}_{18}\text{O}_3$
Exact M. = 246.1256
M. = 246.31 $\text{g}\cdot\text{mol}^{-1}$

To a solution of aldehyde **64** (106.0 mg, 0.43 mmol, 1 eq.) in MeOH (2 mL) at rt under argon at room temperature was added K_2CO_3 (53.5 mg, 0.39 mmol, 0.9 eq.) and the resulting mixture was stirred for 4 h at room temperature. The reaction mixture was then poured into water (10 mL) and extracted with CH_2Cl_2 (20 mL \times 2). The combined organic phase was washed with brine (20 mL), dried over MgSO_4 , filtered, concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 100/1, 95/5, 90/10) gave the desired epimerized aldehyde **65** (88.0 mg, 83%) as a colorless oil.

TLC: $R_f = 0.41$ (petroleum ether/EtOAc = 75/25)

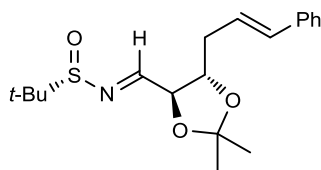
$[\alpha]_D^{27} = +2.6$ (c 0.75, CHCl_3) (lit.³⁸⁸ $[\alpha]_D^{23} = +15.6$ (c 0.75, CHCl_3))

IR (ATR) ν 2987, 2932, 1733, 1495, 1450, 1381, 1240, 1216, 1086, 1066, 968, 747, 694 cm^{-1}

^1H NMR (360 MHz, CDCl_3): δ 1.44 (s, 3H), 1.52 (s, 3H), 2.56-2.72 (m, 2H), 4.08 (dd, 1H, $J = 7.6$, 2.2 Hz), 4.18-4.24 (m, 1H), 6.23 (ddd pseudo dt, $J = 16.2$, 7.2, 7.2 Hz), 6.52 (d, 1H, $J = 16.2$ Hz), 7.20-7.38 (m, 5H), 9.76 (d, 1H, $J = 2.2$ Hz).

^{13}C NMR (90 MHz, CDCl_3): δ 26.3, 27.2, 36.6, 76.6, 84.1, 111.3, 124.2, 126.3 (2C), 127.5, 128.7 (2C), 133.7, 137.1, 201.3.

(*S*)-*N*-((*E*)-((4*S*,5*S*)-5-Cinnamyl-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide **66**³⁸⁸



C₁₉H₂₇NO₃S
 Exact M. = 349.1712
 M. = 349.49 g·mol⁻¹

To a solution of the aldehyde **65** (1.478 g, 6.00 mmol, 1 eq.) in CH₂Cl₂ (60 mL) under argon at room temperature was added (*S*)-*t*-butyl sulfinamide (800.0 mg, 6.60 mmol, 1.1 eq.) and Ti(OEt)₄ (6.3 mL, 30.00 mmol, 5 eq.). The resulting mixture was stirred for overnight (16 h) at rt. The mixture was cooled down to 0 °C and ice-cold water (20 mL) was added. The resulting solution was then filtered through a celite pad, washing the pad with EtOAc (50 mL × 3). The filtrate was washed with brine (100 mL), dried over MgSO₄, filtered, concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 80/20, 70/30) gave the desired sulfinimine **66** (1.443 g, 69%) as a pale-yellow oil.

TLC: *R*_f = 0.22 (petroleum ether/EtOAc = 90/10)

[α]_D²³ = +81.0 (*c* 0.70, CHCl₃) (lit.³⁸⁸ **[α]_D²²** = +71.7 (*c* 0.70, CHCl₃))

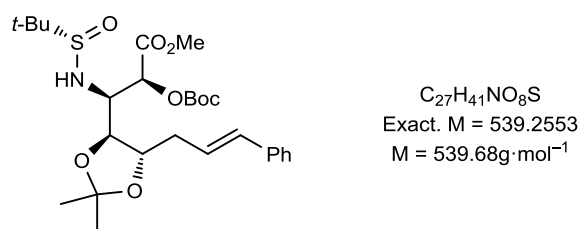
IR (ATR) ν 2984, 1624, 1454, 1381, 1365, 1240, 1215, 1160, 1086, 967, 749, 694 cm⁻¹

¹H NMR (360 MHz, CDCl₃): δ 1.16 (s, 9H), 1.42 (s, 3H), 1.49 (s, 3H), 2.53-2.69 (m, 2H), 4.12-4.17 (m, 1H), 4.50 (dd, 1H, *J* = 7.6, 4.7 Hz), 6.23 (ddd pseudo dt, *J* = 15.8, 7.2, 7.2 Hz), 6.47 (d, 1H, *J* = 15.8 Hz), 7.18-7.35 (m, 5H), 8.09 (d, 1H, *J* = 4.3 Hz).

¹³C NMR (90 MHz, CDCl₃): δ 22.4 (3C), 26.5, 27.2, 36.1, 57.0, 78.6, 81.2, 110.8, 124.5, 126.3 (2C), 127.4, 128.5 (2C), 133.3, 137.0, 167.7.

Methyl

(2*S*,3*R*)-2-((*tert*-butoxycarbonyl)oxy)-3-((*tert*-butyl(λ^1 -oxidanyl)- λ^3 -sulfanyl)amino)-3-((4*S*,5*S*)-5-cinnamyl-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate **67**³⁸⁸



To a solution of Boc-glycate (524.6 mg, 6.00 mmol, 4 eq.) in THF (20 mL) at -78 °C under argon was added a solution of 1 M LiHMDS in THF (6.0 mL, 6.00 mmol, 4 eq.) and the resulting mixture was stirred for 1 h. A solution of sulfinimine **66** (524.6 mg, 1.50 mmol, 1 eq.) in THF (5.0 mL) was then added dropwise and the resulting mixture was stirred at -78 °C for 1 h. The reaction was quenched by sat. NH_4Cl (10 mL) at 0 °C and diluted with water (20 mL). The resulting mixture was extracted with EtOAc (50 mL \times 2) and the combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduced pressure. Flash chromatography (petroleum ether/EtOAc = 70/30) gave a fully-protected APTO **67** (760.3 mg, 94%) as a white solid.

TLC: R_f = 0.33 (petroleum ether/EtOAc = 70/30)

Mp = 161-163 °C

$[\alpha]_D^{26}$ = +32.5 (c 0.90, $CHCl_3$), (lit.³⁸⁸ $[\alpha]_D^{21}$ = +33.7 (c 0.90, $CHCl_3$))

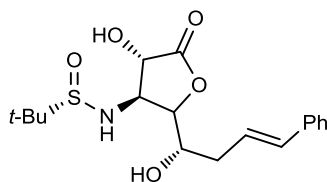
IR (ATR) ν 3335, 2983, 1750, 1457, 1370, 1302, 1254, 1214, 1163, 1136, 1081 cm^{-1}

1H NMR (360 MHz, $CDCl_3$) δ 1.14 (s, 9H), 1.43 (s, 6H), 1.50 (s, 9H), 2.54-2.62 (m, 1H, *ABX*), 2.66-2.73 (m, 1H, *ABX*), 3.56 (d, 1H, J = 10.1 Hz), 3.71 (s, 3H), 3.85 (dd, J = 8.3, 5.4 Hz), 3.95 (1H, J = 10.1, 8.3, 1.8 Hz), 4.50 (ddd, 1H, J = 10.1, 5.4, 5.4 Hz, *ABX*), 5.31 (d, 1H, J = 1.8 Hz), 6.31 (ddd pseudo dt, 1H, J = 15.8, 7.2, 7.2 Hz), 6.50 (d, 1H, J = 15.8 Hz), 7.16-7.21 (1H, m), 7.25-7.30 (m, 2H), 7.37-7.39 (m, 2H).

^{13}C NMR (90 MHz, $CDCl_3$) δ 22.7 (3C), 27.8 (3C), 27.9, 28.0, 38.3, 52.5, 56.9, 61.0, 74.5, 79.3, 79.9, 83.6, 110.1, 126.0, 126.4 (2C), 127.2, 128.5 (2C), 132.8, 137.6, 152.5, 168.9

HRMS (ESI+) Calcd for $C_{27}H_{42}NO_8S$ $[M + H]^+$: 540.2626, found 540.2625.

(S)-N-((3S,4S)-4-Hydroxy-2-((S,E)-1-hydroxy-4-phenylbut-3-en-1-yl)-5-oxotetrahydrofuran-3-yl)-2-methylpropane-2-sulfinamide **224**



C₁₈H₂₅NO₅S
Exact Mass: 367.1453
M. = 367.46 g·mol⁻¹

To a solution of fully-protected APTO **67** (54.0 mg, 0.10 mmol, 1 eq.) in CHCl₂ (2 mL) was added dropwise TFA (3.2 mmol, 0.5 mL) at room temperature. The mixture was stirred for 1 h at room temperature, concentrated under reduced pressure, then diluted with EtOAc (20 mL), washed with sat. NaHCO₃ (20 mL) and brine (20 mL). The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 70/30, 50/50, 40/60) gave a lactone of sulfinamide **224** (36.8 mg, 100 %) as a pale-yellow oil.

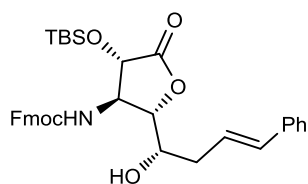
TLC: *R_f* = 0.74 (EtOAc = 100%)

¹H NMR (360 MHz, CDCl₃) δ 1.19 (s, 9H), 2.43-2.54 (pseudo m, 1H, ABX) 2.57-2.65 (pseudo m, 1H, ABX), 4.01 (t, 1H, *J* = 6.8 Hz, ABX), 4.18-4.23 (m, 2H), 4.61 (pseudo brs, 1H), 4.90 (brs, 1H), 6.18 (ddd pseudo dt, 1H, *J* = 15.8, 6.8 Hz), 6.46 (d, 1H, *J* = 15.8 Hz), 7.16-7.37 (m, 5H).

¹³C NMR (90 MHz, CDCl₃) δ 22.8, 37.4, 57.0, 59.8, 67.6, 73.0, 81.1, 125.2, 126.3 (2C), 127.5, 128.6 (2C), 133.6, 137.2, 174.6.

(9H-Fluoren-9-yl)methyl

((2S,3R,4S)-4-((tert-butyldimethylsilyl)oxy)-2-((S,E)-1-hydroxy-4-phenylbut-3-en-1-yl)-5-oxotetrahydrofuran-3-yl)carbamate **227**



C₃₅H₄₁NO₆Si
Exact M. = 599.2703
M. = 599.80 g·mol⁻¹

To an ice cold solution of crude **225** (30 mg) in CH₂Cl₂ (2 mL) was added NaHCO₃ (42.0 mg, 0.50 mmol, 5 eq.) and FmocCl (28.5 mg, 0.11 mmol, 1.1 eq.), respectively. The mixture was stirred for

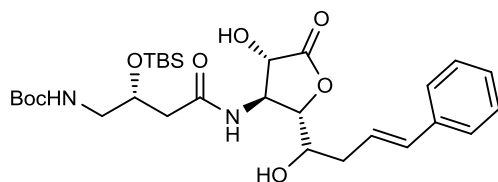
overnight (20 h), diluted with CH₂Cl₂ (20 mL), the washed with water (20 mL) and brine (20 mL). The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 70/30, 50/50, 40/60) to give **226** (13.0 mg, 27%, impure). To an ice cold solution of impure **226** (13.0 mg, 27 μmol) in CH₂Cl₂ (1 mL) was treated with 2,6-lutidine (11.5 mg, 107 μmol, 4 eq.) and TBSOTf (28.3 mg, 107 μmol, 4 eq.) dropwise. The mixture was stirred for 3 h at room temperature. Quenched by sat. NH₄Cl (1 mL), diluted with with CH₂Cl₂ (20 mL), washed with 1 M HCl (15 mL) and brine (20 mL). The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 90/10, 80/20, 70/30) gave compound **227** (6.2 mg, 10%) as a colorless oil.

TLC: *R_f* = 0.22 (petroleum ether/EtOAc = 80/20)

¹H NMR (360 MHz, CDCl₃) δ 0.88 (s, 3H), 0.15 (s, 3H), 0.89 (s, 9H), 2.49-2.64 (m, 2H, ABX), 3.75-3.79 (m, 1H, ABX), 4.17-4.22 (m, 2H), 4.26-4.29 (m, 1H,), 4.50 (d, 2H, *J* = 11.2 Hz), 4.73 (d, 1H, *J* = 9.7 Hz), 5.02 (d, 1H, *J* = 7.6 Hz), 6.21 (ddd pseudo dt, 1H, *J* = 16.6, 7.6 Hz), 6.50 (d, 1H, *J* = 16.6 Hz), 7.20-7.36 (m, 7H), 7.41 (t, 2H, *J* = 7.2 Hz), 7.56 (d, 2H, *J* = 7.2 Hz), 7.77 (d, 2H, *J* = 7.2 Hz).

tert-Butyl

((*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4-(((2*S*,3*S*,4*S*)-4-hydroxy-2-((*R*,*E*)-1-hydroxy-4-phenylbut-3-en-1-yl)-5-oxotetrahydrofuran-3-yl)amino)-4-oxobutyl)carbamate **231**



C₂₉H₄₆N₂O₈Si
Exact. M = 578.3023
M = 578.78 g·mol⁻¹

To a solution of GABOB **223** (40.0 mg, 0.12 mmol, 1.2 eq.) in CH₂Cl₂ (1 mL) was added HATU (0.15 mmol, 57 mg, 1.5 eq.) and DIEA (0.15 mmol, 20 mg, 1.5 eq.), respectively. After stirred for 1 h at room temperature (30 °C) as *solution A*

To a flask containing fully-protected APTO **67** (54.0 mg, 0.10 mmol, 1 eq.) was slowly added a

solution 4 M HCl in dioxane (3.2 mmol, 0.8 mL, 32 eq.) at 0 °C. The mixture was stirred for 50 min at room temperature (30 °C), then evaporated to give a waxy solid, to which was added ether (5 mL), a pale-white solid precipitated, filtered and dried to give our proposed lactone of amine-HCl salt **225** as a white solid (30.1 mg, $\tau = 100\%$). To a solution of lactone of amine-HCl salt **225** in CHCl_2 (2 mL) was added with DIEA (0.45 mmol, 58 mg, 4.5 eq.) at 0 °C. Then diluted with water (20 mL), extracted with EtOAc (20 mL \times 3). The organic phase was dried over MgSO_4 concentrated under reduced pressure to give our proposed free amine crude **230** (as a pale-yellow oil, 16 mg). The crude was in CHCl_2 (1 mL) as *solution B*.

To *solution A* was added *solution B*, the resulting mixture was stirred for overnight (16 h). Diluted with EtOAc (20 mL), then washed with 1 M HCl (10 mL), sat. NaHCO_3 (10 mL) and brine (10 mL), respectively. The organic phase was dried over MgSO_4 , filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/EtOAc = 70/30, 50/50) gave a lactone of dipeptide **231** as a colorless oil (6.0 mg, 10%) as a colorless oil.

TLC: $R_f = 0.25$ (petroleum ether/EtOAc = 70/30)

$[\alpha]_D^{20} = +23.3$ (c 0.30, CHCl_3)

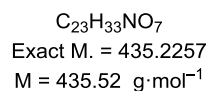
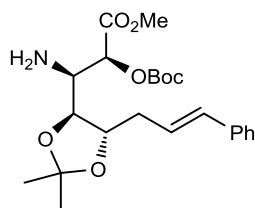
IR (ATR) ν 3333, 2956, 2929, 2854, 1784, 1686, 1658, 1529, 1367, 1253, 1172, 1108, 837 cm^{-1}

^1H NMR (360 MHz, CDCl_3) δ 0.10 (pseudo s, 1H), 0.88 (s, 9H), 1.43 (s, 9H), 2.31-2.67 (m, 4H, two *ABX* mixed), 3.03-3.08 (pseudo m, 1H, *ABX*) and 3.40-3.47 (pseudo m, 1H, *ABX*), 3.90 (pseudo t, 1H, $J = 6.1$ Hz), 4.08-4.11 (m, 2H, two *ABX* mixed), 4.51-4.59 (m, 2H), 4.95 (m, 1H), 6.23 (ddd pseudo dt, 1H, $J = 15.8, 7.2, 7.2$ Hz), 6.23 (d, 1H, $J = 15.8$ Hz), 7.19-7.23 (m, 1H), 7.27-7.36 (m, 4H), 7.26 (d, $J = 2.2$ Hz).

^{13}C NMR (90 MHz, CDCl_3) δ -4.7, 18.1, 25.9 (3C), 28.5 (3C), 36.4, 41.6, 44.8, 55.4, 68.8, 68.9, 72.4, 80.4, 80.8, 125.2, 126.3 (2C), 127.5, 128.7 (2C), 133.6, 137.2, 157.5, 172.6, 173.1.

HRMS (ESI+) Calcd for $\text{C}_{29}\text{H}_{46}\text{N}_2\text{NaO}_8\text{Si}$ $[\text{M} + \text{Na}]^+$: 601.2916, found 601.2890.

Methyl

(2*S*,3*R*)-3-amino-2-((*tert*-butoxycarbonyl)oxy)-3-((4*S*,5*S*)-5-cinnamyl-2,2-dimethyl-1,3-dioxolane-4-yl)propanoate 232

To a pear-shaped flask containing fully-protected APTO **67** (54.0 mg, 0.10 mmol, 1 eq.) in at $-10\text{ }^{\circ}\text{C}$ under argon was added a solution of 4 M HCl in dioxane (0.50 mL, 2.00 mmol, 20 eq.). The resulting mixture was stirred for 30 min at $-5\text{ }^{\circ}\text{C}$, completed, diluted with CH_2Cl_2 (25 mL), and then basified with DIEA (387.7 mg, 3.00 mmol, 30 eq.) at $-5\text{ }^{\circ}\text{C}$. The resulting organic phase was washed with water and brine, dried over MgSO_4 , filtered, concentrated under reduced pressure. Flash chromatography (petroleum ether/EtOAc = 90/10, 80/20, 70/30) gave an APTO derivative of amine **231** (28.1 mg, 64%) as a colorless oil, as well as *O*-Boc migrated by-product **232** (5.0 mg, 11%) as a colorless oil. Data below for the main product **232**.

TLC: $R_f = 0.56$ (petroleum ether/EtOAc = 70/30)

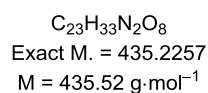
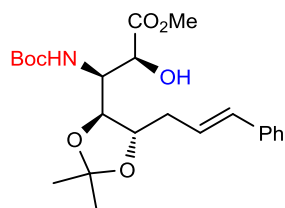
IR (ATR) ν 3400, 2984, 2934, 1748, 1438, 1370, 1303, 1253, 1218, 1163, 1135 cm^{-1} .

^1H NMR (360 MHz, CDCl_3) δ 1.40 (s, 3H), 1.42 (s, 3H) 1.50 (s, 9H), 2.51-2.59 (m, 1H, *ABX*), 2.68-2.75 (m, 1H, *ABX*), 2.67-2.74 (1H, m), 3.23 (dd, 1H, $J = 9.4, 1.8$ Hz), 3.65 (dd, 9.4, 6.5 Hz), 3.79 (s, 3H), 4.12 (ddd, 1H, $J = 6.8, 4.3, 4.3$ Hz, *ABX*), 5.20 (d, 1H, $J = 1.8$ Hz), 6.30 (ddd pseudo dt, 1H, $J = 15.8, 6.8, 6.8$ Hz), 6.47 (d, 1H, $J = 15.8$ Hz), 7.17-7.21 (1H, m), 7.27-7.31 (m, 2H), 7.35-7.39 (m, 2H).

^{13}C NMR (90 MHz, CDCl_3) δ 27.6, 27.8 (4C), 38.5, 52.6, 56.4, 75.6, 79.8, 80.8, 83.4, 109.4, 126.3 (2C), 127.2, 128.6 (2C), 132.5, 137.6, 152.8, 170.0.

HRMS (ESI+) Calcd for $\text{C}_{23}\text{H}_{33}\text{NNaO}_8$ $[\text{M} + \text{Na}]^+$: 458.2130, found 458.2149.

Methyl

(2*S*,3*S*)-3-(((*tert*-butoxycarbonyl)oxy)amino)-3-((4*S*,5*S*)-5-cinnamyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxypropanoate 233

To a flask containing fully-protected APTO **67** (54.0 mg, 0.10 mmol, 1 eq.) at $-10\text{ }^{\circ}\text{C}$ under argon was added a solution of 4 M HCl in dioxane (0.50 mL, 2.00 mmol, 20 eq.). After stirred for 30 min (followed by TLC), completed. Then diluted with CH_2Cl_2 (10 mL), and basified with Et_3N (303.6 mg, 3.00 mmol, 30 eq.) at $-5\text{ }^{\circ}\text{C}$. The resulting was washed with water and brine, and the aqueous phase was extracted with CH_2Cl_2 (10 mL \times 2). The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. The crude was directly purified by flash chromatography on neutral Aluminium oxide (petroleum ether/ EtOAc , 95/5, 90/10, 80/20) gave the main product *O*-Boc migrated APTO derivative **233** (16.0 mg, 37%) as a white solid, as well as APTO derivative **232** (15.1 mg, 35%) as a colorless oil. Data below for the main product *O*-Boc migrated APTO derivative **233**:

TLC: $R_f = 0.35$ (petrum ether/ $\text{EtOAc} = 70/30$)

Mp = 124-127 $^{\circ}\text{C}$

$[\alpha]_D^{20} = -13.0$ (c 0.54, CHCl_3)

IR (ATR) ν 3445, 3364, 2925, 2854, 1741, 11716, 1497, 1453, 1368, 1246, 1214, 1163, 1112, 1080 cm^{-1}

^1H NMR (360 MHz, CDCl_3) δ 1.41 (pseudo s, 3H), 1.44 (s, 3H), 2.43-2.60 (pseudo m, 2H, ABX), 3.11 (brs, 1H), 3.77-3.82 (m and s, 4H), 4.16-4.21 (m, 2H), 4.58 (pseudo s, 1H), 4.84 (d, 1H, $J = 10.1$ Hz), 6.23 (ddd pseudo dt, 1H, $J = 15.8, 6.8, 6.8$ Hz), 6.45 (d, $J = 15.8$ Hz), 7.18-7.22 (m, 1H), 7.26-7.31 (m, 2H), 7.34-7.36 (m, 2H).

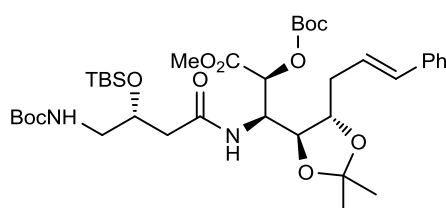
^{13}C NMR (90 MHz, CDCl_3) δ 27.3, 27.7, 28.4 (3C), 37.9, 53.1, 55.4, 70.1, 78.5, 79.6, 80.2, 109.5, 125.7, 126.3 (2C), 127.3, 128.6 (2C), 132.8, 137.4, 155.2, 174.1.

HRMS (ESI+) Calcd for C₂₃H₃₃NNaO₇ [M + Na]⁺: 458.2149, found 458.2137.

Methyl

(2S,3R)-3-((R)-4-((tert-butoxycarbonyl)amino)-3-((tert-butyl dimethylsilyl)oxy)butanamido)-2-((tert-butoxycarbonyl)oxy)-3-((4S,5S)-5-cinnamyl-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate

234



C₃₈H₆₂N₂O₁₁Si
 Exact M. = 750.4123
 M = 751.00 g·mol⁻¹

See Table 11, entry 2:

To a flask containing fully-protected APTO **67** (108.0 mg, 0.20 mmol, 1 eq.) at -5 °C under argon was slowly added a solution of 4 M HCl in dioxane (1.00 mL, 4.00 mmol, 20 eq.) and the mixture was stirred for 35 min between -5 °C until completed. Then diluted with 10 mL ether, and evaporated to give a colorless sticky oil, which was dissolved in CH₂Cl₂ (10.0 mL). To the resulting solution was then added PyBroP (140.0 mg, 0.30 mmol, 1.5 eq.) and GABOB (100.0 mg, 0.30 mmol, 1.5 eq.) and DIEA (129.4 mg, 1.0 mmol, 5.0 eq.) dropwise, respectively. The resulting mixture was stirred at room temperature for 48 h. The reaction was then diluted with CH₂Cl₂ (50 mL), and then washed with water, sat. NaHCO₃ and brine, respectively. The organic phase was dried over MgSO₄, filtered, concentrated under reduced pressure. Flash chromatography (petroleum ether/EtOAc = 70/30) gave the desired peptide GABOB–APTO **234** (108.2 mg, 72%) as a colorless sticky oil.

TLC: *R*_f = 0.36 (petrum ether/EtOAc = 80/20)

[α]_D²⁰ = -4.7 (*c* 0.43, CHCl₃)

IR (ATR) ν 3342, 2982, 2956, 2932, 2857, 1750, 1717, 1681, 1511, 1369, 1251, 1165, 1106, 838 cm⁻¹

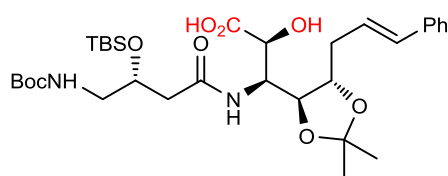
¹H NMR (360 MHz, CDCl₃) δ 0.11 (s, 3H), 0.15 (s, 3H), 0.93 (s, 9H), 1.42 (s, 3H), 1.44 (s, 9H,

NBoc and one methyl of acetone), 1.49 (s, 9H), 2.31-2.53 (m, 4H, two ABX mixed), 3.12-3.29 (m, 2H, ABX), 3.69-3.71 (m and s, 4H), 4.10-4.17 (m, 2H, two ABX mixed), 4.70 (ddd pseudo td, 1H, $J = 18.9, 8.6, 1.4$ Hz), 4.89 (t, 1H, $J = 5.8$ Hz), 5.19 (d, 1H, $J = 1.4$ Hz), 6.22 (ddd pseudo dt, 1H, $J = 15.8, 6.8, 6.8$ Hz), 6.47 (d, $J = 15.8$ Hz), 7.16 (d, 1H, $J = 10.0$ Hz), 7.18-7.22 (m, 1H), 7.26-7.31 (m, 2H), 7.34-7.36 (m, 2H).

^{13}C NMR (90 MHz, CDCl_3) δ -4.7, -4.6, 18.2, 26.1 (3C), 27.3, 27.7, 27.8 (3C), 28.6 (3C), 38.0, 41.2, 44.5, 52.5, 52.8, 68.1, 73.1, 78.5, 79.7 (2C), 83.4, 109.8, 125.5, 126.3 (2C), 127.4, 128.6 (2C), 132.8, 137.6, 152.5, 156.2, 169.4, 17.6.

HRMS (ESI+) Calcd for $\text{C}_{38}\text{H}_{62}\text{N}_2\text{NaO}_{11}\text{Si}$ [$\text{M} + \text{Na}$] $^+$: 773.4015, found 773.3982.

(2*S*,3*R*)-3-((*R*)-4-((*tert*-Butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-3-((4*S*,5*S*)-5-cinnamyl-2,2-dimethyl-1,3-dioxolan-4-yl)propanoic acid **236**



$\text{C}_{32}\text{H}_{52}\text{N}_2\text{O}_9\text{Si}$
Exact M. = 636.3442
M = 636.86 $\text{g}\cdot\text{mol}^{-1}$

See Table 12, entry 3:

To a solution of GABOB-APTO **234** (45.0 mg, 60 μmol , 1 eq.) in MeOH/THF/ H_2O (v/v/v, 0.2/0.2/0.3 mL) was added LiOH· H_2O (26.0 mg, 0.60 mmol, 10 eq.). After stirred for 16 h at room temperature, quenched with 10% citric acid aq. until pH = 2-3. The acidic aqueous phase was extracted with EtOAc (3 \times 20 mL). The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. Preparative thin layer chromatography on silica gel (MeOH/ CH_2Cl_2 = 5/95) gave a 2-hydroxyl acid **236** (30.2 mg, 80%) as a colorless oil (without *O*-Boc).

TLC: $R_f = 0.20$ (MeOH/ CH_2Cl_2 = 10/90)

$[\alpha]_D^{22} = -5.8$ (c 0.50, CHCl_3)

IR (ATR) ν 3333, 2928, 2852, 1674, 1529, 1369, 1250, 1205, 1165, 1139, 1081 cm^{-1}

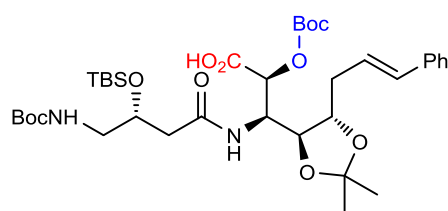
^1H NMR (3600 MHz, MeOD- d_4) δ 0.09 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 1.39-1.44 (m, 15H),

NBoc and acetonide), 2.31-2.55 (m, 4H, two ABX mixed), 3.03-3.17 (m, 2H, ABX), 3.78-3.92(m, 1H), 4.14-4.21 (m, 2H, two ABX mixed), 4.30 (pseudo s, 1H), 4.58-4.60 (m, 1H), 5.06 (pseudo s, 1H), 6.27 (dt, 1H, $J = 16.0, 6.8$ Hz), 6.44 (d, $J = 16.0$ Hz), 7.16-7.36 (m, 5H).

^{13}C NMR (90 MHz, MeOD- d_4) δ -4.5 (2C), 18.9, 26.5 (2C), 27.6, 27.8, 28.9 (2C), 38.9, 42.5, 46.4, 55.6, 69.7, 71.9, 80.1, 80.4, 80.6, 110.2, 126.9, 127.1 (2C), 128.2, 129.5 (2C), 133.7, 138.8, 158.4, 172.8, 178.0.

HRMS (ESI+) Calcd for $\text{C}_{37}\text{H}_{61}\text{N}_2\text{NaO}_{11}\text{Si}$ $[\text{M} + \text{Na}]^+$: 659.3334, found 659.3315.

(2*S*,3*R*)-3-((*R*)-4-((*tert*-Butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2-((*tert*-butoxycarbonyl)oxy)-3-((4*S*,5*S*)-5-cinnamyl-2,2-dimethyl-1,3-dioxolan-4-yl)propanoic acid **234**



$\text{C}_{37}\text{H}_{60}\text{N}_2\text{O}_{11}\text{Si}$
Exact M. = 736.3966
M = 736.97 g·mol $^{-1}$

See Table 12, entry 4:

To a solution of GABOB-APTO **234** (19.0 mg, 25 μmol , 1 eq.) in MeOH/THF/ H_2O (v/v/v, 0.4/0.4/0.6 mL) was added LiOH· H_2O (10.5 mg, 250 μmol , 10 eq.). After stirred for 4 h at room temperature, completed, then diluted with water (10 mL), cooling down at -10 °C and carefully acidified with a solution of citric acid (72 mg, 370 μmol , 15 eq.) (pH = 3-4). The acidic aqueous phase was extracted with CH_2Cl_2 (10 mL \times 3). The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. Preparative thin layer chromatography on silica gel (MeOH/ CH_2Cl_2 = 5/95) gave the desired acid **235** (10.0 mg, 54%) as a colorless oil, as well as 2-hydroxyl acid **236** (6.0 mg, 38%) as a colorless oil. Data below for the desired acid **235**:

TLC: $R_f = 0.36$ (MeOH/ CH_2Cl_2 = 10/90)

$[\alpha]_D^{22} = -7.8$ (c 0.55, CHCl_3)

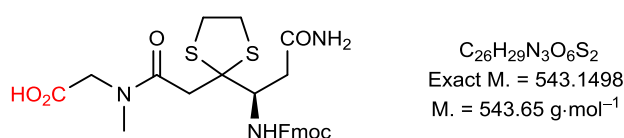
IR (ATR) ν 3330, 2979, 2931, 2860, 1750, 1698, 1657, 1511, 1369, 1271, 1253, 1166, 1093 cm^{-1}

¹H NMR (400 MHz, MeOD-*d*₄) δ 0.09 (s, 3H), 0.13 (s, 3H), 0.89 (s, 9H), 1.41 (s, 3H), 1.44 (s, 9H, NBoc and one methyl of acetonide), 1.47 (s, 9H), 2.33-2.57 (m, 4H, two *ABX* mixed), 3.05-3.18 (m, 2H, *ABX*), 3.79 (pseudo t, 1H, *J* = 6.4 Hz), 4.11-4.18 (pseudo m, 2H, two *ABX* mixed), 4.75-4.84 (m, 1H), 5.06 (pseudo s, 1H), 6.26 (ddd pseudo dt, 1H, *J* = 16.0, 6.8, 6.8 Hz), 6.47 (d, *J* = 16.0 Hz), 7.17-7.21 (m, 1H), 7.26-7.32 (m, 2H), 7.33-7.37 (m, 2H).

¹³C NMR (100 MHz, MeOD-*d*₄) δ -4.4, -4.3, 19.0, 26.5 (3C), 27.7, 27.9, 28.1 (3C), 28.9 (3C), 39.0, 42.5, 46.6, 54.3, 69.7, 76.5, 79.7, 80.2, 80.8, 83.3, 110.7, 126.6, 127.2 (2C), 128.2, 129.5 (2C), 133.9, 138.8, 154.4, 158.3, 173.4, 175.0.

HRMS (ESI+) Calcd for C₃₇H₆₁N₂NaO₁₁Si [M + Na]⁺: 759.3826, found 759.3858.

(*R*)-*N*-(2-(2-(1-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-amino-3-oxopropyl)-1,3-dithiolan-2-yl)acetyl)-*N*-methylglycine **238**



Step1: To a solution of dipeptide **D-mPyrAA-Sar (*R*)-189** (180 mg, 0.30 mmol, 1 eq.) in CH₂Cl₂ (1 mL) under argon was added TFA (0.5 mL, 6.00 mmol, 20 eq.). The resulting mixture was stirred at room temperature for 4 h, then concentrated under reduced pressure to give a proposed TFA complex **237** (20 mg, τ = 100%).

Step2: The proposed TFA complex **237** was dissolved in EtOAc (20 mL), then basified with DIEA (775 mg, 6.00 mmol, 20 eq.) in ice bath. The basified solution was washed with water (10 mL × 3) to give the aqueous phase, which was then acidified with 4 M HCl until pH = 2-3 and extracted with a mixture solvents of CH₂Cl₂/MeOH = 95/5 (20 mL × 3). The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure to give the pure desired the pure desired free dipeptide acid **238** (133.5 mg, 82%) as a white solid.

TLC: *R*_f = 0.50 (EtOAc/MeOH = 90/10)

[α]_D²¹ = +23.1 (*c* 0.50, MeOH)

IR (ATR) ν 3329, 2922, 1708, 1636, 1506, 1448, , 1401, 1322, 1230, 1045, 759, 738 cm⁻¹

¹H NMR (400 MHz, MeOD-*d*₄) δ 2.51 (dd, 1H, *J* = 25.2, 12.0 Hz *ABX*), 2.90 (s, rotamer) and 2.92 (s, 3H), 2.96-3.31 (m, 7H), 3.78-4.34 (m, 5H), 4.82-4.86 (m, 1H), 7.28-7.37 (m, 4H), 7.59-7.65 (m, 2H), 7.75 (d, 2H, *J* = 7.2 Hz).

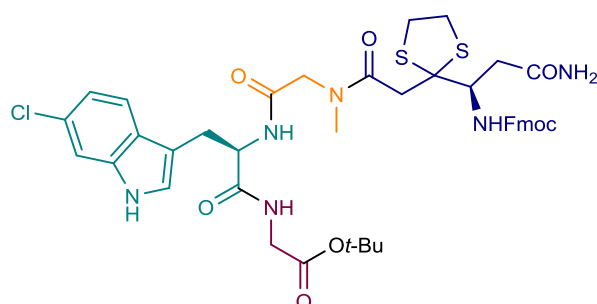
¹³C NMR (100 MHz, MeOD-*d*₄) δ 35.5 (rotamer) and 37.3, 39.4 and 39.5 (rotamer), 39.9 (rotamer) and 40.0, 41.1 (rotamer) and 41.2, 46.3 (rotamer) and 46.5, 48.3, 50.7 (2C) and 53.0 (one rotamer of the two carbon), 57.3, 67.8, 73.7 and 73.8 (rotamer), 120.9 (2C), 126.2, 126.4, 128.2 (2C), 128.8 (2C), 142.5, 145.0, 145.5, 158.4, 172.4, 172.5, 176.1.

HRMS (ESI⁺) Calcd for C₂₆H₂₉N₃NaO₆S₂ [*M* + Na]⁺: 566.1390, found 566.1378.

HRMS (ESI⁻) Calcd for C₂₆H₂₉N₃NaO₆S₂ [*M* - H]⁻: 542.1391, found 542.1403.

tert-Butyl

((*R*)-2-(2-(2-(2-((*R*)-1-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-amino-3-oxopropyl)-1,3-dithiolan-2-yl)-*N*-methyleacetamido)acetamido)-3-(6-chloro-1*H*-indol-3-yl)propanoyl)glycinate **239**



C₄₃H₄₉ClN₆O₈S₂
Exact M. = 876.2742
M. = 877.47 g·mol⁻¹

To a solution of D-mPyrAA-Sar-OH (*R*)-**238** (8.5 mg, 15.6 μmol, 1.1 eq.) in CH₂Cl₂ (1 mL) under argon at room temperature was added PyBroP (8.0 mg, .17.0 μmol, 1.2 eq.) and DIEA (7.3 mg, 4.00 mmol, 4 eq.), respectively. A solution of H-Trp-Gly-O*t*-Bu **217** (5.0 mg, 14.2 μmol, 1 eq.) in CH₂Cl₂ (1 mL) was added. The resulting mixture was stirred at room temperature for 48 h. Diluted with CH₂Cl₂ (20 mL) and the solution was subsequently washed with 1 M HCl (20 mL), sat. NaHCO₃ (20 mL) and brine (20 mL), then dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography on silica gel (EtOAc/MeOH = 95/5, 90/10) gave the pure desired tetrapeptide D-Fmoc-mPyrAA-Sar-Trp(6-Cl)-Gly-O*t*-Bu **239** (10.2 mg, 82%) as a waxy solid.

TLC: $R_f = 0.50$ (EtOAc/MeOH = 90/10)

$[\alpha]_D^{21} = +23.1$ (c 0.50, MeOH)

IR (ATR) ν 3329, 2922, 1708, 1636, 1506, 1448, , 1401, 1322, 1230, 1045, 759, 738 cm^{-1}

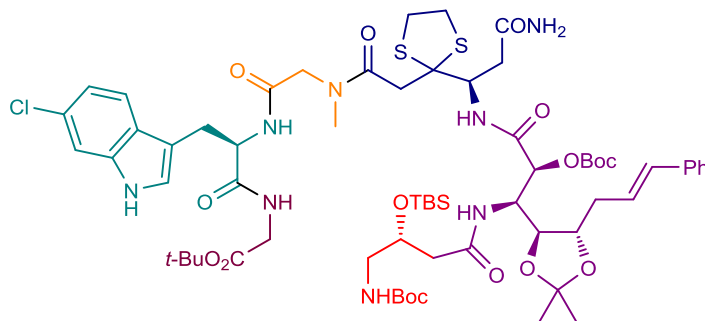
^1H NMR (400 MHz, MeOD- d_4) δ 2.51 (dd, 1H, $J = 25.2, 12.0$ Hz ABX), 2.90 (s, rotamer) and 2.92 (s, 3H), 2.96-3.31 (m, 7H), 3.78-4.34 (m, 5H), 4.82-4.86 (m, 1H), 7.28-7.37 (m, 4H), 7.59-7.65 (m, 2H), 7.75 (d, 2H, $J = 7.2$ Hz).

^{13}C NMR (100 MHz, MeOD- d_4) δ 35.5 (rotamer) and 37.3, 39.4 and 39.5 (rotamer), 39.9 (rotamer) and 40.0, 41.1 (rotamer) and 41.2, 46.3 (rotamer) and 46.5, 48.3, 50.7 (2C) and 53.0 (one rotamer of the two carbon), 57.3, 67.8, 73.7 and 73.8 (rotamer), 120.9 (2C), 126.2, 126.4, 128.2 (2C), 128.8 (2C), 142.5, 145.0, 145.5, 158.4, 172.4, 172.5, 176.1.

HRMS (ESI+) Calcd for $\text{C}_{43}\text{H}_{49}\text{ClN}_6\text{NaO}_8\text{S}_2$ $[\text{M} + \text{Na}]^+$: 899.2634, found 899.2614.

tert-Butyl

((*R*)-2-(2-(2-(2-((*7R,11R,12S,15R*)-17-amino-12-((*tert*-butoxycarbonyl)oxy)-7-((*tert*-butyldimethylsilyl)oxy)-11-((*4S,5S*)-5-cinnamyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-4,9,13,17-tetraoxo-3-oxa-5,10,14-triazaheptadecan-15-yl)-1,3-dithiolan-2-yl)-*N*-methylacetamido)acetamido)-3-(6-chloro-1*H*-indol-3-yl)propanoyl)glycinate **240**



$\text{C}_{65}\text{H}_{97}\text{ClN}_8\text{O}_{16}\text{S}_2\text{Si}$
Exact M. = 1372.5922
M. = 1374.19 $\text{g}\cdot\text{mol}^{-1}$

Step (1) Fmoc-deprotection: To a solution of tetrapeptide Fmoc-mPyrAA-Sar-Trp(6-Cl)-Gly-*Ot*-Bu **239** (9.0 mg, 10 μmol , 1.1 eq.) in MeOH (1 mL) at room temperature was added Et_2NH (29.3 mg, .040 mmol, 40 eq.). The resulting mixture was stirred at room temperature for overnight (> 16 h), completed. Then concentrated under reduced pressure, and evaporated with CH_2Cl_2 (2 mL \times 3) to remove the residue of Et_2NH cleanly, to give the crude of desired free tetrapeptide amine (9.2 mg, $\tau = 100\%$, combined with DBF, TLC: $R_f =$

0.10 (EtOAc/MeOH = 95/5)) as a pale-yellow waxy solid.

Step (2) Coupling with GABOB–APTO derivative **236**: To a solution of GABOB–APTO derivative **236** (8.1 mg, 11 μmol , 1.1 eq.) in CH_2Cl_2 (0.5 mL) under argon at room temperature was added PyBroP (5.6 mg, 12 μmol , 1.2 eq.) and DIEA (5.2 mg, 40 μmol , 4 eq.), respectively. A solution of free tetrapeptide amine crude **239** (9.2 mg, 10 μmol , 1 eq.) in CH_2Cl_2 (0.5 mL) was then added at room temperature. The resulting mixture was stirred for 16 h at room temperature. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with brine (20 mL) to give the organic layer, which was dried over MgSO_4 , filtered and concentrated under reduced pressure. Flash chromatography on silica gel (EtOAc/MeOH = 95/5, 90/10) gave the desired hexapeptide Boc–GABOB–APTO–mPyrAA–Sar–Trp(6-Cl)–Gly–Ot-Bu **240** (4.5 mg, 33%) as a colorless oil.

TLC: $R_f = 0.50$ (EtOAc = 100%)

IR (ATR) ν 3330, 2951, 2927, 2855, 1748, 1664, 1529, 1456, 1368, 1276, 1252, 1162, 1093, 839 cm^{-1}

^1H NMR (400 MHz, CDCl_3) δ 0.10 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 1.35 (s, 3H), 1.43 (s, 21H), 1.50 (s, 9H), 2.36-2.68 (m, 5H), 2.89 (s, 3H), 2.97-3.06 (m, 2H), 3.17-3.34 (m, 9H), 3.66-3.81 (m, 3H), 3.90-4.02 (2H), 4.12-4.31 (m, 2H), 4.64-4.67 (m, 1H), 4.75-4.81 (m, 1H), 4.83-4.87 (m, 1H), 5.06 (brs, 1H), 5.24 (s, 1H), 6.07-6.14 (m, 1H), 6.37 (d, 1H, $J = 16.0$ Hz), 7.04-7.13 (m, 3H), 7.19-7.23 (m, 3H), 7.26-7.36 (m, 5H), 7.57 (d, 1H, $J = 8.4$ Hz), 7.93 (brs, 1H), 8.61 (brs, 1H).

HRMS (ESI+) Calcd for $\text{C}_{65}\text{H}_{97}\text{ClN}_8\text{NaO}_{16}\text{S}_2\text{Si}$ $[\text{M} + \text{Na}]^+$: 1395.5814, found 1395.5774.

FRENCH SUMMARY

Le but de cette thèse est de réaliser la première synthèse totale de la microsclerodermin D, un peptide macrocyclique d'origine marine possédant des propriétés biologiques intéressantes. Nous envisageons de développer une voie de synthèse de la microsclerodermine D modulable qui pourrait être valable pour la préparation d'autres membres de la famille et également d'analogues. La difficulté majeure concerne le résidu d'acide hydroxypyrrolidinoacétique qui est très sensible et se déshydrate spontanément en milieu acide comme basique. Notre stratégie est donc de maintenir ce résidu sous une forme masquée tout le long de la synthèse et de le libérer lors de l'ultime étape de la synthèse.

Ainsi, nous avons décidé d'assembler l'hexapeptide macrocyclique par couplage peptidique dans des positions stratégiques entre trois dipeptides. Parmi les six amino acides qui composent la microsclerodermine D, deux sont disponibles commercialement et donc notre premier objectif était d'établir une voie d'accès pour chacun des quatre amino acides restant.

Dans un premier temps, nous nous sommes focalisés sur le dipeptide mask-(*R*)-PyrAA–Sar. Nous avons réussi à développer une nouvelle voie d'accès aux γ -amino- β -cétoesters benzyliques sous forme énantiomériquement pure par condensation de Fmoc-UNCA avec un hémimalonate de magnésium. Ce dipeptide a été choisi comme modèle pour étudier notre stratégie de masquage permettant l'installation du résidu de l'acide hydroxypyrrolidinoacétique qui est extrêmement sensible, et nous avons pu établir la preuve de concept de la validité de notre stratégie.

Ensuite, nous avons développé une synthèse asymétrique du D-6-chlorotryptophane en utilisant une méthode classique de synthèse asymétrique d' α -amino acides basée sur l'alkylation d'une base de Schiff chirale obtenue à partir de la glycine et de la 2-hydroxypinanone. Pour finir un simple couplage avec un glycinate nous a fourni le deuxième dipeptide 6-Cl-Trp–Gly.

Puis nous avons préparé un dérivé protégé du GABOB en adaptant les méthodes disponibles dans la littérature, ainsi qu'un dérivé de l'APTO grâce à la voie de synthèse développée au laboratoire, et en adaptant les groupements protecteurs. Le couplage de ces deux amino acides nous a donné le troisième dipeptide GABOB–APTO.

Pour terminer les trois dipeptides ont été assemblés séquentiellement pour fournir un hexapeptide linéaire. Cet hexapeptide sera ensuite cyclisé pour construire le macrocycle. Après déprotection des différentes chaînes latérales, le résidue de l'acide pyrrolidinoacétique masqué sera déprotégé pour libérer le motif γ -cétoamide qui cyclisera spontanément pour fournir la microsclerodermine D.

Titre : Synthèse totale de la microsclerodermine D

Mots clés : synthèse énantiosélective, peptide macrocyclique, couplage peptidique, β -amino acide, β -cétoester

Résumé : La microsclerodermine D est un peptide macrocyclique d'origine marine qui comporte six amino acides, dont deux sont disponibles commercialement : la glycine (Gly) et la sarcosine (Sar). Les quatre autres amino acides : l'acide (*R*)- γ -amino- β -hydroxybutyrique (GABOB), le D-6-chlorotryptophane (6-Cl-Trp), un β -amino acide polyhydroxylé (APTO) et l'acide 3-amino-4-hydroxypyrrolidinoacétique (PyrAA) seront préparés *via* de nouvelles voies de synthèse.

Notre objectif est de développer une voie de synthèse de la microsclerodermine D modulable et qui permettrait la synthèse d'autres membres de la famille des microsclerodermines et d'analogues. Nous nous intéresserons également à de potentielles études permettant d'évaluer leurs propriétés biologiques et leur potentiel en tant qu'agent anticancéreux.

Title : Total synthesis of microsclerodermin D

Keywords : enantioselective synthesis, macrocyclic peptide, peptide coupling, β -amino acid, β -ketoester

Microsclerodermin D is a macrocyclic peptide of marine origin which contains six amino acids, of which two are commercially available: glycine (Gly) and sarcosine (Sar). The four other amino acids: (*R*)- γ -amino- β -hydroxybutyric acid (GABOB), D-6-chlorotryptophan (6-Cl-Trp), a polyhydroxylated β -amino acid (APTO) and 3-amino-4-hydroxypyrrolidinoacetic acid (PyrAA) will be prepared by new synthetic routes.

Our goal is to develop a modular synthetic route to microsclerodermin D that could be applicable for the preparation of other microsclerodermin family members and analogues thereof. We are also looking forward to make some investigations on their biological activities or potential as anticancer drug.